Glass Wool Fibers Expert Panel Report

Part A – Peer Review of the Draft Background Document on Glass Wool Fibers

The Report on Carcinogens (RoC) expert panel for glass wool fibers exposures met at the Sheraton Chapel Hill Hotel, Chapel Hill, North Carolina on June 9-10, 2009, to peer review the draft background document on glass wool fibers exposures and make a recommendation for listing status in the 12th Edition of the RoC.

Members of the expert panel are as follows:

Karl Kelsey, M.D., M.O.H., Chair
Department of Pathobiology and
Laboratory Medicine
Brown University

Aaron Blair, Ph.D., M.P.H.
Occupational & Environmental Epidemiology
Division of Cancer Epidemiology & Genetics
National Cancer Institute

Michael Elwell, Ph.D., D.V.M.
Pathology Department
Covance Laboratories

Andrij Holian, Ph.D.
Pharmaceutical Sciences
University of Montana

Marie-Claude Jaurand, Ph.D.
IFR105 – CEPH – IUH
INSERM U67 Paris

Peter Lees, Ph.D., C.I.H.
Bloomberg School of Public Health
The Johns Hopkins University

Morton Lippmann, Ph.D.
Environmental Medicine
New York University School of
Medicine

Allan Smith, M.D., Ph.D.
School of Public Health
University of California, Berkeley

Kyle Steenland, Ph.D.
Rollins School of Public Health
Emory University

J. Michael Rigsbee, Ph.D.*
Department of Materials Science and
Engineering
North Carolina State University

*Non-member, technical expert

One of the charges to this panel was to determine whether the information in the draft background document on glass wool fibers exposures is presented in a clear and objective manner, to identify any missing information from the body of knowledge presented in the document, and to determine the utility of the body of knowledge in the background document for drawing conclusions about the carcinogenicity of a candidate substance and for applying the RoC criteria for listing.

Following the discussion of all sections of the draft background document the expert panel reached a consensus concerning the critique of the draft background document, including its adequacy and any proposed revisions and voted 8 yes/0 no to accept the draft background

document (with the proposed changes suggested by the expert panel). Therefore, the expert panel agreed that the background document is adequate for drawing conclusions about the carcinogenicity glass wool fibers exposures and for applying the RoC listing criteria. Following are the expert panel's proposed revisions for each section of the glass wool fibers exposures background document:

General Comments

The term "durability" should be defined in the glossary. A statement on this concept should be added. The large number of terms: "durability, dissolution, biopersistence, biopersistence/durability, biodurability," and quantitative parameters "K_{dis} (different values depending on the conditions), Z-score" used to approach or anticipate the time-dependent state of fibers in the lung is confusing. It is not always clear what value is referred to, and in which conditions.

Section 1. Introduction

1. Page 8. Table 1-4 – Reported chemical compositions for various glass fibers (expressed as oxide mass percentages)
   - F_2 content in MMVF 10a and MMVF33 are not reported in the table; they should be 0.36 and 0.62, respectively.
   - JM475. CaO, MgO, and ZnO are not reported. This sample contains CaO, MgO and ZnO (according to Table 1 in Pott *et al*. 1991): 3% (including both CaO and MgO), and 3.9% for ZnO.
   - MMVF33 in McConnell *et al*. (1999): ZnO is 4.02% for MMVF 33 (see Table 1 in the paper). (Table 1-4 has 4.9%)
   - The data for chemical composition (oxide mass percentages) of A and C fibers used in experimental studies in Table 4-9 should be added in Table 1-4.

	Fiber	
	A	C
SiO_2	65.00	61.70
Al_2O_3	1.90	0.97
B_20_3	4.70	9.20
CaO	7.40	7.15
MgO	2.55	2.94
BaO	–	–
ZnO	–	–
ZrO_2	–	–
TiO_2	0.02	0.02
$Na_2O + K_2O$	–	–

	Fiber	
Na_2O	16.10	16.06
K_2O	0.65	0.59
$FeO + Fe_2O_3$	–	–
Fe_2O_3	0.11	0.11
P_2O_5	1.10	1.05
MnO	–	0.01
SO_3	0.03	0.20
F_2	–	–

Section 2. Human Exposure

General Comments

1. Where available, include the fiber counting conventions and averaging times (e.g., task length or 8 h) used to arrive at exposure concentrations.
2. Text should be included describing the relevance of fiber counting and averaging in interpreting exposure concentrations (proposed text follows).

   The development and evolution of sampling and analytical techniques combined with the adoption of different fiber definitions over the last 50 years makes comparison of airborne fiber concentrations across time somewhat problematic. In addition, U.S. and European conventions are not exactly comparable. Because of widely varying fiber size distributions, there is no universally appropriate conversion factor between methods. This means that the reader should not draw fine distinctions in interpreting reported exposures. Differences in averaging times (often unspecified) also make comparison of fiber concentration estimates of exposure between studies difficult. In general, reported exposure concentrations in manufacturing environments generally represent 8-hour time weighted averages (TWA) while reported exposure concentrations in non-manufacturing environments generally represent task length averages (TLA).
3. In exposure tables (2-5 and 2-6) better describe the types of means that are provided (i.e., are they plant means, job means, etc.)
4. Provide in the exposure tables, and text where appropriate, the type of fiber for which exposure data are presented; i.e., special purpose fibers or insulation wool.
5. When reporting nominal or mean fiber sizes clarify if discussing bulk or aerosol fraction.

Specific Comments

1. Section 2.1.1 Uses for glass fibers - Glass wool for insulation
   - Page 18, line 4 – add to text, Table 2-1 “as defined by IARC.”
2. Section 2.2.1 Production, import, and export information
   - Page 23, lines 3-6 – clarify if the discussion of lengths is for bulk product or airborne.

- Page 24, lines 3 and 12 – review values and also provide data in similar units.

3. Section 2.3.1 Occupational exposures - Exposure during manufacturing
   - Page 26, Lines 11-13 – add to end of discussion that concentrations presented during manufacturing are 8-h TWA unless otherwise noted; also discuss that during manufacturing, shorter duration measurements are still representative of 8 hr TWA concentrations.
   - Page 27, line 5 – delete the sentence "Results are presented as . . . "
   - Page 27, line 8 – delete last sentence of first paragraph.
   - Page 28, line 28 – add "size" between "respirable" and "range."
   - Page 30, lines 2, 4, 6 & 8 – change "simple mean" to "unweighted mean."
   - Page 31, line 13 – specify which counting methods were used for both the Cherrie and the Ottery study. Cherrie used an accepted, standard method, note what it was and provide method used by Ottery.
   - Page 31, line 26 – add that aspect ratio is "greater than or equal to" 3. Consider shortening the discussion of fiber counting rules to be consistent with discussions of other studies.
   - Page 32, line 11 – add "bulk" before "glass wool."
4. Section 2.3.2 Occupational exposures - Non-manufacturing occupational exposures
   - Page 37, line 7 – add sentence at end of paragraph that discusses the fact that unlike manufacturing operations, exposure during non-manufacturing operations is frequently significantly less than 8 hours and therefore most authors present fiber concentration data for the periods of active work (i.e., task-length). Note that as such, exposure levels between the two are not directly comparable.
5. Section 2.4.2 Environmental occurrence and general population exposure in the United States - World Trade Center levels
   - Page 45, line 3 – change heading to "*Other possible sources of exposure*."
   - Reduce the section to one paragraph discussing the possible sources as demolition and the WTC incident. Note that there are no ambient exposure levels, but there are data that suggest the potential (i.e., settled dust). Provide any ambient levels that are available.
6. *Section 2.6.2 Regulations and Guidelines - Guidelines*
   - Page 49, line 14 – review and confirm.

Section 3. Human Cancer Studies

General Comments

1. The panel considered that the background document well-characterized the literature on glass wool epidemiology. There were a few changes that were recommended.
2. The use of the words "significant" and "non-significant" in the Executive summary (and elsewhere) is not helpful and detracts from the evidence. Give the effect measures and confidence intervals, and the *p*-values when available. Add the modifier statistically in front of "significant" and "non-significant" where appropriate. Focus on confidence intervals in the discussion of the power of the studies (e.g. with respect to small numbers of subjects (e.g. Stone *et al*. and Rodelsperger studies.)

3. Mesotheliomas should have their own subsection in the executive summary and each subsequent section.

Specific Comments

1. Executive summary and section summary:
   - Page ix, lines 3 to 5 and Page 114, lines 8-10 “Adjusting for ever/never smoking ....reduced the risk of lung cancer among U.S. glass wool workers to non-significance”. No reference is given for this statement. Add relative risk estimate with confidence intervals (and preferably p-values also) before and after adjustment for smoking, avoiding the use of the word “non-significant”. Replace text as follows:
   - “Adjusting for ever/never smoking (using data obtained from a sample of proxies) reduced the risk of lung cancer mortality among male U.S. workers exposed to respirable fibers (mostly from glass wool) from 1.79 (95% CI = 0.77 to 4.14; p = 0.17) to RR = 1.37 (95% CI = 0.55 to 3.42; p = 0.50).”
   - Page x, line 5 (mesothelioma) and Page 115, line 10 – Delete “a deficit of cases was observed” and replace with the number of observed cases. See comment 7 (below).
2. Section 3.1.1 Glass wool exposure: cohort and case-control studies – U.S. cohort
   - Page 53, Table 3-1 – Provide the numbers of workers in each cohort in addition to person-years. Check whether they are person-years of follow-up or person-years of exposure.
   - Page 55, lines 21-26 – Provide the risk estimates and confidence intervals.
   - Page 59, line 11 – (re: risk for female workers with 10 or more years of employment) Better to give the number, and ideally the point estimate and confidence interval if available.
   - Page 60, lines 14-17 – (re: Enterline *et al.* 1987 nested case-control study of earlier update). Add the relative risks from cumulative exposure adjusted and unadjusted for smoking to the text. It provides direct information on possible confounding by tobacco use.
3. Section 3.2.1 Mixed glass wool and continuous filament - U.S. cohort
   - Page 84, lines 3-8 – Include the number of cancer deaths for the various groupings of mixed exposure populations. Numbers are probably small for meaningful comparisons and this should be noted.
4. Section 3.3 Mixed SVF exposure (not otherwise specified)
   - Page 85, lines 16 and 17 – Comments that a limitation was that the smoking data were self reported seems odd, since almost all smoking data are self reported. This limitation does not need to be mentioned here.
5. Section 3.3.2 Mixed SVF exposure (not otherwise specified) - Other case-control and cancer registry studies
   - Page 90, lines 24-25 – Text says “exposure to SVF was associated with a nonsignificant increase in the risk of lung cancer…”. The OR was 1.03. It is okay to report it, but it should not be labeled as an “increase.”
   - Page 93, line 15-25 - The Rodelsperger data needs to be presented in greater detail. Unlike other studies it included detailed lifetime job histories from all participants assessed by experts. The odds ratios from this study need to be presented before and after adjusting for asbestos exposure, including dose-response trends. Add relative risks for cumulative exposure to the relevant table. Suggested new text:

In a case-control incidence study, Rodelsperger *et al.* (2001) investigated mesotheliomas among 137 German men recruited from clinics in Hamburg and compared their occupations, 125 of which were determined by interview, with those of 125 age-, sex-, year of birth- and residence-matched controls randomly selected from population registries and also interviewed using a structured questionnaire. [Note that the response rate among controls was only 63%.] Cases of mesothelioma were confirmed by a panel of pathologists. Detailed self-reported job histories were used to categorize workers according to potential exposure to SVF (not otherwise classified) and asbestos, and to estimate quantitative average levels of fiber exposure according to three levels of exposure, and cumulative exposure. Conditional logistic regression was used to calculate odds ratios separately for job categories and industries. The risk of mesothelioma among SVF-exposed cases was OR = 6.12, 95% CI = 2.90 to 12.83, 55 cases), 85 cases, for men ever-exposed to SVF, and OR = 3.08 (95% CI = 1.17 to 8.07, 55 cases) after adjusting for asbestos exposure. There were 2 cases of mesothelioma that were not exposed to asbestos.

6. Section 3.4 Other reviews
   - Page 102, cite review by Steenland and Stayner, 1997.
7. Section 3.5.1 Summary by tumor site - Lung cancer and mesothelioma
   - Page 104, line 25 to page 105, line 2 – Expand the discussion of the findings of the meta-analysis by Berrigan (2002). Suggested new text:

     Berrigan (2002) conducted a meta-analysis of SMRs for respiratory cancers in 10 case-control and 10 cohort mortality studies of SVF exposure, including a combined analysis of five cohorts exposed to glass wool, i.e., Boffetta *et al.* (1997), 140 deaths; Enterline and Henderson (1975), 5 deaths; Marsh *et al.* (2001a), 243 deaths; Morgan *et al.* (1981), 39 deaths; Shannon *et al.* (1987), 19 deaths, representing a total of 446 observed deaths from respiratory cancers (370.1 expected). Aggregate estimates of risk were calculated using standard methods for fixed effects; individual SMRs were weighted by the inverse of the variance estimate. National rates were used to calculate expected SMRs, with the exception of the data from Marsh *et al.* (2001a). The authors noted that the use of local rates tended to yield lower SMR estimates than national rates in seven of the cohort studies included in the meta-analysis. The case-control studies of glass wool-exposed workers included Enterline *et al.* (1987), Engholm *et al.* (1987), Gardner *et al.* (1988); Chiazze *et al*. (1992, 1993, 1997); Bruske-Hohlfeld *et al.* (2000), and Marsh *et al.* (2001a). Aggregate estimates of risk were not calculated for case-control studies due to heterogeneity of results and the use of different exposure levels. The combined SMR for all five cohorts was 1.23 (95% CI = 1.10 to 1.38), compared with SMRs of 1.08 (0.93 to 1.26) for glass filament and 1.32 (1.15 to 1.52) for rock wool.
8. Create a new subsection for mesotheliomas
   - Mesothelioma is strongly linked to asbestos, and extremely rare without asbestos exposure. Unlike lung cancer, there is just one major established cause. The largest study in the U.S. showed that 88% of pleural mesothelioma in adult men was attributable to asbestos (Spirtas *et al.* 1994). The consequence of this is that the "expected" numbers from the general population are largely due to asbestos exposure and cannot be used as a comparison to observed mesotheliomas among glass wool workers not exposed to asbestos. Therefore the SMR for glass wool workers not known to be exposed to asbestos is underestimated.
   - A second concern with evaluating mesothelioma is that while there is a need to assess the medical evidence that deaths labeled on death certificates as being due to

mesothelioma actually had mesothelioma, there is also a parallel need to review deaths from other causes as well. Selikoff *et al.* 1992 reviewed medical records for all deaths in the U.S. insulator cohort, and the overall effect was to increase the numbers of mesothelioma identified in the study. In the Marsh *et al*. cohort study, medical evidence was obtained only for deaths classified on death certificates as due to mesothelioma, with a reduction in the number of known cases.

- A table should be prepared giving results from all studies reporting data concerning mesothelioma. This might include the number in the cohort, the number of mesotheliomas observed in the cohort if any, the number of cases of mesothelioma who had asbestos exposure, the number who had possible asbestos exposure, and the number not known to have been exposed to asbestos. For case-control studies it would give the number of cases, the number exposed to glass wool, and the numbers of these also having asbestos exposure. A comment column could give other information such as accuracy of diagnosis. (See table on pages 8-9 of these comments).

9. Section 3.6 [Methodological Issues]
   - Mention that average concentrations of respirable glass wool fibers are 10 or more times lower than exposure to asbestos in the cohorts studied (e.g., Armstrong *et al.* 1988, Levin *et al*. 1998, Newhouse and Berry, 1985.)
10. Section 3.6.6 [Methodological Issues] – Potentially confounding exposures
    - Page 111, lines 16-21 – Some comment should be made regarding the possibility of actual confounding from these substances. Some are not even clear lung carcinogens, e.g., formaldehyde. For the most likely confounding substance, i.e., asbestos, there was no evidence of confounding in the U.S. cohort. In the absence of clear evidence of confounding the conclusion should be that it probably does not occur.

Mesotheliomas among glass wool-exposed populations.

Reference Geographical location	Study design, Population,	Exposure	Effects	Comments
Marsh *et al.* 2001a, 2001b U.S.	Retrospective cohort mortality study of manufacturing workers in 8 glass wool (GW) or glass wool + glass filament (F) plants 32,100 male + female workers GW: 91,931 person-years of follow-up GW + F: 220,694 person-years of follow-up	Respirable fibers: Average: 0.018 – 0.167 f/cm^3 Cumulative: 0.892 – 6.382 f/cm^3-mo 4 plants also made specialty (< 1.5 µm) fibers	10 "possible" deaths from malignant mesothelioma 7 in GW or GW + F plants 3 mostly exposed to mostly GW; all male; no pathology reports 4 exposed to GW + F; pathology report available; pathology or medical reports on 3 cases found that 1 case was unlikely to be a mesothelioma and 2 cases was "50%" likely to be mesothelioma 1 case in filament-only plant; pathology available for 1 case, unlikely to be a mesothelioma 2 cases in rock wool plants; pathology report available for 1 case found it was unlikely to be a mesothelioma	Asbestos exposure was considered probable for 2 GW + F workers (0.38 years and 2.46 years of exposure; otherwise not quantified) and for 1 rock wool-exposed worker (2.18 fibers/cm^3-mo.) Using a broad definition of possible malignant mesothelioma deaths (164 GW or GW + F deaths) SMR = 0.89 (95% CI = 0.76 – 1.04, county comparison); using malignant + benign codes for later period yielded similar results. Note: Only 1 possible case of pleural mesothelioma observed (rock wool worker); ruled out on pathology report
Boffetta *et al.* 1997 U.K., Norway, Finland, Sweden, Italy	Retrospective cohort mortality study 6936 male and female GW workers > 1 year of employment 167,675 person-years of follow-up	Previous study of exposures in these plants conducted (Cherrie *et al.* 1986). Range of mean respirable fiber concentrations: 0.01 - 1.00 fibers/cm^3 (similar to U.S. plants). Highest concentrations in superfine fiber processes.	1 death from mesothelioma in GW cohort (U.K. factory) (plus 4 cases observed among rock wool-exposed workers)	Possible small-scale asbestos exposure due to use of asbestos yarn or cloth noted in 2 of the GW plants (Finland and U.K), but not otherwise noted.

Reference Geographical location	Study design, Population,	Exposure	Effects	Comments
Boffetta *et al.* 1999 Norway, Sweden, Finland	Retrospective cohort incidence study 2611 male and female manufacturing workers 68,523 person-years of follow-up	See Boffetta *et al.*. 1997	No cases of mesothelioma observed	
Engholm *et al.* 1987 Sweden	Registry-based incidence cohort; nested case-control study Male construction workers (inc. wood workers, insulators, metal workers, plumbers, etc.) 23 cases of pleural mesothelioma diagnosed after 1st health check; 5 controls per case	Job histories obtained by self-reported questionnaire; SVF and asbestos potential for exposure assigned by industrial hygienists to one of 6 levels (0 = 0; 1-5 low to high; 6 = unknown)	Unadjusted RRs for pleural mesothelioma and asbestos exposure: Level, RR, (cases) 0: 1.0 (12) 1: 0.82 (5) 2: 16.3 (3) 3: 2.2 (2) 5: no cases Unknown: 0.49 (1) Analysis by SVF exposure not performed.	21 cases of pleural mesothelioma were among subjects self-reporting no asbestos exposure but were considered to have potential for asbestos exposure by job type.
Rodelsperger *et al.* 2001 Hamburg, Germany	Hospital-based case-control study 125 male cases 125 male controls	Job histories obtained by questionnaire; SVF and asbestos cumulative exposure assigned by industrial hygienists Range 0 - >1.5 fiber-years (geometric mean x5) for SVF; Range 0 - >15.0 fiber-years for asbestos	ORs: SVF no asbestos = 15.1 (1.05-218.0) 2 cases SVF + asbestos = 61.3 (12.9-292.0) 53 cases Asbestos no SVF = 19.8 (4.7-83.0) 61 cases OR for SVF adjusted for asbestos: Ever vs. never: 3.08 (1.17-8.07; p <0.05 two-sided) 55 cases Cum. exp. to SVF vs. non-exposed ranged from 0.78 to 5.43, all n.s. ORs for asbestos (unadj.) cum. exp. ranged from 7.9 to 45.4	Considerable overlap of periods when estimated exposure to both SVF and asbestos occurred. Cumulative exposure to SVF approx. one tenth levels for asbestos. Residual confounding by asbestos possible for observed association between SVF and mesothelioma.

See NTP background document for the complete citation.

Section 4. Studies of Cancer in Experimental Animals

1. Introduction
   - Page 117, lines 4-7 – Add Ellouk-Achard and Jaurand, 1994 to the list of review references in this paragraph.
2. Section 4.1 Inhalation Studies
   - Page 119, line 7 – There are some conflicting data on the biopersistence of long vs. short fibers. Add: "Nevertheless, as long fibers may be broken into short fibers, short fibers biopersistence may be greater than for longer fibers."
   - Page 142, Table 4-8 - footnote the study duration.
   - Pages 150-154, Table 4-9 - Lambre *et al.* 1998 (pg 147-148) bracket in text discussion that [the fiber dose number is less than recommended for highly soluble fibers (Grimm *et al*. 2002)].
3. Section 4.1.1 Inhalation Studies - Early studies in rodents
   - Page 119, line 20 (Scherpers and Delahant 1955) – "[No controls were mentioned.]" should be bracketed.
   - Page 120, line 11 (Gross *et al*. 1970) – after "Control groups included 20 rats and 20 hamsters": add "[No positive controls were tested.]"
   - Page 120, line 18 (Gross *et al*. 1970) – Add: "No tumors were found in hamsters exposed to asbestos. There was no group of rats exposed to asbestos. Pneumonia and the endemic presence of chronic bronchitis and its sequelae were observed in rats. Some hamsters died of pneumonia [number not provided]."
   - Page 121, lines 3-4 – Change sentence to read: "…but there was no evidence of treatment-related neoplastic lesions in the respiratory tract."
   - Page 122 -124, Table 4-3 – The F344 study by Mitchell and Moorman (1986 and 1988) should be included in the table. Add these results (space down in table and add the F344 study and include information for mononuclear cell leukemia in the comments section of that row).
4. Section 4.1.2 Inhalation Studies - Later studies in rodents: Rat
   - Page 127, lines 19-20 (Davis *et al*. 1996) – Replace the sentence beginning with "Glass fibers produced less…", with: "Glass fibers produced less inflammation and very little fibrosis. Animals exposed to JM100/475 developed lung tumors (11%, adenomas). Exposure to 104E resulted in 23% total lung tumors including 7 lung carcinomas and 2 mesotheliomas. One lung adenoma and one lung carcinoma were found in controls (5.3%) (Table 4-4)."
   - Page 127, line 27 – Delete the sentence after "*P* values not reported."
   - Page 127, line 27 (Cullen *et al*. 2000) – Add "The number of fibers, 15-20 µm and >20 µm of length present in the lung after 12 months of exposure was lower in the 100/475 group than in the 104E group, respectively 11 x 10^6/lung and 83 x 10^6/lung".
   - Page 127, line 29 – Delete "also" from "The author also noted…"
   - Page, 129, Replace Table 4-4 with the revised table (see below), which includes additional statistical analyses.
5. Section 4.1.2 Inhalation Studies - Later studies in rodents: Hamsters [ref. McConnell *et al.* 1999]

- Page 128, lines 10-11 – Replace the sentence "MMVF10a was essentially the same as the MMVF10 used in previous studies but had a lower fluorine content due to production changes." to: "MMVF10a was a mixture of two types of 901 fiberglass; one of the 901 glasses contained fluorine and was the same as the one used in previous studies and the other did not contain fluorine."
- Page 128, lines 17-20 – Add sentence: "Nevertheless average diameter of MMVF10a and MMVF33 was 1.5 times greater than that of amosite. Moreover, asbestos fibers form bundles of fibrils that may defibrillate in the lung while glass fibers do not [Increased fiber burden after recovery may be accounted for by this process]".
- Page 130, lines 12-13 – The sentence should be completed: "Fiber burdens… group than in any of the amosite-exposed groups, but were higher than with MMVF10a. [This may be linked to a higher fiber deposition.] A six-hour deposition study showed a greater deposition of MMVF33 compared to MMVF10a". [Differences between MMVF33 compared to MMVF10a (more severe inflammation, some mild fibrosis, one mesothelioma) may be related to the different deposition. Hyperplasia may reflect early signs of cell transformation]."
- Page 130, line 17 – Add between "…off." and "Incidence…" sentences, insert the following: "Lung fiber burden with MMVF33 was higher than with MMVF 10a."
- Page 130, line 17 – Add at the end of this paragraph: "Mesothelial hyperplasia was found in 21.7% of hamsters after exposure to MMVF33. The percentage was 1.2% in both control and MMVF10a groups."

6. Section 4.2 Intraperitoneal administration
   - Page 133 – Add revised Table 4-6 (see below) with statistical analyses to the document.
7. Section 4.3.2 Other exposure routes – Hamsters, guinea pigs, mice, and rabbits
   - Page 135, line 14 (Vorwald *et al.* 1951) – Add: "[This study did not include positive controls, the number of animals was limited, the fiber diameter was large and the delay post inoculation was limited to 12 months.]"
   - Page 135, line 19 (Gross *et al*. 1970) – Add: "[This study did not include positive controls and the number of animals was limited.]"
   - Page 136, lines 4-5 (Pott *et al*. 1984b) – Add "Mohr *et al*. 1984" to the Pott reference.
8. Section 4.4 Studies of fiber characteristics and tumorigenicity
   - Page 140, line 24 – 104/475, > 20 µm of length in Davis *et al.* (IOM) Add: [The parameters used to define durability in the Stanton *et al*. paper are not defined.]
   - Page 141, after line 28 – Add: "Stanton *et al*. (1981) concluded that the best fit for probability of tumor formation was found for fibers of less than 0.25 µm in diameter and more than 8µm in length. Another correlation was found for fibers with a diameter up to 1.5 µm of diameter and more than 4 µm of length. Experimental data from Stanton *et al*. publications were re-analyzed by other authors. Bertrand and Pezerat (1980) confirmed the dependence with fiber dimensions. Oehlert (1991) also confirmed the hypothesis that the logarithm of the number of fibers more than 8 µm of length and less 0.25 µm of diameter allowed to predict the tumor yield. Stanton *et al*. also underlined that some samples did not fit well, especially some asbestos samples. This point was studied by Wylie *et al*. (1987). These authors first confirmed that the number of fibers of the above given dimensions well reflect the differences in the carcinogenic potency and that the outliers were related to the mathematic calculations when samples contained a low number of fibers such dimensions."

- Page 146, lines 20, 24 and 30 – JM fiber is referred to as 475 in Pott *et al*. paper. "104" should be changed to "475".
- Page 146, line 28 – Calculated Z-score for B3 is 20.7 according to Table 1-4, in agreement with data in Pott *et al* paper. Then "15.7" should be changed into "20.7".
- Page 147, line 3 – Add "[It can be noted that the most carcinogenic B3 fibers were also the thinnest.]"
- Page 147, line 27 – Add reference to Table 1-4 on line 27 "…borosilicates (see Tables 1-4 and 4-9)."
- Page 148, line 13 – Change ">20 mm" to ">20 µm".
- Page 149, lines 10-11 – Change the sentence "Z-scores could be calculated for P (45.45) and V (26.36) fibers only". Z-scores are quoted on page 153, Table 4-9. The values correspond to data provided in Table 1.4. The sentence should be replaced with: "Calculated Z-scores for B, M, P and V fibers are 34.42, 30.04, 45.45 and 26.36, respectively."
- Page 149, lines 17-22 – Complete the sentence "[statistical test and level of significance not reported. However, according to Fisher's exact test, against saline controls, significant P values at the highest dose are found: 1.6×10^{-3}, 3.4×10^{-3}, and $< 10^{-4}$ for B, P, and V respectively. When all (saline and untreated controls) are associated, all doses (except the lowest for P glass) provide highly significant *P* values.]"
- Page 149, line 17 – Delete the end of this line following the bracketed comment and add: "However, calculations can be made (see Table 4-9) showing significant tumor incidence with fine diameter samples of B fibers. B glass produces 17% (9/53) tumor incidence when inoculated at the dose of 5×10^9 fibers. This incidence is significantly different from the saline controls (*P* = 0.0018, Fisher's exact test). Hence, fiber B cannot be considered as non-carcinogenic."
- Page 149, lines 20-22 – Delete the following two sentences to the end of the paragraph: "Also, they noted that no statistical difference…The authors speculated…"
- Page 151, Table 4-9 – Replace the Z-score (15.7) for B-3 fibers in Table 4-9 with 20.7 (From Table 1-4).

9. Section 4.5.2 Routes of exposure – Animal models
   - Page 160, line 14 – There is reference to Figure 4-4. Clarify in figure legend which points are related to SPF (IOM) and which ones to glass fibers (RCC).
   - Page 161, Figure 4-3 – Add a bracketed footnote to the figure legend stating that the data for 104/475, fibers > 20 µm of length from Davis *et al.* (IOM) do not appear in the figure. It should be an open triangle. In addition, the closed triangle at 38 fibers/ml more than 20 µm of length likely refers to 100/475 in Cullen *et al.* 2000, and should be an open triangle.
10. Section 4.7 Summary
   - Page 164, lines 22-23 – 'which the authors considered to be better designed" Replace this phrase with "designed to address limitations of earlier studies".
   - Page 164, line 28 – add after MMVF11: there was an apparent positive trend for MMVF10 (*P* = 0.047, one-tailed Cochrane-Armitage trend test)."
   - Page 166, Table 4-10 – The table title indicates this is a summary of carcinogenicity of glass wool in animals. Studies for the F344 rat are listed as negative in this table. Moorman and Mitchell papers concluded the MCL was a tumor effect of exposure to glass wool. Please add this information as a footnote: "Moorman and Mitchell papers

concluded the MCL was a tumor effect of exposure to glass wool." Please use the revised Table 4-10.

- Page 166, Table 4-10 – indicates the inhalation study in hamster (Hesterberg, 1997; McConnell, 1999) as negative. McConnell *et al*. reference discussed the single mesothelioma and many possible explanations/causes but stated that the most scientifically responsible position is that this neoplasm is treatment-related.

Table 4-4. Tumor incidences in male rats exposed to glass fibers and asbestos by inhalation

Test animal	Exposure group[a,d]		Lung fiber burden[b] × 10^5	Tumor incidence (%)				Reference(s)
	(mg/m^3)	WHO fibers/cm^3		Lung adenoma	Lung carcinoma	Total lung tumors	Mesothelioma	
F344	Controls	0	0	3/123 (2.4)	1/123 (0.8)	4/123 (3.3)	0/123 (0)	Hesterberg *et al.* 1993 McConnell 1994 Hesterberg *et al.* 1995
	Chrysotile (10)	10,600	28.1 ± 7.8	7/69 (10.1)	6/69 (8.7)[*] c	13/69 (18.9)*	1/69 (1.4)	
	Crocidolite (10)	1,600	NR	10/106 (9.4)	6/106 (5.7)[*] c	15/106 (14.2)*	1/106 (0.9)	
	MMVF10 (3)	29	0.24 ± 0.08	0/117 (0)	0/117 (0)	0/117 (0)	0/117 (0)	
	MMVF10 (16)	145	1.85 ± 0.53	1/118 (0.8)	0/118	1/118 (0.8)	0/118 (0)	
	MMVF10 (30)	232	2.88 ± 0.56	6/119 (5.0)	1/119 (0.8)	7/119 (5.9)	0/119 (0)	
	Trend[e]							
	one-sided *P*			[0.0414]	[0.4979]	[0.0467]	[No trend]	
	two-sided *P*			[0.0724]	[0.8784]	[0.0842]	[No trend]	
	MMVF11 (3)	41	0.48 ± 0.11	3/118 (2.5)	1/118 (0.9)	4/118 (3.4)	0/118 (0)	
	MMVF11 (16)	153	2.35 ± 0.63	6/120 (5.0)	3/120 (2.5)	9/120 (7.5)	0/120 (0)	
	MMVF11 (30)	246	5.03 ± 2.9	3/112 (2.7)	0/112	3/112 (2.7)	0/112 (0)	
	Trend[e]							
	one-sided *P*			[0.3233]	[0.4669]	[0.3749]	[No trend]	
	two-sided *P*			[0.6473]	[0.9118]	[0.7531]	[No trend]	
Wistar	Controls	0	0	1/38 (2.6)	1/38 (2.6)	2/38 (5.3)	0/38 (0)	Davis *et al.* 1996 Cullen *et al.* 2000
	Amosite (NR)	980	1,230 ± 180	9/42 (21)*[c]	7/42 (17)[*] c	16/42 (38)***	2/42 (4.8)	
	JM100/475 (NR)	1,100	110 ± 110	4/38 (11)	0/38 (0)	4/38 (11)	0/38 (0)	
	104E (NR)	1,000	830 ± 220	3/43 (7)	7/43 (16)[*] c	10/43 (23)*	2/43 (4.7)	

* $P < 0.05$ vs. controls; *** $P < 0.001$ vs. controls (Fisher's exact test).
NR = not reported; WHO fibers/cm^3 = the number of fibers ≥ 5 μm in length, < 3 μm in diameter, with an aspect ratio ≥3:1.
See NTP background document for the complete citations.
[a]Nose only exposure in studies with F344 rats, whole-body exposures with Wistar rats.
[b] Number of WHO fibers per mg dry lung at 24 months for F344 rats; total lung fiber burden > 20 μm at 12 months in Wistar rats.
[c][Statistics were not reported by the study authors; Fisher's exact test conducted by NTP.]
[d]WHO fibers in the F344 study were similar to total exposure mass of fibers in fibers/cm^3.
[e] [Cochran-Armitage test conducted by NTP; control group in first line of table included with all data sets.]

Table 4-6. Tumor incidences in rats treated with glass wool fibers by i.p. injection

Strain (Sex)	Treatment group	Dose		No. doses	Tumor incidence (%)[a]	Reference
		mg	% Fibers > 5 µm long			
Wistar (F)	Saline (1 mL) TiO_2 JM104/475	0 10 0.5 2.0	0 0 28%	1 1 1 1	2/32 (6) 0/32 (0) 5/30 (16.7)[*] 8/31 (25.8)[*]	Muhle *et al.* 1987. Pott *et al.* 1987
Wistar (F)	TiO_2 JM104/1974	5 5	0 NR	1 1	0/47 (0) 20/45 (44.4)[***]	Pott *et al.* 1987
Wistar (M) Wistar (F)	JM104/1974	10 10	NR NR	1 1	13/26 (50)[b] 18/33 (54.6)[b]	Pott *et al.* 1987
Osborne-Mendel (F)	Untreated Saline JM100	0 0.5 mL 25	0 0 56%	0 1 1	0/125 (0) 0/25 (0) 8/25 (32) [**]	Smith *et al.* 1987

* $P < 0.05$, compared with combined saline and TiO_2 control groups; χ^2-test reported by authors.
[*] $P < 0.05$, [**] $P < 0.01$; [compared with saline control by NTP, Fisher's exact test].
[***] $P < 0.001$; [compared with TiO_2 control by NTP, Fisher's exact test].
NR = not reported.
[a] Most tumors were abdominal sarcomas or mesotheliomas. Pott *et al.* (1987) also reported a few carcinomas.
[b] No concurrent controls reported by study authors.
See NTP background document for the complete citations.

Table 4-9. Tumor incidences in rats treated with glass wool fibers by i.p. injection

Strain (Sex)	Treatment group	Biopersistence, $T_{1/2}$, days (95% CI) *in vivo*	Z-score	Diam. (median) µm	Length (median) µm	Dose		No. doses	Tumor incidence (%)[a]	Reference
						mg	Fibers × 10^9 or % > 5 µm long				
Wistar (NR)	Saline (2 mL) Glass fiber	– NA	– NA	– 0.5 (avg.)	– 72.6% < 5	0 25	0 ~27%	4 4	0/80 (0) 23/40 (57.5)[***]	Pott *et al.* 1974
Wistar (F)	Saline (2 mL) German glass wool (S&S 106) Trend[e] one-sided *P* two-sided *P*	– NA	– NA	– NA	– NA	0 2 10 25	0 0.024 0.12 1.2	4 1 1 4	0/72 (0) 1/34 (3) 4/36 (11)[*] 23/32 (72)[***] [< 0.0001] [< 0.0001]	Pott *et al.* 1976a
	MN104 [JM104] Trend[e] one-sided *P* two-sided *P*	NA	NA	NA	NA	2 10 25	NR	1 1 2	20/73 (28)[***] 41/77 (53)[***] 55/77 (71)[***] [< 0.0001] [< 0.0001]	
	MN112 [JM112]	NA	NA	NA	NA	20	NR	1	14/37 (38)[***]	
Wistar (F)	JM100	NA	NA	0.33 0.24	2.4 1.4	2 2	NR	1 1	2/44 (5)[b] 2/44 (5)[b]	Pott *et al.* 1984a
	JM104	NA	NA	0.29 0.29 0.29 0.29 0.39	4.8 4.8 4.8 4.8 2.7	2 10 10 10 10	NR	1 1 1 1 1	14/44 (32)[b] 27/37 (73)[b] 29/44 (66)[b] 19/39 (49)[b] 4/45 (9)[b]	
Sprague-Dawley (F)	TiO_2 JM104/1974	– NA	– NA	– NA	– NA	5 5	0 NR	1 1	2/52 (3.8) 44/54 (81.5)[***]	Pott *et al.* 1987

Strain (Sex)	Treatment group	Biopersistence, $T_{1/2}$, days (95% CI) *in vivo*	Z-score	Diam. (median) µm	Length (median) µm	Dose		No. doses	Tumor incidence (%)[a]	Reference
						mg	Fibers × 10^9 or % > 5 µm long				
Sprague-Dawley (F)	Saline (2 mL)					0		2	3/54 (5.6)	Pott *et al.* 1987
	JM100/L&V					2		1	26/54 (48.1)[***]	
	JM100/Pen					2		1	21/54 (38.9)[***]	
	JM100/Pen					10		1	24/53 (45.3)[***]	
Wistar (F)	Saline (2 mL)	–	–	–	–	0	0	5	2/102 (2)	Pott *et al.* 1989
	JM104	NA	NA	0.15	2.6	1	0.68	5	34/53 (64)[***]	
Wistar (F)	Saline (2 mL)	–	–	–	–	0	0	5	2/50 (4)	Pott *et al.* 1991[c]
	B-1K	107	35.8	1.06	7.4	20	0.24	3	3/46 (7)	
	B-1K	(98–119)		1.06	7.4	50	0.60	3	1/32 (3)	
	B-1M			1.68	10.7	20	0.05	1	1/48 (2)	
	B-1M			1.68	10.7	20	0.16	3	1/46 (2)	
	B-1ML			1.19	11.0	50	0.51	2	1/39 (2)	
	B-1L			1.40	17.8	20	0.04	1	1/48 (2)	
	B-1L			1.40	17.8	20	0.11	3	5/46 (11)	
	B-2K	38	35.8	0.49	4.2	6.7	0.29	1	0/48 (0)	
	B-2K	(35–41)		0.49	4.2	20	0.86	1	0/46 (0)	
	B-2L			0.51	6.0	6.7	0.39	1	0/45 (0)	
	B-2L			0.51	6.0	20	1.16	1	2/44 (5)	
	B-2L			0.51	6.0	50	5.8	2	1/35 (3)	
	B-2L Trend[e]									
	one-sided *P*								[0.4381]	
	two-sided *P*								[0.9392]	
	B-3K	238	20.7	0.37	3.3	6.7	0.38	1	10/48 (21)[**]	
	B-3K	(183–340)		0.37	3.3	20	1.14	1	30/47 (64)[***]	
	B-3L			0.34	5.6	6.7	0.15	1	19/48 (40)[***]	
	B-3L			0.34	5.6	20	0.46	1	31/47 (66)[***]	
	JM104	NR	21.0	0.40	10.60	2	0.32	1	8/48 (17)[*]	
Wistar (F)	Saline (2 mL)	–	–	–	–	0	0	3	0/38 (0)	Roller *et al.* 1996, 1997
	MMVF11	199	27.1	0.77	14.6	35	0.4	2	12/40 (30)[***]	
		(172–235)				30	1.0	6	16/23 (70)[***]	

Strain (Sex)	Treatment group	Biopersistence, $T_{1/2}$, days (95% CI) *in vivo*	Z-score	Diam. (median) µm	Length (median) µm	Dose		No. doses	Tumor incidence (%)[a]	Reference
						mg	Fibers × 10^9 or % > 5 µm long				
	Saline (2 mL)	–	–	–	–	0	0	3	0/38 (0)	
	M 753	NA	24.8	0.22	~3.3	17	1	1	30/40 (75)[***]	
						50	2.9	1	36/40 (90)[***]	
Wistar (F)	Untreated	–	–	–	–	0	0	0	0/37 (0)	
	Saline (2 mL)	–	–	–	–	0	0	20	0/93 (0)	
	B-01-0.9	32 (26–45)	35.8	~0.7	9.60	25	2.5	5	3/39 (8)[*]	
						25	5.0	10	4/37 (11)[**]	
						25	10	20	3/36 (8)[*]	
	Trend[e]									
	one-sided *P*								[0.0189]	
	two-sided *P*								[0.0243]	
Wistar (M)	Saline (2 mL)	–	–	–	–	0	0	0	1/69 (1)	
	B-01-0.9	32 (26–45)	35.8	~0.7	9.60	25	10	20	10/48 (21)[***]	
						25	20	40	33/50 (66)[***]	
Wistar (F)	Saline (2 mL)	–	–	–	–	0	0	3	0/38 (0)	
	B-09-0.6	NA	26.7			50	2.0	2	1/40 (3)	
						50	6.1	6	4/39 (10)	
	Saline (2 mL)	–	–	–	–	0	0	3	0/38 (0)	
	B-09-2.0	NA	26.7	0.49	3.3	50	1.1	3	9/40 (23)[**]	
						50	3.2	9	21/40 (53)[***]	
Wistar (F)	Saline	–	–	–	–	0	0	0	0/102 (0)	Lambré *et al.* 1998
	Fiber A	129 (K_{dis})[d]	26.7	0.70	24.6	0.7	0.009	1	2/51 (4)	
						2.1	0.027	1	0/51 (0)	
						7.0	0.092	1	0/51 (0)	
						17.5	0.460	2	1/51 (2)	
	Trend[e]									
	one-sided *P*								[0.3108]	
	two-sided *P*								[0.7310]	

Strain (Sex)	Treatment group	Biopersistence, $T_{1/2}$, days (95% CI) *in vivo*	Z-score	Diam. (median) µm	Length (median) µm	Dose		No. doses	Tumor incidence (%)[a]	Reference
						mg	Fibers × 10^9 or % > 5 µm long				
	Saline	–	–	–	–	0	0	0	0/102 (0)	
	Fiber C	309 (K_{dis})	26.74	0.69	27.2	0.7	0.013	1	1/51 (2)	
						2.1	0.038	1	1/51 (2)	
						7.0	0.126	1	0/51 (0)	
						17.5	0.630	2	0/51 (0)	
	Trend[e]									
	one-sided *P*								[0.4614]	
	two-sided *P*								[0.7224]	
Wistar (M)	MMVF10	122.4 (K_{dis})	NA	NA	> 5	144	0.66	1	13/22 (59)[b]	Miller *et al.* 1999b
	JM100	9.1 (K_{dis})	22.9	NA	> 5	8.3	1.87	1	8/24 (33)[b]	
Wistar (M)	104E	NA	NA	NA	NA	12.6	~1	1	21/24 (88)[b]	Cullen *et al.* 2000
F344	Glass wool	NA	NA	NA	NA	10	NR	1	NR (0)[b]	Adachi *et al.* 2001
	Micro fiber glass	NA	NA	NA	NA	10			NR (0)[b]	

Strain (Sex)	Treatment group	Biopersistence, $T_{1/2}$, days (95% CI) *in vivo*	Z-score	Diam. (median) µm	Length (median) µm	Dose		No. doses	Tumor incidence (%)[a]	Reference
						mg	Fibers × 10^9 or % > 5 µm long			
Wistar (F)	Untreated	–	–	–	–	0	0	0	0/51 (0)	Grimm *et al.* 2002
	Saline (2.5 mL)	–	–	–	–	0	0	20	0/51 (0)	
	B glass	580 (K_{dis})	34.42	0.52	8.90	216	2	8	3/51 (2)	
						541	5	20	9/53 (17)[**]	
	M glass	103.7 (K_{dis})	30.04	0.41	7.70	41	0.5	2	0/50 (0)	
						164	2	8	0/51 (0)	
						410	5	20	0/52 (0)	
	M glass Trend[e]									
	one-sided *P*								[No trend]	
	two-sided *P*								[No trend]	
	P glass	610 (K_{dis})	45.45	0.40	9.60	51	0.5	2	0/51 (0)	
						205	2	8	4/51 (8)	
						512	5	20	8/52 (15)[**]	
	P glass Trend[e]									
	one-sided *P*								[0.0001]	
	two-sided *P*								[0.0001]	
	V glass	450 (K_{dis})	26.36	0.80	9.90	72	0.5	2	2/51 (4)	
						290	2	8	1/51 (2)	
						724	5	20	14/51 (27)[***]	
	V glass Trend[e]									
	one-sided *P*								[< 0.0001]	
	two-sided *P*								[< 0.0001]	

* P < 0.05 ** P < 0.01, *** P < 0.001; [compared with controls by NTP, Fisher's exact test].
NR = not reported. See NTP background document for the complete citations.

[a] Most tumors were abdominal mesotheliomas or carcinomas. Some studies (Pott *et al.* 1976a, 1984a, 1987, 1989, 1991) also reported a few carcinomas.

[b] No concurrent controls reported by study authors.
[c] B-1 and B-2 are experimental low-durability glass wool; B-3 is an experimental durable glass fiber. K, M, and L designate short, medium, and long fiber ranges, respectively.
[d] K_{dis} = dissolution coefficient *in vitro*, reported in units of ng/cm^2 per hour.
[e] Cochran-Armitage test conducted by NTP.

Table 4-10. Summary of carcinogenicity studies of glass wool fibers in experimental animals.

Fiber type/source	Exposure route					
	Species	Inhalation	Intraperitoneal	Intratracheal	Intrathoracic	Intrapleural
Insulation wool	Rat (not specified)			–		
	Wistar		+			
	Sprague-Dawley					–
	Osborne-Mendel				±	
	F344	±[a]	–			
	Syrian golden hamster	–		–		
	Guinea pigs			–		
	BALB/c mice					–
	Rabbits			–		
475 glass	Wistar	–	+	+		±
	Sprague-Dawley		+			+
	Osborne-Mendel		+	–		
	F344	+[a]	–			
	Syrian golden hamster	+[b]		±		
E glass	Wistar	+	+			
753 glass	Wistar		+			
Experimental fibers	Wistar		±			

– = negative studies; + = positive studies (considered as a treatment-related effect by study authors); ± = both positive and negative studies.
[a] The only positive study reported an increase in mononuclear cell leukemia.
[b] The only positive study reported that 1 of 83 hamsters developed a mesothelioma. Although this was not statistically significant, the authors considered it treatment-related.

Section 5. Other Relevant Data

1. Section 5.1 Respirability, deposition, clearance, and retention
   - Page 167, line 13 – change “filtered” to “deposited”” (Larger particles settle out of the air faster and are more readily deposited in the extrathoracic region.”)
   - Page 167, line 17 – insert “for aerodynamic diameters above 0.5 µm” after “(D_A)” (”Variations in fiber density, length, and diameter can be normalized using the equivalent aerodynamic diameter (D_A) for aerodynamic diameters above 0.5 µm.”)
   - Page 168, line 18 – insert “anatomic” after “general” (”There are three general anatomic regions of the respiratory tract where inhaled particles deposit.”)
   - Page 168, line 20 – insert “ciliated” before “bronchioles”, and (AI) after “interstitial” (”These are the extrathoracic region (mouth, nose, pharynx, and larynx), the tracheobronchial region (trachea, bronchi, and ciliated bronchioles), and the alveolar-interstitial (AI) region (respiratory bronchioles, alveolar ducts, alveoli, and pulmonary interstitium) (IARC 2002).”)
2. Section 5.1.1 Respirability, deposition, clearance, and retention - Deposition
   - Page 168, line 24 – change “alveoli” to “AI” (“Respirability determines the concentration of particles in the air reaching the AI, whereas, deposition is the actual dose deposited in the lung.”)
   - Page 168, line 26 – change “lower lung” to “AI region” ”In humans, 40% to 80% of fibers with D_A < 1 mm that are inhaled into the AI region are not deposited and are subsequently exhaled from the lung (Hesterberg and Hart 2001).”
   - Page 168, line 30 – change “an alveolus” to “AI region”, and “alveolar” to “airway” (”Distribution of fibers within an AI region is dependent on airway geometry and the composition and physical properties of alveolar fluid.”)
   - Page 169, lines 17 and 19 – change “filter” to “deposit” and change “lung” to “extrathoracic airways” (”Nasal turbinates in rodents are more complex than in humans and deposit fibers more efficiently; this, along with other differences in size and physiology, results in more and larger fibers depositing in human extrathoracic airways than in the rodent,”)
   - Page 169, lines 20 and 22 – insert “more” after “are” and insert “more” before “distal” (”The conducting airways in humans are more dichotomous and symmetrical resulting in greater impaction of fibers at branch points while in rodents they are monopodial and asymmetrical favoring a more uniform airflow resulting in more distal deposition of fibers,”)
   - Page 170, line 5 – change “approaching” to “less than” (“Further, alveolar deposition in rodents does not occur when DA is greater than 3.5 µm and the aspect ratio is greater than 10; whereas, considerable alveolar deposition occurs in humans with particles having aerodynamic diameters less than 5 µm.”)
3. Section 5.1.2 Respirability, deposition, clearance, and retention - Clearance
   - Page 170, line 10 – insert “anterior” before “nasal” (“Particles within the anterior nasal cavity may be cleared by nose-blowing or sneezing.”)
   - Page 170, lines 11 and 12 – change “airway” to “lung conductive airways” and insert “fibers,” before “cells” (”Ciliated epithelial cells line the lung conductive airways from the pharynx caudally to the terminal (respiratory) bronchioles and clear the airway by moving particles, fibers, cells, and fluids back to the pharynx where they can be swallowed or coughed out.”)

- Page 170, line 18 – change “airway” to “respiratory tract” (“Phagocytosis is the primary clearance mechanism in the alveolar region and is slower than clearance from other regions of the respiratory tract.”)
- Page 170, line 22 – insert “effective” before “phagocytosis” (“Fiber length is known to be an important factor for effective phagocytosis, and there are species differences in alveolar macrophage size and number.”)
- Page 170, line 30 – change “extinction” to “clearance” (“Tracking percent fiber retention in the lung over time (days following cessation of exposure) resulted in a bi-phasic clearance curve.”)

4. Section 5.1.3 Respirability, deposition, clearance, and retention - Retention
   - Page 172, line 21 – insert “effective” before “phagocytosis” (“Long fibers are resistant to effective phagocytosis but may be subject to dissolution or transverse breakage.”)
   - Page 172, line 25 – insert “amphibole” before “asbestos” (“If long fibers are resistant to transverse breakage or dissolution (*e.g.*, amphibole asbestos), they are retained.)”
   - Page 173, line 2 – change “dissolution” to “retention” (“Thus, the solubility of long fibers at neutral pH would be an important factor in retention of the fiber.”)
   - Page 173, line 3 – change “is” to “are” (“A limited number of studies are available regarding retention of fibers in humans; however, the average overall retention half-time for poorly soluble fibers has been reported to be hundreds of days.”)
   - Page 173, line 19 and 20 – insert “SVF” before “fibers” (“The authors concluded that either the synthetic fibers disappeared from the lung in less than 12 years, or the exposed workers did not inhale enough respirable SVF fibers to show a difference from controls; alternatively, fixative fluids might have altered some retained SVF fibers in the lung.”)
5. Section 5.2.2 Biodurability and biopersistence of glass fibers - Fiber dissolution
   - Page 175, line 9 – insert “*in vivo*” before “fiber” (“These authors concluded that the intracellular and the extracellular dissolution of the fibers differ, and that cell-culture systems were preferable to cell-free systems for assessing *in vivo* fiber durability and dissolution.”)
   - Add the following discussion of the *in vitro* studies on dissolution rates by Eastes and colleagues:

     The *in vivo* clearance of fibers > 20 µm in length from the lungs of F344 rats has been reported to result from the dissolution of the fibers in extracellular fluid at approximately the same rate as the dissolution rate (k_{dis}) measured in simulated lung fluid *in vitro*, a process that depends on the chemical composition of the fibers (Eastes and Hadley 1995, Eastes *et al.* 1995). The predicted dissolution rates were similar for inhalation studies of MMVF10 and MMVF11 glass fibers, MMVF21 rock wool, MMVF22 slag wool, and crocidolite asbestos (Eastes and Hadley 1995) and for intratracheal instillation studies of MMVF10 and MMVF11 glass fibers and three experimental glass fibers, X7779, X7753, and X7484, with k_{dis} values of 2, 100, and 600 ng/cm^2/h, respectively (Eastes *et al.* 1995). For fibers < 20 µm in length they proposed that physical removal occurred by a macrophage-mediated process that did not differ by fiber type. The authors also reported that computer simulations of fiber clearance based on these processes agreed well with *in vivo* measurements of fibers remaining in the lung up to a year after exposure.

The dependence of the *in vitro* dissolution rate constant (k_{dis}) of fibers on their chemical composition was the basis for a method of calculating those rate constants by Eastes *et al.* (2000a). The individual dissolution rates for the oxides were summed based on their weight percent multiplied by a coefficient (P_i) determined by fitting experimental data for k_{dis} measured *in vitro* for a set of 62 fiber types, which resulted in a correlation coefficient (R^2) of 0.96 for the calculated versus the measured values. The authors also calculated k_{dis} values for approximately 30 additional fiber types not used to determine the coefficients for the oxides and reported a reasonably good fit over a range of k_{dis} of 100,000, much larger than the range of approximately 100 for the k_{dis} values on which the coefficients were based. The same authors also estimated dissolution rates from *in vivo* biopersistence data obtained from published intratracheal instillation and short-term inhalation studies, as well as for an unpublished inhalation biopersistence study of 6 fiber types, and they reported good agreement with dissolution constants measured *in vitro* for the same fiber types (Eastes *et al.* 200b). The dissolution rates were estimated from the decrease in diameter of fibers > 20 µm retained in the lungs. The authors noted that the majority of datasets (19 of 31) for different fiber types had R^2 values above 70%, and the overall correlation between *in vivo* k_{dis} and k_{dis} measured *in vitro* for the same fibers was 0.727, which the authors considered to be in reasonably good agreement.

6. Section 5.3 Studies of fiber characteristics and tumorigenicity
   - Page 178, line 18 - The major problem is the inclusion, in Chapter 5, of Section 5.3 entitled: “Studies of fiber characteristics and tumorigenicity.” Chapter 4 had Section 4.4 with exactly the same title. Why does Chapter 5 need another version of the same literature review (albeit with somewhat different tabulations of the same studies and a similar, but different, interpretive discussion). At least in Chapter 4, the subsection on “Studies of fiber characteristics and tumorigenicity” was followed by subsection 4.5 entitled “Routes of Exposure,” which placed the IP studies in a reasonable perspective with the more relevant chronic inhalation exposures. By contrast, Section 5.3 gives only a description of the IP studies of Pott and his coworkers. While this body of work has had virtually uncritical acceptance as being highly relevant to fiber tumorigenicity in Germany and elsewhere in Europe, it is viewed much more skeptically elsewhere. The section should be reorganized as follows:
     a Section 5.3.1 (Page 178) should have a description of the chronic inhalation studies (comparing fiber characteristics to tumorigenicity). In addition to the studies reported on page 205 to 206, the section should also include the following text to discuss the findings from studies discussed in Section 4 that were not discussed in section 5.3 (Cullen *et al.* 2000, Davies *et al.* 1996, and McConnell *et al.* 1999. These studies have important messages concerning the roles of fiber length, diameter, and biopersistence of asbestos and other mineral fibers on carcinogenesis that are highly relevant to glass fibers and other SVFs. Table 5-2 should be expanded to include other SVF fibers (RCF1a, a refractory fiber, X607, a hybrid SVF, MMVF22, a slag wool fiber, and MMVF34, a stone wool fiber).

     Chronic inhalation studies on glass wool fibers (microfibers and insulation glass wool fibers) were described in detail in Section 4. Several of these studies also evaluated fiber characteristics (such as fiber length, *in vitro* dissolution, and biopersistence and tumorigenicity (see Section 5.3.4 for modeling studies).

     Cullen *et al.* 2001 and Davis *et al.* 1996 reported results of a chronic inhalation study with an E-glass microfiber (104E) and another microfiber type (JM100/475). The 104E fibers caused increased incidences of lung carcinoma and adenoma combined compared with controls, but the JM100/475 fibers did not (see Section 4.1.2 and

Table 4-4). The authors reported that long fibers (15–20 µm and > 20 µm) of JM100/475 sample persisted longer than those from 104E. However, fiber analyses after 12-months exposure and 12-months recovery period showed a decrease in Ba, Ca, K in JM100/475. These elements were not present in native 104E fibers. The authors suggested that the different pathogenicity between the two fiber types was partly due to differences in numbers of long fibers and to differences in surface properties, possibly due to dissolution of 100/475 fibers. The authors also noted that the latency period for mesotheliomas was shorter with 104E fibers than with amosite asbestos fibers tested in this study.

In an inhalation carcinogenicity study conducted in male Syrian golden hamsters, McConnell *et al.* (1999) presented data for MMVF10a, MMVF33 (special-purpose glass fibers prepared by mixing three types of commercially manufactured 475 glass [codes 104, 108B, and 110]), and amosite asbestos. The aerosol dimensions and lung doses of the asbestos (0.6 µm diameter) and the test fibers (MMVF10a and MMVF33) (0.9 µm diameter) were comparable (Hesterberg and Hart 2001). No lung tumors were observed in any group, but incidences of mesotheliomas were increased in positive controls (amosite asbestos; 22/85 for mid-dose and 17/87 for high-dose) compared with 1 of 83 in the MMVF33 group (see Section 4.1.2 and Table 4-5). McConnell *et al.* concluded that the severity of the lung and pleural lesions in their study increased as the cumulative fiber burden (particularly fibers > 20 µm in length) increased in the lung, thoracic wall, and diaphragm, and the severity of the lesions was inversely related to the *in vitro* dissolution rates (ng/cm^2/h: MMVF10 259, MMVF33 12, amosite 0.2) for the fibers, which they considered to determine the cumulative fiber burden.

b Section 5.3.2 (Page 203) should review the intrathoracic and intraperitoneal studies with the focus being on what they add to the inhalation studies.

c Section 5.3.4 (Page 207) should be a discussion of the modeling studies. The following description of Miller *et al*. 1999b and Eastes and Hadley 1996 should be added to this section:

Miller *et al.* (1999a) examined the influence of fiber characteristics on tumor development in rat lungs for inhalation studies with the same set of 9 fiber types that they reported on for intraperitoneal studies (Miller *et al.* 1999a). The factors of fiber dimensions, persistence in the lung, dissolution *in vitro*, and cell toxicity *in vitro* were assessed. In the inhalation studies, the determining factors were the number of long, thin fibers (< 1 µm in diameter and > 20 µm long) and the dissolution rate adjusted for mass lost per unit initial mass. Short-term cell toxicity tests *in vitro* were not significantly related to cancer risks in any model tested. The authors noted that the effect of dissolution rate rather than biopersistence in the lung was contrary to expectations, but they suggested that larger measurement error for *in vivo* biopersistence compared with *in vitro* dissolution might be responsible. The authors noted that overall the results for modeling of inhalation studies were “broadly consistent” with the studies for intraperitoneal injection of the same fibers.

A model designed to predict the development of fibrosis or tumors after inhalation or intraperitoneal injection of fibers was developed based on the hypothesis that the effect of a rapidly dissolving fiber (> 20 µm in length) is equivalent to a smaller dose of a durable fiber (Eastes and Hadley 1996). As discussed in Section 5.2 fibers > 20 µm in length have been proposed to be cleared by dissolution in extracellular fluid, and Eastes and Hadley considered the dose of a fiber that dissolves in 1 year to have the same effect as half that dose for a fiber that dissolves in 2 years or more,

which the authors considered the approximate lifespan for the rat. The authors noted that their model did not rely on adjustable parameters, but only on the dissolution rate constant (k_{dis}), which could be measured *in vitro* and used to estimate the lifetime for the fibers. An adjustment factor (α) was calculated as the ratio of the time the fiber would remain in the lung compared with the lifetime of the animal and introduced into the dose-response relation. The predictions of the model were compared with *in vivo* results obtained by the Research and Consulting Company in Geneva, Switzerland for 7 fiber types, i.e., crocidolite asbestos, chrysotile asbestos, kaolin refractory ceramic fibers, MMVF10 and MMVF11 glass wools, MMVF21 rock wool, and MMVF22 slag wool, with endpoints of fibrosis and lung cancer after inhalation, and mesothelioma after intraperitoneal injection. The k_{dis} values for these 7 fiber types ranged from 0.1 ng/cm^2/h for crocidolite to 400 ng/cm^2/h for MMVF22 slag wool. The authors noted that the predicted response depended only on the dissolution rate of the fibers, and not on the fiber family, but they felt the model was limited in its ability to predict results for different durable fibers, which might differ in their tumorigenicity despite being similarly durable. When the predictions of the model with adjustments for dose were compared with the observed incidences of fibrosis or tumors, the values of χ^2 and their associated *P* values were, respectively, 109 and 0.62 for fibrosis by inhalation, 17 and 0.16 for lung tumors by inhalation, and 35 and 0.051 for mesothelioma by i.p. injection. The authors considered a *P* value greater than about 0.05 to be good evidence that the model predicted the observed values to within the error involved in the experimental data.

7. Section 5.3.1 Studies of fiber characteristics and tumorigenicity: Intrathoracic and intraperitoneal studies
   - Pages 178 to 180 – Suggested comment to add: “Stanton *et al.* (1981) concluded that the best fit for probability of tumor formation was found for fibers of less than 0.25 µm in diameter and more than 8 µm in length. Another rather good correlation was found for fibers with a diameter up to 1.5 µm of diameter and more than 4 µm of length. Experimental data from Stanton *et al.* publications were re-analyzed by other authors. Bertrand and Pezerat (1980) confirmed the dependence with fiber dimensions. Oehlert (1991) also confirmed the hypothesis that the logarithm of the number of fibers more than 8 µm of length and less 0.25 µm of diameter was consistent with the prediction of tumor yield. Stanton *et al.* also underlined that some samples did not fit well, especially some asbestos samples. This point was studied by Wylie *et al.* 1987. These authors first confirmed that the number of fibers of the above given dimensions well reflect the differences in the carcinogenic potency. The reanalysis dealt with the presence or absence of index particles. Add additional discussions of these papers
   - Page 179, line 19 – insert “testing fibers by implantation” and change “tested fibers by” to “relied on” (“After the studies <u>testing fibers by implantation</u> by Stanton and co-workers, most investigators have <u>relied on</u> intraperitoneal injection.”)
   - Page 201, Table 5-1H – Dissolution rates appear to differ between different experiments [Hesterberg and Hart 2001 noted an *in vitro* dissolution rate of MMVF10 of about 300 ng/cm^2/h (SiO_2) (Table 5-2 on page 206) while it was 122.4 on Table 5-1H (Page 201) [Miller *et al.* 199b]. These are the values as reported by 2 different sets of researchers. Hesterberg and Hart 2001 noted in a footnote to the table reporting the K_{dis} value for MMVF10 that “K_{dis} values may differ from those published elsewhere due to varying methodologies.”
8. Section 5.6 Mechanisms of fiber carcinogenicity

- Page 239. There needs to be some discussion of epigenetic mechanisms. Christensen *et al.* (2008, 2009) are suggested as papers to consider for this discussion. A summary of these papers is provided.

  Malignant pleural mesothelioma is highly associated with asbestos exposure, which occurs in 70% to 80% of cases of this type of mesothelioma (Christensen *et al.* 2008, 2009). Christensen *et al.* (2008) noted that asbestos is a nonmutagenic carcinogen, and they focused their investigations on the epigenetic mechanism of gene silencing through hypermethylation of cytosines in CpG islands in tumor-suppressor genes. Using a biochemical pathway-based approach, they examined promoter hypermethylation of an array of genes involved in cell-cycle control. One or more of these genes were methylated in 60% of a set of 70 cases of pleural mesothelioma. In a larger study of 158 pleural mesotheliomas and 18 non-tumorigenic parietal pleura samples, the methylation patterns of 1,505 CpG loci associated with 803 cancer-related genes were determined (Christensen *et al.* 2009). The number of asbestos bodies, which reflects the exposure to asbestos, was significantly ($P < 0.03$) associated with the pattern of methylation, and there was a clear distinction between the methylation patterns for malignant versus normal pleura ($P < 0.0001$). The lung burden of asbestos bodies also was found to be significantly ($P < 0.02$) associated with methylation of any of the 6 cell-cycle genes in the earlier paper by Christensen *et al.* (2008). A significant ($P < 0.05$) trend between increasing asbestos body count and increasing number of methylated cell-cycle pathway genes remained after controlling for age, gender, and tumor histology, consistent with the hypothesis that asbestos body burden contributes to epigenetic dysregulation of cell-cycle genes. Gender was associated with asbestos body count, with significantly ($P < 0.001$, more than 5-fold) higher asbestos body count in males compared with females. The authors of these papers suggested that methylation could represent a novel tumorigenic mechanism of action for asbestos as an epigenetic cause for malignant mesothelioma. That is, mesotheliomas are driven by both genetic and epigenetic alterations (Tsou *et al*. 2007).

9. Section 5.6.2 Mechanisms of fiber carcinogenicity - Chronic inflammation
   - Add a discussion of Poland *et al.* 2008
   - Poland *et al.* (2008) reported that concerns over the potential pathogenicity of carbon nanotubes had been raised because their needle-like fiber shape was similar to asbestos. Therefore, the pathogenicity of multiwalled carbon nanotubes was compared to long-fiber and short-fiber amosite asbestos (used as positive and negative controls, respectively). Four samples of carbon nanotubes were prepared. Two of the samples contained a substantial proportion of straight fibers than were longer than 20 µm while the other two samples consisted of nanotubes that were arranged in low-aspect-ratio tangled aggregates. Each material was injected i.p. into mice (50 µg), and the peritoneal cavity was washed out after 24 h or 7 days post exposure with physiological saline. The authors reported that carbon nanotubes produced an asbestos-like, length dependent, pathogenic response, which included inflammation and formation of granulomas. Polymorphonuclear leukocytes, protein exudation, and granulomas were observed only in samples that contained long fibers.
   - Add a discussion of Dostert *et al.* 2008

     Interleukin-1 beta (IL-1ß) is a cytokine released from activated macrophages and, like TNF-alpha, is a mediator of inflammation, cell proliferation/differentiation and apoptosis. It is involved in recruitment of inflammatory cells and has been shown, along with TNF-alpha, to regulate mesothelial cell proliferation (Wang *et al.* 2004).

Dostert *et al.* (2008) has studied the proinflammatory response of macrophages to asbestos and silica particles. Using a macrophage-like cell line, THP1, mature IL-1ß was released after 6-h exposure to asbestos or silica particles, but not to cigarette smoke or diesel exhaust particles. Further experiments demonstrated that reactive oxygen species (ROS) generated upon actin-mediated phagocytosis activated the Nalp3 inflammasome within the macrophage. Caspase-1 within this multiprotein complex then cleaved pro-IL-1ß releasing mature IL-1ß. Inhibitors of NADPH oxidase decreased IL-1ß production, providing evidence in support of activation of ROS through generation of NADPH oxidase. Using a mouse model, the role of Nalp3 inflammasome in asbestos-induced inflammation was further investigated. Nalp3$^{-/-}$ and Nalp3$^{+/+}$ mice were exposed for 9 days to chrysotile asbestos and markers of inflammation were analyzed. Lymphocytes, eosinophil, and neutrophil infiltrations were decreased in the lungs of Nalp3$^{-/-}$ mice, as were the levels of IL-1ß and KC, a neutrophil chemokine. These data support the role of the Nalp3 inflammasome in particulate-induced pulmonary inflammation.

1. Section 5.7.1 Summary – Deposition, clearance, and retention
   - Page 250, Section 5.7.1, 1st paragraph, revise the second sentence to "Fibers that are inhalable but non-respirable … can cause adverse effects, but the effects of these fibers are beyond the scope of this review.
   - 2nd paragraph, 2nd and 3rd sentence modify as follows: Short fibers are readily … through the mucociliary escalator, and can be cleared by lymphatics. Long fibers are not effectively cleared by phagocytosis and can effectively kill the phagocyte, but depending on the fiber type, may be subject to dissolution and transverse breakage.
2. Section 5.7.2 Summary – Biodurability and biopersistence of glass fibers
   - Page 251, Section 5.7.2, add new sentence before the last sentence: The literature indicates that the special purpose fibers cited in this document tend to have greater biopersistence than the insulation glass wools.
3. Section 5.7.5 Summary – Mechanisms of fiber carcinogenicity
   - Page 253, Section 5.7.5, 2nd paragraph, 9th line, add new sentence after … chronic inflammation: Fibers may also induce epigenetic changes.
   - Delete "frustrated macrophages" from line 13 of the second paragraph.

Report Approved: _____ _____
Karl Kelsey, M.D., M.O.H., Chair Date

References[1]

1. Armstrong BK, de Klerk NH, Musk AW, Hobbs MS. 1988. Mortality in miners and millers of crocidolite in Western Australia. *Br J Ind Med* 45(1): 5-13.
2. Bertrand R, Pezerat H. 1980. Fibrous glass: carcinogenicity and dimensional characteristics. *IARC Sci Publ*(30): 901-11.
3. Christensen BC, Godleski JJ, Marsit CJ, Houseman EA, Lopez-Fagundo CY, Longacker JL*, et al.* 2008. Asbestos exposure predicts cell cycle control gene promoter methylation in pleural mesothelioma. *Carcinogenesis* 29(8): 1555-9.
4. Christensen BC, Houseman EA, Godleski JJ, Marsit CJ, Longacker JL, Roelofs CR*, et al.* 2009. Epigenetic profiles distinguish pleural mesothelioma from normal pleura and predict lung asbestos burden and clinical outcome. *Cancer Res* 69(1): 227-34.
5. Coussens LM, Werb Z. 2001. Inflammatory cells and cancer: think different! *J Exp Med* 193(6): F23-6.
6. Coussens LM, Werb Z. 2002. Inflammation and cancer. *Nature* 420(6917): 860-7.
7. Dostert C, Petrilli V, Van Bruggen R, Steele C, Mossman BT, Tschopp J. 2008. Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica. *Science* 320(5876): 674-7.
8. Eastes W, Hadley JG. 1995. Dissolution of fibers inhaled by rats. *Inhal Toxicol* 7: 179-196.
9. Eastes W, Morris KJ, Morgan A, Launder KA, Collier CG, Davis JA, Mattson SM, Hadley JG. 1995. Dissolution of glass fibers in the rat lung following intrtracheal instillation. *Inhal Toxicol* 7: 197-213.
10. Eastes W, Hadley JG. 1996. A mathematical model of fiber carcinogenicity and fibrosis in inhalation and intraperitoneal experiments in rats. *Inhalation Toxicology* 8(4): 323-343.
11. Eastes W, Potter RM, Hadley JG. 2000a. Estimation of dissolution rate from in vivo studies of synthetic vitreous fibers. *Inhal Toxicol* 12(11): 1037-54.
12. Eastes W, Potter RM, Hadley JG. 2000b. Estimating in vitro glass fiber dissolution rate from composition. *Inhal Toxicol* 12(4): 269-80.
13. Levin JL, McLarty JW, Hurst GA, Smith AN, Frank AL. 1998. Tyler asbestos workers: mortality experience in a cohort exposed to amosite. *Occupational And Environmental Medicine* 55(3): 155-160.
14. Mohr U, Pott F, Vonnahme FJ. 1984. Morphological aspects of mesotheliomas after intratracheal instillations of fibrous dusts in Syrian golden hamsters. *Exp Pathol* 26(3): 179-83.
15. Newhouse ML, Berry G. 1979. Patterns of mortality in asbestos factory workers in London. *Ann N Y Acad Sci* 330: 53-60.
16. Oehlert GW. 1991. A reanalysis of the Stanton et al. pleural sarcoma data. *Environ Res* 54(2): 194-205.
17. Poland CA, Duffin R, Kinloch I, Maynard A, Wallace WA, Seaton A*, et al.* 2008. Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study. *Nat Nanotechnol* 3(7): 423-8.

[1] New references identified by the expert panel

18. Selikoff IJ, Seidman H. 1992. Use of death certificates in epidemiological studies, including occupational hazards: variations in discordance of different asbestos-associated diseases on best evidence ascertainment. *Am J Ind Med* 22(4): 481-92.

19. Spirtas R, Heineman EF, Bernstein L, Beebe GW, Keehn RJ, Stark A, Harlow BL, Benichou J. 1994. Malignant mesothelioma: attributable risk of asbestos exposure. *Occup Environ Med* 51(12): 804-11.

20. Steenland K, Stayner L. 1997. Silica, asbestos, man-made mineral fibers, and cancer. *Cancer Causes Control* 8(3): 491-503.

21. Tsou JA, Galler JS, Wali A, Ye W, Siegmund KD, Groshen S*, et al.* 2007. DNA methylation profile of 28 potential marker loci in malignant mesothelioma. *Lung Cancer* 58(2): 220-30.

22. Wang Y, Faux SP, Hallden G, Kirn DH, Houghton CE, Lemoine NR, Patrick G. 2004. Interleukin-1beta and tumour necrosis factor-alpha promote the transformation of human immortalised mesothelial cells by erionite. *International journal of oncology* 25(1): 173-178.

23. Wylie AG, Virta RL, Segreti JM. 1987. Characterization of mineral population by index particle: implication for the Stanton hypothesis. *Environ Res* 43(2): 427-39.