PEER REVIEW COMMENTS
DRAFT RCF CRITERIA DOCUMENT

REVIEWER 1

GENERAL COMMENT

The committee is of the opinion that the draft is very thorough and well written. It contains most of the experimental animal studies as well as all the published epidemiology. The original data are adequately presented and very clear.

COMMENTS ON THE REL

Reviewer 1 agrees with NIOSH that RCF causes irritation and pulmonary dysfunction, and also is suspected to cause lung cancer. The REL for RCF is set to prevent both type of effects. However, it is based on the existence of a threshold level. NIOSH concludes that there is still a significant cancer risk at 0.25 f/cm^3 and that this risk estimate could be an underestimation. We believe that this should be mentioned in paragraph 1.1 (page 1.1/1.2) and in the executive summary (v/vi).

Furthermore, it should be clarified in the document whether the REL concerns only respirable RCF or not (chapters 1 and 8). This is important, because respiratory fibers penetrate the deep lungs, whereas part of the inhalable fibers do not and, therefore, have quantitatively a different hazard. In addition, it is essential to mention the length of the RCF for which the REL is set.

Reviewer 1 agrees with NIOSH that RCF has similar effects as asbestos fibers. The current observation that no mesotheliomas are observed in humans with RCF exposure compared with asbestos fiber exposure, may indeed be explained by lower exposure concentrations of RCF and the lack of epidemiologic data on long-term RCF-exposure.

COMMENTS ON NON-CARCINOGENIC EFFECTS

NIOSH recommends for RCF a REL of 0.2 f/cm^3 as a 10-h TWA (40-h workweek). This REL is based on epidemiologic studies showing increased incidence of pleural plaques, respiratory symptoms (dyspnea and cough), skin and eye irritation, and decreased pulmonary function with increasing exposures to airborne fibers at a concentration of as low as 0.2 to 0.6 f/cm^3 . Reviewer 1 noted that this REL is among others based on a lowest-observed adverse effect level (LOAEL) for respiratory effects at 0.2 f/cm^3 in humans and that this REL does not completely protect workers. Reviewer 1 agrees with the LOAEL of 0.2 f/cm^3 for non-carcinogenic effects. Reviewer 1 would have done a step further and would have set a health-based OEL based on a no-observed adverse effect level (NOAEL) by using uncertainty factors, so that workers were completely protected.

In among others including reviewer 1, a discussion is going whether there exists a relationship between RCF exposure and the occurrence of lung sarcoidosis (granulomatous reticulosis). Reviewer 1 is missing a discussion on this matter in the draft document.

COMMENTS ON CARCINOGENIC EFFECTS

Reviewer 1 agrees with NIOSH that RCF may pose a carcinogenic risk. Furthermore, classification of RCF as a potential carcinogen for animals, but not proven for man, aligns well with the recent classification by IARC. In its evaluation, IARC classified RCF as possibly carcinogenic to humans (Group 2B). This IARC evaluation is missing in the draft *(IARC*

monographs on the evaluation of carcinogenic risk in humans. Volume 81, man-made vitreous fibres, 2002).

Reviewer 1 finds it important to know whether RCF acts by a genotoxic or a non-genotoxic mechanism. In the draft, however, a discussion on the genotoxicity of RCF is missing. In our view, we question whether it is appropriate to set a REL, when RCF acts by a genotoxic mechanism

ADDITIONAL COMMENTS

Page 1.3, line 7 and 8: 'mineral fibers' should be 'naturally occurring mineral fibers'.

Page 4.20, line 10: '… with higher concentrations of fibers.' Higher than what?

Page 5.4, line 11: What means the abbreviation MAN?

Page 5.4, line 13-20: give the number or percentages for each tumor type.

Page 5.4, line 16-17 and Table 5-1: also add all doses used for Chrysotile in Table 5-1.

Page 5.6, line 4-9 and 11-17, including Table 5-3: add more details concerning observation period, exposure duration and tumor description.

Page 5.7, line 17: delete the words 'benign' and 'malign'.

Page 5.8, line 12 and Table 5-4: 182±66 WHO f/cm^3 RCF3 should be 162±66 according to Table 5-4 (page 5.56).

Page 5.16, lung overload argument: one reference is missing here and concerns *Brown RC,Sebastien P, Bellmann and Muhle H (2000) Particle contamination in experimental fiberpreparations. Inhal Toxicol 12 (Suppl 3): 99-107*. This paper describes the difference in inflammatory response in rats exposed to an original fiber preparation (RCF) with 25% non-fibrous particles, and a purified preparation (RCF1a) with about 2% of non-fibrous particles. The results show that RCF1a shows less inflammatory (total cells, PMN number) than RCF1, and that the percentage of PMN is dramatically lower than in RCF1a compared to RCF1.

Page 5.18, line 16: how can an unpublished study be cited?

Page 5.19, line 12-15: is this a correct statement? See page 5.21, line 18-19.

Page 5.20, cellular effects of RCF: A general comment that these types of studies are necessary to elucidate the mechanism of fiber genotoxicity or effects on cell proliferation. This insight is crucial for selecting extrapolation models for TLV setting later on. One specific paper *(Brown DM, Beswick PH, Donaldson K (1999) Induction of nuclear translocation of NF-kappaB in epithelial cells by respirable mineral fibres. J Pathol 189(2):258-64*) is missing here, since it studies the effect of a large set of fibers on NFkB activation in epithelial cells, to investigate this test as a potential short term screening test. It suggests that RCF1 but not RCF4 should be considered carcinogenic based on the test outcomes. In relation to this the overview of literature later on (Appendix C) effects on the different target cells (macrophages, epithelial cells, mesothelial cells) could be separated more clearly as currently done. Although C2 details

on indirect effects of RCF via inflammation, and more specifically macrophages, these cells are also discussed as target cells in C1 (page C4 and C5). A similar remark can be made for salient point 3 on page **6.14.**

Page 5.27, line 18-19: This sentence is unclear. Please add more details.

Page 5.54, Table 5-3, Smith et al.: Specify the type of tumors found (adenomas, carcinonomas, mesotheliomas).

Page 5.55, Table 5-4, Davis et al., column tumor incidence: delete the word 'benign' in the second sentence; there are no malign adenomas.

Page 8.13, line 18-21: In understanding the rationale behind these risk estimates, it would help to refer again to Table 5-10.

Page 9.8, line 4: '… persist longer in the lungs'. Longer than what?

Finally, Reviewer 1 noted that in the draft document a new set of data is presented, which have been published after the publication of DECOS' final document on man-made mineral fibers in 1995. These data, specifically those from epidemiologic studies, do urge the need to reconsider the Dutch occupational exposure limit and cancer risk values for refractory ceramic fibers.

REVIEWER 2

OVERALL COMMENTS
NIOSH QUESTION:*Is there consistency throughout the text?*
Reviewer: Yes

NIOSH QUESTION: *Please comment on how accurately and clearly information is presented in the document.*
Reviewer: The presentation is quite accurate and clear.

NIOSH QUESTION: *Is there adequate presentation of original data? Are there additional concerns, issues, or research areas which should be considered?*
Reviewer: The original data are presented quite adequately, and no other issues need coverage.

NIOSH QUESTION: *Assess the organization of sections and chapters and provide comment.*
Reviewer: The organization is sound, but there is more redundancy than necessary.

HUMAN STUDIES
NIOSH QUESTION: *Please provide a copy of any important reference that should be incorporated into these sections of the document.*
Reviewer: I am not aware of any important reference that is missing.

NIOSH QUESTION: *Have the important medical endpoints been adequately discussed?*
Reviewer: Yes.

NIOSH QUESTION: *Assess the presentation and comparison of data from the U.S. and European*

cohorts.
Reviewer: Very fair.

NIOSH QUESTION: *Is the discussion adequate?*
Reviewer: Yes.

EXPOSURE ASSESSMENT
NIOSH QUESTION: *Please provide a copy of any important reference that should be incorporated into these sections of the document. Are there additional studies or data characterizing exposure to RCF which should be included?*
Reviewer: I am not aware of any important reference that is missing.

NIOSH QUESTION: *What is your impression of the presentation of the exposure data?*
Reviewer: It is thorough.

NIOSH QUESTION: *Please identify any data gaps or suggest recommendations for further characterization of RCF exposures.*
Reviewer: Future exposure measurement data should be presented in terms of bivariate length and diameter distributions.

ANIMAL AND *IN VITRO* STUDIES
NIOSH QUESTION: *Please provide a copy of any important reference that should be incorporated into these sections of the document.*
Reviewer: I have no such documents.

NIOSH QUESTION: *Are the animal studies accurately described and summarized?*
Reviewer: Yes.

NIOSH QUESTION: *Comments on any additional information that should be included regarding the Maximum Tolerated Dose discussion in the rat chronic inhalation study.*
Reviewer: The discussion is adequate.

NIOSH QUESTION: *Comment on any additional information that should be included regarding the association of particle to fiber ratio with tumor formation in the chronic inhalation studies.*
Reviewer: Discuss, to the extent possible, the likely extent of lung overload and its influence on tumor yield.

NIOSH QUESTION: *Comments on the NOAEL values presented for fibrosis and lung cancer.*
Reviewer: *No comment.*

NIOSH QUESTION:*Comment on the validity of the RCF / amosite comparison using data from two different chronic inhalation studies. Please provide any additional data that should be provided in this comparison.*
Reviewer: The discussion was quite adequate.

NIOSH QUESTION: *Is the discussion of the in vitro sections adequate? If not, comment on additional information that should be included.*
Reviewer: Yes

NIOSH QUESTION: Is the discussion of the animal studies adequate? If not, comment on additional information that should be included.
Reviewer: Yes

NIOSH QUESTION: *Are the in vitro studies adequately summarized and explained?*
Reviewer: Yes

BASIS FOR THE STANDARD
NIOSH QUESTION: *Is the derivation of the REL adequately explained?*
Reviewer: Yes

NIOSH QUESTION: *Assess the use of data collected during the EPA consent agreement to characterize exposure levels in RCF industries and determine achievable levels given engineering controls, work practices, and other considerations. Please provide suggestions or alternative approaches which might improve the presentation, interpretation, and use of these data.*
Reviewer: Good use was made of these data.

NIOSH QUESTION: *Are there additional data that should be presented in support of the REL?*
Reviewer: No.

WORKER PROTECTION/RECOMMENDATIONS
NIOSH QUESTION: *Please comment on the recommendations for respirator use*.
Reviewer: They are reasonable.

NIOSH QUESTION: *Are there other engineering controls, work practices, or other factors that should be discussed? (Please specify.)*
Reviewer: No.

MEDICAL MONITORING
NIOSH QUESTION: *Please comment on the overall presentation of the medical monitoring program. Is it presented in a logical manner?*
Reviewer: Yes.

NIOSH QUESTION: *Are there specific elements of the program which should be modified?*
Reviewer: No.

NIOSH QUESTION: *Are there additional elements which could be implemented to help ensure the safety and health of workers?*
Reviewer: No.

Suggestions for Technical Corrections

page	line	change
Vi	12	insert: "or overestimate" after "underestimate"
2.5	6,19	On text line, and at many other locations, the term "thoracic- and respirable-sized fibers" is used to refer to fibers <3 to 3.5 μm in diameter. There is no definition provided of either "thoracic" or "respirable", and the reader could presume that they were equivalent. The ACGIH and international (ISO and EEC) definition should be provided, indicating that "thoracic" refers to particles penetrating to the thorax (50% cut at 10 μm aerodynamic diameter). It should also be made clear that mineral and vitreous fibers with diameters 3 to 3.5 μm have an aerodynamic diameter of ~10 μm, and that "respirable fibers" will be those with physical diameters ≤1.3 μm.
2.7	17	This discussion of surface area and dissolution is inadequate. It should be noted that thinner fibers have a greater surface/volume ratio and dissolve more rapidly than thicker fibers.
4.3	3	change: "respirable" to "thoracic" (see comment above - for p. 2.5), and at subsequent places which give a similar wrong impression.
4.12	3,4	For clarity, change "with respect to the" to "in having a lower". These
4.14	6-9	numbers have too many significant figures.
4.18	4	change: "oxide" to "dioxide".
4.20	10	"higher" than what?
5.5	20,21	change: "may result" to "results".
6.5	12,13	"aspect ratio" has no independent affect on fiber toxicity.
6.6	2	add: "or more" at end of the line.
6.7	12	change: "alveoli" to "gas-exchange region". Most of the deposition in this region is actually in respiratory bronchioles and alveolar ducts rather than in the alveoli they serve. This same correction is needed on subsequent pages as well.
6.8	15	insert: "in rats" after "diameter". Human alveolar macrophages are closer to 20 μm.
6.8	16,19	There is an obvious (and important) inconsistency in the ingestion limit, with 10 μm cited on line 16, and 20 μm cited on line 19.
9.4	2	If you want to cite "Hagopian and Bastress 1976", it should not be the first of the citations.

9.8	8	delete: "extreme" or justify it. It is hard to envision a circumstance where a more soluble SVF would be more (or at least much more) hazardous.
9.13	Section 9.3	There should be a citation somewhere in this section to the recommended sampling and laboratory analytical methods.

REVIEWER 3

Comment: My main comment concerns the description of the REL on page 1.1, where it is described "as a time-weighted average (TWA) concentration for up to a 10-hr work shift in a 40-hr workweek." My reading of this is that the limit is placed on the average concentration regardless of the length of the working day, up to a maximum of 10 hours. So someone working 4 hours per day for five days would be permitted to have up to 4fiber/cm3.hrs cumulative exposure in a week. Another person working 40-hr would be permitted 8fiber/cm3.hrs cumulative exposure. In other words the limit is placed on the average concentration not the average concentration normalised to a fixed time period. If I have misunderstood then it would perhaps be appropriate to clarify the text here.

Comment: The definition you have adopted is a little different in basis from the approach taken in the Europe Union, as described in Directive 97/69/EC. I have attached a brief document that explains what the directive says. Essentially RCF's are defined as a Category 2 carcinogen but the basis for that they should be a MMVF with alkali earth oxide content less than 18% by weight. Note also that the UK health and Safety Executive (HSE) now describe MMVF as machine-made vitreous fibres.

Comment: In Chapter 4 you do not describe the European exposure monitoring, other than that reported by Krantz. However, I note that in the epidemiological section one of the relevant reports are cited (Groat *et al*, 1999). The other report is also published by the Institute of Occupational Medicine - it is Cherrie et al (1989) A report on the environmental conditions at seven European ceramic fibre plants. IOM TM 89/07. Edinburgh: IOM. Let me know if you would like copies of either of these reports.

Comment: I thought you would be interested to know that the UK HSE are currently consulting about the introduction of a new Maximum Exposure Limit for RCF. You can access the document, which is much shorter than your own, at http://www.hse.gov.uk/consult/condocs/cd187.pdf. HSE have proposed either a limit of 1 or 0.5 fibres/ml, with a gravimetric limit of 5mg/m3.

Comment: The document is comprehensive and I am not aware of any exposure or epidemiological study that you have not included. However, I'm not sure if you know that the results of the Cowie *et al* study and some further analysis was reported in the journal Occupational and Environmental Medicine (Cowie HA, Wild P, Beck J, Auburtin G, Piekarski C, Massin N, Cherrie JW, Hurley JF, Miller BG, Groat S, Soutar CA. An epidemiological study of the respiratory health of workers in the European refractory ceramic fibre industry. Occup Environ Med. 2001 Dec;58(12):800-10.).

REVIEWER 4

NIOSH QUESTION: *Is there consistency throughout the text?*
Reviewer: Some better coordination and explanations are needed between the text in Sections 5 and 8.2.2 describing the findings for noncancer respiratory effects in occupationally exposed RCF workers (and the exposure levels at which they occur) and conclusions in Section 8.3 [on page 8.19 that "These conditions are documented for exposure concentrations in a range as low as 0.2 to 0.6 f/cm^3, which NIOSH considers the lowest observed adverse effect level (LOAEL) in humans.", and on page 8.21 that 0.2 f/cm^3 is a LOAEL for respiratory effects].

NIOSH QUESTION: *Please comment on how accurately and clearly information is presented in the document.*
Reviewer: The information on health effects in humans and animals exposed to RCF appears to be accurately and comprehensively presented in Section 5, with the exception that the findings for nonneoplastic respiratory lesions in the chronic rat bioassays with RCF1 (Mast et al., 1995a,b) have not received enough emphasis. The data presented in Mast et al. (1995a, b) describe doseresponse relationships for severity scores for several measures of noncancer respiratory lesions (pulmonary inflammation, pulmonary fibrosis, and pleural fibrosis) that are not adequately described in the NIOSH document. These data are important because the dose-response curves for these effects appear to be shifted to the left on the dose axis relative to the dose-response curves for the tumor responses. Thus, the noncancer responses in rats exposed to RCF 1 appear to be more sensitive than the cancer responses and should be considered when selecting the REL.

In supporting its REL of 0.2 f/cm^3, NIOSH may want to consider an analytical approach similar to that used by ATSDR (2002; Toxicological Profile for Synthetic Vitreous Fibers) in deriving an MRL for refractory ceramic fibers. (It is my understanding that EPA is currently considering a similar approach in deriving an RfC for refractory ceramic fibers, as per conversations and correspondence with Dr. David Lai.) The approach involved a benchmark dose analysis of several variables indicative of pulmonary inflammation (lung weight, macrophage aggregation score, and bronchiolization score) from the Mast et al. (1995a, b) rat bioassay and human equivalent exposure concentrations derived using rat and human lung deposition and clearance models for RCFI developed by CP Yu and colleagues. The analysis predicted human equivalent concentrations for an average population severity score of "minimal" of about 2 f/cm^3 for macrophage aggregation and 3 f/cm^3 for bronchiolization; lower 95% confidence limits on these estimates were about 1 f/cm^3 and 2 f/cm^3, respectively.

NIOSH QUESTION: *Is there adequate presentation of original data?*
Reviewer: Yes, but see suggestions below for new human data which should be incorporated into the document, and concern (described above) about a lack of emphasis on the data for noncancer respiratory effects observed in the chronic rat inhalation bioassay with RCFI (Mast et al., 1995a,b).

NIOSH QUESTION: *Are there additional concerns, issues, or research areas which should*

be considered?

Reviewer: I have two major issues in Sections 5 and 8, which I think should be considered by the authors of the document.

1. The derivation (or selection) of the REL of 0.2 fibers/cm^3 needs to be more clearly explained in Section 8. This reader is confused as to whether the REL was primarily selected because the estimates of risks for health effects at this exposure level (cancer based on tumor findings in rats and noncancer respiratory effects based on pulmonary function deficits, increased respiratory symptoms, and increased pleural changes in RCF manufacturing workers) are finite, but low (as implied from statements on page 8.21- "The selection of 0.2 f/cm^3 was based on the convergence of information summarized in this chapter…....."); or because NIOSH determined, based on the exposure data collected under the consent agreement between RCFC and EPA, that 0.2 f/cm^3 can be achieved in most work places where RCF or RCF products are handled.

   If the exposure data indicated that a lower exposure level (say 0.01 or 0.05 f/cm^3) could be achieved in most workplaces, would NIOSH have selected (or derived) a lower REL? After reading this document, I cannot answer this question with confidence, but believe I should be able to do so.

   The first sentence of Section 8.2 (Rationale for the REL) notes that the recommended REL of 0.2 f/cm^3 is based on "the evaluation of animal and human health data, risk assessment results, and the recognition of methods for controlling exposure to RCF at the REL in many workplaces", but the ensuing text does not clearly specify how these elements were used to make the recommendation.

Reviewer: The document notes that the available human data give some indication that exposure levels in the range of 0.2 to 0.6 f/cm^3 have been associated with noncancerous respiratory effects in workers, but does not adequately analyze and emphasize the findings from the rat chronic inhalation bioassay with RCFI (Mast et al., 1995a,b) describing dose-response relationships for pulmonary inflammation, pulmonary fibrosis, and pleural fibrosis.

NIOSH QUESTION: *Assess the organization of sections and chapters and provide comment.*

Reviewer: NIOSH may want to supplement sections 5.4 and 8.2.3 (or include new sections) to describe "risk assessment" analyses of the nonneoplastic findings from the chronic rat bioassay with RCF 1 (Mast et al., 1995a,b), such as the analyses described in Appendix A of the ATSDR (2002) Toxicological Profile for Synthetic Vitreous Fibers.

HUMAN STUDIES (SECTION 5.3)

NIOSH QUESTION: *Please provide a copy of important references that should be incorporated into these sections of the document.*

Reviewer: Discussion of results from the following reports of updated surveillance of the U.S. and European cohorts of RCF workers should be added (and included in the discussion in Section 5.3.7, as well as in Section 8):

Lockey, JE et al. 2002. A longitudinal study of chest radiographic changes of workers in the refractory ceramic fiber industry. Chest 121: 2044-2051.

Cowie , HA et al. 2001. An epidemiological study of the respiratory health of workers in the European refractory ceramic fibre industry. Occup Environ Med 58: 800-8 10.

Lockey et al. (2002) found statistically significant associations between measures of RCF exposure (duration, latency, or cumulative exposure) and the occurrence of pleural changes including pleural plaques in U.S. RCF workers (updated through December 31, 1996). Cowie et al. (2001) reported that logistic regression analyses found statistically significantly elevated odds ratios for pleural changes in European RCF workers (updated through 1996) with >10 years since first exposure to RCF compared with workers with <10 years since first exposure to RCF. No significant associations were found between pleural changes or plaques and duration or intensity of exposure to RCF. In addition, regression analyses of FEV 1 and FVC in European RCF workers found statistically significant (inverse) relationships with cumulative measures of exposure to respirable fibers only for men who were current smokers (Cowie et al., 2001).

NIOSH QUESTION: *Have the important medical endpoints been adequately discussed?*
Reviewer: Yes. Section 5.3 presents a clear and comprehensive account of the findings from the human studies.

NIOSH QUESTION: *Assess the presentation and comparison of data from the U.S. and European cohorts.*
Reviewer: The presentation and comparison is adequate.

NIOSH QUESTION: *Is the discussion adequate?*
Reviewer: Yes, the discussion section (5.3.7) presents a useful and well-organized synthetic evaluation and overview of the findings from the human studies. However, the text in section 5.3.7 should be expanded to more clearly explain how the results from the human studies support NIOSH's conclusion in Section 8 (page 8. 21) that 0.2 f/cm^3 (or 0.2 to 0.6 f/cm^3) is a LOAEL for respiratory effects in occupationally exposed humans. In addition, section 5.3.7 (and Section 8) should be updated to include discussion of the findings from the new reports by Lockey et al. (2002) and Cowie et al. (2001).

EXPOSURE ASSESSMENT (SECTION 4)
NIOSH QUESTION: *Please provide a copy of any important reference that should be incorporated into these sections of the document. Are there additional studies or data characterizing exposure to RCF which should be included?*
Reviewer: I am not aware of any additional data which should be included.

NIOSH QUESTION: *What is your impression of the presentation of the exposure data?*
Reviewer: The presentation of the data is logical and appears to be comprehensive. I did not check the information against information in the primary research reports, so I cannot attest to the detailed accuracy of the presentation.

NIOSH QUESTION: *Please identify any data gaps or suggest recommendations for further characterization of RCF exposures.*
Reviewer: Consistent with the data presented in this section, the discussion in Section 4.13 specifies the degree to which exposure levels in manufacturing scenarios have declined during the period between the 1950s and 1997 (from a maximum of about 10 f/cm^3 in the 1950s to arithmetic mean concentrations in the 1990s ranging from <0.3 to 0.6 f/cm^3). However, the text should more quantitatively document the difference in exposure levels between manufacturing scenarios (which are clearly specified in this section) and "end use" scenarios, such as those involving RCF installation and removal. Currently, the discussion gives the impression that end use scenarios produce higher air concentrations of fibers than do manufacturing scenarios, but does not specify the magnitude or range of this difference. If there are data to allow such quantitation, they should be specifically discussed in this section.
NIOSH RESPONSE: Discussion of available exposure data includes studies showing higher concentrations of airborne fibers associated with end-use of RCF products.

ANIMAL AND IN VITRO STUDIES (SECTIONS 5.1 AND 5.2)
NIOSH QUESTION: *Please provide a copy of any important reference that should be incorporated into these sections of the document.*
Reviewer: The findings from the following report should be incorporated into these sections: Bellman B. et al. 2001. Effects of nonfibrous particles on ceramic fiber (RCFI) toxicity in rats. Inhalation Toxicol 13: 877-901.

The study compared alveolar clearance activities and pulmonary lavage fluid levels of polymorphonuclear leukocytes (PMNs) following 3-week exposure of female Wistar rats to concentrations of 125 f/mL RCF 1 or RCF 1 a (a sample of RCF 1 which contained about 8 % of the nonfibrous mass of regular RCFI). Retardation of alveolar clearance activities by RCFIa was much less than retardation induced by RCFI. Both materials induced an increase (compared with controls) in PMNs in pulmonary lavage fluid, 3 days after the exposure period, but the increase persisted for a longer period of time following exposure to RCFI compared with RCFIa. The current document (page 5.18) cites these results to Muhle and Belleman 1996 (as cited by Mast et al., 2000).
NIOSH QUESTION: *Are the animal studies accurately described and summarized?*

Reviewer: Yes, with the exception (as described in my "overall" comments) that the findings for nonneoplastic respiratory lesions in the chronic rat bioassays with RCFI (Mast et al., 1995a,b) have not received enough emphasis in Section 5.1.2, and in other places in the document where the results from the animal studies are discussed (such as in Section 8.2.1 and Section 8.3, which now only discuss the cancer findings from the animal studies).

NIOSH QUESTION: *Comment on any additional information that should be included regarding the Maximum Tolerated Dose discussion in the rat chronic inhalation study.*
Reviewer: The discussion in Section 5.1.4, while discussing the concept that "lung overload" may have been exceeded at the highest exposure level (30 mg/m^3) in the chronic rat inhalation bioassays with RCFs (Mast et al., 1995a) and RCFI (Mast et al, 1995b), does not clearly articulate NIOSH's opinion/position on whether or not the results are useful for extrapolating to risks for cancer or noncancer respiratory effects in occupationally exposed

humans.

NIOSH QUESTION: *Comment on the NOAEL values presented for fibrosis and lung cancer.*
Reviewer: On page 5.13, it was noted that the low dose of 3 mg/m^3 was the NOAEL for fibrosis and that the NOAEL for lung cancer was 16 mg/m^3 in the chronic rat inhalation bioassay with RCF 1 (Mast et al., 1995a,b). This statement is consistent with the data, but I think the discussion in this paragraph should be expanded to emphasize and illustrate how the dose-response data in this study indicate that nonrespiratory effects from RCF may be more sensitive than carcinogenic effects.

NIOSH QUESTION: *Comment on the validity of the RCF/amosite comparison using data from two different chronic inhalation studies. Please provide any additional data that should be provided in this comparison.*
Reviewer: I have no suggestions for changes to this section.

NIOSH QUESTION: *Is the discussion of the animal studies adequate? If not, comment on additional information that should be included.*
Reviewer: See previous comments on inadequacy of the discussion of the nonneoplastic findings in the chronic rat bioassay with RCF 1.

NIOSH QUESTION: *Are the in vitro studies adequately summarized and explained?*
Reviewer: I have no suggestions for changes.

NIOSH QUESTION: *Is the discussion of the in vitro sections adequate? If not, comment on additional information that should be included.*
Reviewer: I have no suggestions for changes.

BASIS FOR THE STANDARD
NIOSH QUESTION: *Is the derivation of the REL adequately explained?*
Reviewer: No, see "overall" comments.

NIOSH QUESTION: *Assess the use of data collected during the EPA consent agreement to characterize exposure levels in RCF industries and determine acheivable levels given engineering controls, work practices, and other considerations. Please provide suggestions or alternative approaches which might improve the presentation, interpretation, and use of these data.*
Reviewer: See "overall" comments.

NIOSH QUESTION: *Are there additional data that should be presented in support of the REL?*
Reviewer: See suggestion to include risk assessment analyses of data for non-neoplastic respiratory effects in rats coupled with estimations of human equivalent concentrations based on CP Yu's lung deposition and clearance models.

WORKER PROTECTION/RECOMMENDATIONS
NIOSH QUESTION: *Please comment on the recommendations for respirator* use.
Reviewer: The recommendations appear adequate and appropriate.

NIOSH QUESTION: *Are there other engineering controls, work practices, or other factors that should be discussed?*
Reviewer: I am not aware of any.

MEDICAL MONITORING
NIOSH QUESTION: *Please comment on the overall presentation of the medical monitoring program. Is it presented in a logical manner?*
Reviewer: Yes.

NIOSH QUESTION: *Are there specific elements of the program which should be modified?*
Reviewer: No, but this is not my area of expertise.

NIOSH QUESTION: Are there additional elements which could be implemented to help ensure the safety and health of workers?
Reviewer: I am not aware of any.

REVIEWER 5

OVERALL COMMENTS
The document is well organized and written. The presentation and discussion of the original scientific data is very good. I found no omissions of important scientific data in the document. While NIOSH did not conduct an independent risk assessment, the discussion and analyses of other published assessments provide an adequate basis for the proposed REL.

HUMAN STUDIES
Reviewer: The available human data has been presented and summarized in. the document. A major limitation off the human data is the availability of worker cohorts of sufficient size, exposure, and latency to address the risk of respiratory system cancer. This is addressed in Section 5 where the unpublished mortality study by the University of Cincinnati presented. In addition to the small size of this cohort, it should be pointed out that the many of the risk- estimates, although statistically significant, are very imprecise due to small numbers off cases.

Reviewer: A NIOSH HHE is summarized on page 5.36. While interesting, this study provides no useful information concerning RCF and health risks. This discussion could easily be removed from the document without loss of information.

EXPOSURE ASSESSMENT
Reviewer: The presentation and discussion of human exposure data is generally adequate. I would recommend a little more assessment off the airborne fiber dimensions, where such data exists. For example, Table 4-8 has a column which provides the airborne fiber dimensions for NIOSH HHE's; however, this information is missing in the other tables in this section. Fiber diameter is potentially important not only

with regard to fiber respirability but also with regard to the potential for fibers to become and remain airborne.

BASIS FOR THE STANDARD

Reviewer: As previously stated, I believe NIOSH. has presented reasonable arguments and data in support of the REL recommmendation. Use of the EPA consent agreement data is appropriate and clearly demonstrates the technical feasibility off the proposed REL.

WORKER PROTECTION/RECOMMENDATIONS

Reviewer: NIOSH has not made a recommendation for a warning label on RFC products of packages. This would. seem to be important but may be adequately addresses by the OSHA Hazard Communication Standard_ A discussion of this would be helpful.

MEDICAL MONITORING

Reviewer: I would highly recommended that NIOSH make medical monitoring consistent with recommendations .for asbestos, given. the outcomes to be monitored. The recommendation with regard to periodic chest x-rays seems weak. I would recommend that NIOSH snake a specific recommendation here and not leave the decision to a `qualified health care provider'.