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Summary

I, Dr. Anderson, have previously provided two sets of written comments to the EPA prior to and during the February 6–8, 2012, SAB meeting (Anderson 2012a,b). The additional comments provided herein are provided in response to questions I was asked during that meeting and in light of the new studies and data requested by the SAB. Because of his vast experience on these topics, obtained while at NIEHS and subsequently, I have asked Dr. David Hoel to join me in this submission. A brief biosketch for Dr. Hoel is appended. The main points we would like to make are summarized below, and further discussion is provided in subsequent sections.

Selection of Critical Endpoint

1) It appears that the adverse effects that EPA is ultimately endeavoring to prevent are primarily decreased lung volume and decreased measures of lung function. EPA arrives at these endpoints by using pleural plaques, because EPA asserts that the presence of pleural plaques leads to lung function deficits. This relationship is not clearly supported by the literature, particularly for low exposure.

2) We agree with members of the SAB who recommended that EPA consider all non-cancer endpoints and the dose-response relationships, including those for pulmonary function deficits. Of special importance, if the Rohs et al. (2008) cohort data are to be used, EPA needs to base its assessment on the full cohort data set and include the pulmonary function data that we understand will be available later this year.

3) Pleural plaques are a sensitive endpoint, because they require far less cumulative exposure compared to pleural and interstitial diseases. They are also difficult for differential diagnosis, because other conditions can be mistaken for pleural plaques on x-rays.

4) The ILO (2000) guidelines define localized pleural thickening as pleural plaques that are located in the parietal pleura and appear predominantly on the chest wall, diaphragm, or other sites. In contrast, the location of diffuse pleural thickening is on the visceral pleura (the outermost covering of the lung tissue), where it is conceivable that the condition could impair lung function. It is far less biologically plausible that pleural plaques (located on the chest
wall and not in direct contact with lung tissue) would encroach on lung volume and thereby interfere with lung function.

5) For this draft assessment, we are in the rare position of deriving the inhalation reference concentration (RfC) from human data rather than from laboratory animal studies. This fact should remove some of the precautionary measures that are often involved when selecting the critical endpoint from experimental studies. If the quantitative relationship between LPT (pleural plaques) is not clearly confirmed to be associated with an adverse effect such as decreased lung function, and the biological mechanism for such a relationship is unknown, then LPT (pleural plaques) can be viewed only as a marker of exposure that is not verifiably causative of an adverse effect or on a biological pathway to cause disease. In this case, using a marker of exposure as a surrogate for an adverse effect and as the critical endpoint for the derivation of the RfC, raises serious questions of appropriateness and public policy. Markers of exposures from human data have not typically formed the bases for RfC and RfD derivation. Further setting this precedent will present challenges for many other substances in the environment where biomonitoring data define markers of exposure for many substances. The NAS has addressed the importance of these data and concluded that our ability to measure these markers far exceeds our ability to assess related risk (NAS 2006). Setting RfCs, RfDs and cancer risk levels of acceptability based on these markers will be highly precautionary and will raise serious challenges of social and economic consequence, reminiscent of the early 1970s when zero risk tolerance was abandoned in favor of risk assessment and risk management policies (Albert et al 1977).

Recommendations:

- Consider all non-cancer endpoints and the dose-response relationships, including for pulmonary function deficits.

- Despite the deficiencies for RfC derivation, if this study is to be used, the reassessment should rely on the full cohort and include the pulmonary function data, which are expected later this year.

- Further consider whether localized pleural thickening, in general and as defined by the ILO (2000), is plausibly linked to impairment of lung function. If not, consider this precautionary policy choice in light of the social and economic consequence of setting RfCs, RfDs, and unit cancer risk based on markers of exposure.

Derivation of the Reference Concentration (RfC)

6) EPA’s benchmark dose modeling, based on the Rohs et al. (2008) sub-cohort, appears to be a case where the prevalence rates at the highest doses dominate the model fit, whereas the key interest is at lower doses. The available data are extremely limited (only 12 cases) for characterizing effects at lower doses.

7) EPA’s display of a putative good fit for their dose-response model to the raw data in Figure E-1 is misleading. Other more common ways of summarizing the raw data, such as in the original Rohs publication, are at least as legitimate as EPA’s method, do not show a
monotonic response at low doses, and more clearly show that there is little dose-response at low doses.

8) Because the cumulative exposure point of departure (POD) was converted to average air concentration over a 70-year lifetime (minus 10 years) to derive the RfC, the RfC will be below an effects threshold for almost all exposure scenarios used in risk assessment (e.g., a 30-year residential scenario).

9) The proposed RfC is currently equal to the POD divided by 6000. Although this factor includes both uncertainty factors and an adjustment for lifetime exposure, it essentially provides a margin of exposure on the POD. EPA has placed a cap of 3,000 on the upper end of the safety factors, with the notation that uncertainties exceeding this level make the resulting guidance levels too uncertain to be of use.

10) Depending on the inclusion and assessment of the available literature from other asbestos exposures, we agree with several members of the SAB that the database deficiency factor of 10 could be reduced to 3.

Recommendations:

- Consider whether sufficient information currently exists for an RfC derivation.
- Resolve issues with the choice and goodness of fit of the proposed BMD model.
- Evaluate the significance of low-exposure dose-response data limitations.
- Resolve the issue of lifetime averaging and real-world applications of the RfC that would result in erroneous findings of unacceptable non-cancer hazard.

Practical Considerations

11) From a practical standpoint, the resulting non-cancer RfC, 0.00002 f/cc, is so low that use of this level will frustrate cleanup efforts and confuse the public. This is because distinguishing the incremental contribution of source contamination over background will be difficult, time consuming, and costly.

12) The RfC is below detection limits for years of data collected at Libby, rendering those data either useless or confusing to the public as they try to understand risks. It will not be appropriate, nor will it meet data quality objectives, to use data with inadequate sensitivity that cannot detect at least a non-cancer hazard quotient of 1; simply equating non-detects in the existing data to zero will not be acceptable for this purpose.

13) Although the EPA draft assessment is focused on Libby Amphibole Asbestos (LAA), for the novel non-cancer proposed RfC, there is no convincing literature that would preclude application of these results to all types of asbestos exposures.
Recommendations:

- Taking the above considerations into account, outline a plan of action to implement this very low RfC.
- Because of the potentially profound implications of this draft RfC, confirm that it is based on a solid scientific foundation.

Selection of Critical Endpoint for RfC Derivation

Pleural plaques have long been regarded as markers of exposure but not necessarily of risk; pulmonary function deficits and parenchymal interstitial abnormalities are also associated with asbestos exposure. Clearly, diffuse pleural thickening is associated with pulmonary function deficits, and this is biologically plausible because they are defined according to their intimate association with the lung tissue (visceral pleura). The POD needs to rely on a data set that, at a minimum, allows for proper characterization of exposure and provides information on all three endpoints, to determine whether low-level exposure to asbestos leads only to markers of exposure (e.g., pleural plaques) or whether these markers are risk factors for pulmonary function deficits. At present, no data specific to LAA allow for this analysis to be conducted adequately. More data are needed for the Marysville cohort to characterize pulmonary function for the Rohs et al. (2008) full data set. These additional data may be available by the end of 2012. Further, the entire body of available literature to address these non-cancer issues for all asbestos types should be used to further explore the appropriateness of this choice for this critical endpoint and the resulting POD. No final RfC should be issued until all important studies are considered; the full Rohs et al. data set should be used together with the anticipated pulmonary deficit data.

It appears from EPA’s Draft Toxicological Review that the adverse effects that they are ultimately endeavoring to prevent are “chronic chest pain, decreased lung volume, and decreased measures of lung function” (p. 5-21). EPA arrives at these endpoints by using pleural plaques as the critical endpoint and assumes an association, both biologically and statistically, with pulmonary function deficits. Thus, it relies on the Rohs et al. (2008) data to characterize a dose-response relationship between pleural plaques and cumulative exposure in the absence of pulmonary function deficit data and relies on other studies as a foundation for linking pleural plaques with this deficit. The challenge is that other studies do not provide a reliable basis for this linkage, either biologically or statistically.

The Rohs et al. team has lung function data, as we are sure was expressed to EPA during the course of communications regarding these data. We know that EPA was informed formally of this in a January 12, 2012, letter from Dr. Lockey to Dr. Wong. In addition, Dr. Lockey’s previous study of the Marysville cohort reported on just this subject (Lockey et al. 1984), and he actually did not find a statistically significant relationship between “restrictive lung defect” (defined as FEV1/FVC ratio of equal to or greater than 70% and FVC less than 80% predicted) and cumulative exposure (p. 954). Lockey et al. goes on to state:

“The lack of association between simple spirometric and DLcoSB measurements and fiber exposure most likely reflects the low cumulative fiber exposure and
short interval period. Simple spirometric measurements have been shown to be sensitive indicators of the toxic effects of cumulative asbestos exposure… The level of cumulative fiber exposure needed to cause a change in spirometric values is greater than the exposure levels reported in the present study. Weill and colleagues (18) reported decrease in lung function after 100 mppcf-year dust exposure, while Becklake and colleagues (19) showed an effect at a cumulative dust exposure index of 10 to 100 mppcf-year. Berry and Lewinsohn demonstrated a 12.1% reduction for FEV, and 10.6% reduction for FVC per 100 fiber/cc-years (20)” (p. 956).

All of these cumulative exposure values are orders of magnitude greater than those relied upon by EPA in the Rohs et al. study.

Since the Draft Toxicological Review was published, Larson et al. (2012a) evaluated the dose-response relationship between cumulative exposure of Libby mine and mill workers and restrictive spirometry, showing that the odds of restrictive spirometry were significantly elevated at 166 f/cc-yr, similar to the studies summarized by Lockey et al. (1984) above. Comparatively, the cumulative dose at which pleural plaques was significantly elevated in the Larson et al. study was less than 1 f/cc-yr. If there truly was a relationship between pleural plaques and restrictive spirometry, one would not have expected a nearly 200-fold difference between these two values (166 vs. 1 f/cc-yr).

Assuming that EPA will continue to consider using pleural plaques as associated with adverse effects such as decreased lung function, it should more strongly recognize that it is still highly debated in the medical/scientific community whether or not discrete pleural thickening (plaque) impairs lung function. This issue is the topic of a multitude of published articles spanning nearly 50 years. Cugell and Kamp (2004) recognize nearly 80 articles published on this topic by 2001. However, EPA discusses only 10 of these studies in the Draft Toxicological Review. Of those, EPA reports that only 5 found a potential association between pleural plaques and decreased lung function, though even some of those results may have been confounded by parenchymal changes.

Further, ILO (2000) defines localized pleural thickening (pleural plaques) as being located in the parietal pleura, which lines the diaphragm, chest wall, and cupula. This definition makes it difficult to understand how lesions at these sites (which are not on the lungs themselves [visceral]) are biologically plausible causes of pulmonary deficits.
At the beginning of the review article that EPA references to support an association between pleural plaques and lung function deficit (Rockoff et al. 2002), the editor of the journal in which the article was published felt the need to place the following disclaimer on the article:

“Whether or not Pleural plaques cause significant pulmonary function impairment and/or clinical symptoms remains controversial. Currently, an international panel of experts is being assembled to reach consensus on a variety of asbestos-related disease issues, including the topic addressed by this report. In spite of the controversial nature of this subject, the editorial board decided to publish this provocative review.”

We suspect that the assembled panel of experts to which this disclaimer refers produced the American Thoracic Society’s “Diagnosis and Initial Management of Nonmalignant Diseases Related to Asbestos” (ATS 2004), which EPA does reference throughout the Draft Toxicological Review. The ATS document itself concludes:

“This [decrements in vital capacity associated with pleural plaques] has not been a consistent finding and longitudinal studies have not shown a more rapid decrement in pulmonary function in subjects with pleural plaques. Decrements, when they occur, are probably related to early subclinical fibrosis... There is a significant but small association between the extent of circumscribed pleural plaques and FVC, which is not seen with diffuse pleural thickening. Even so, most people with pleural plaques alone have well preserved lung function” (p. 705).
This conclusion is reiterated in a more recent article that is co-authored by a member of the SAB (Dr. Kane):

“Plaques may be associated with decreases in lung function and symptoms of dyspnea, but most individuals with pleural plaques alone display no apparent symptoms and no obvious impaired lung function” (Broaddus et al. 2011, p. 164).

The amount of materials that the EPA relied upon to formulate their opinion of an association between pleural plaques and decrements in lung function is limited. In contrast, the recent Toxicological Review on Tetrachloroethylene contains tens of detailed tables containing tens to hundreds of articles reviewed and summarized (U.S. EPA 2012). Given the unprecedented step by EPA to formulate an RfC for an asbestos fiber, a more detailed analysis needs to be performed and documented.

LPT (pleural plaques) are a very sensitive endpoint, requiring far less cumulative exposure to cause them than the other distinct pleural condition, diffuse pleural thickening, and interstitial disease (ATS 2004). They are also difficult for differential diagnosis, because other conditions can be mistaken for pleural plaques on x-rays. These other conditions include subpleural fat in obese individuals, intrathoracic muscles, soft tissue shadows along the ribs, and healed rib fractures (Hillerdal 1997; Cugell and Kamp 2004).

LPT (pleural plaques) are caused not only by exposure to asbestos, but can also be caused by prior tuberculosis, trauma, hemothorax, chronic empyema, and talc instillation (ATS 2004; Broaddus et al. 2011). The other causes typically result in unilateral pleural thickening. As stated in Broaddus et al. (2011), “multiple and bilateral pleural plaques, particularly when calcified, are considered to be pathognomonic for asbestos or erionite exposure.” Also, the ATS (2004) report states that “Pleural plaques are bilateral, but not symmetric, lesions of the parietal pleura.”

The rate of pleural abnormalities in an unexposed population is uncertain and can vary (Gujral et al. 2010). It can differ depending on the population studied, the study’s ability to clearly define the exposure or lack of exposure to asbestos in the population studied, and the definition of the pleural abnormality of interest.

More recently published studies, not referenced in the Draft Assessment, have been noted by the SAB. The Larson et al. (2012b) article addresses pleural plaques and lung function in the Libby community. This article concluded, “Controlling for the presence of these abnormalities as well as age, smoking status and other covariates, restrictive spirometry was also associated with LPT (OR 1.4; 95% CI 1.1 to 1.8).” We note that Larson et al.’s population included those with occupational exposure to non-Libby asbestos. Weill et al. (2011), who analyzed the same initial cohort of 7,307 as Larson et al., excluded 1,327 of the study participants because they had “occupations or activities likely to be associated with exposure to traditional, non-vermiculite asbestos-containing materials” (p. 377). Larson et al. recognized:

“A caveat of this study is the body habitus of participants; 4591 (71%) were classified as overweight or obese (table 1). Obesity is associated with reduced FVC and restrictive changes27 as well as increased perception of circumscribed
pleural thickening. Evidence for potential confounding can be seen in the high prevalence of restriction among obese participants (table 1). In addition, some argue that the excess of pleural abnormalities in this cohort may be due in part to obesity with subpleural fat being misclassified as plaque in up to 30% of the cases. To offset the confounding effect of obesity, we controlled for BMI in all models.”

However, given the high percentage of overweight or obese persons in the population, it should be considered when interpreting the results.

Larson et al. also recognized: “Thus, although our analysis controlled for the presence of parenchymal abnormalities, our observed association between LPT and restriction may be due to ‘subradiographic’ fibrosis.”

It is rare that RfCs are based on human data. If the quantitative relationship between LPT (pleural plaques) is not confirmed to be associated with an adverse effect such as decreased lung function, and the mechanism for such a relationship is unknown, it can be viewed only as a marker of exposure that is not verifiably causative of an adverse effect. If this is the case, the question arises as to whether using a marker of exposure as a surrogate for an adverse effect and as the critical endpoint for the derivation of the RfC is appropriate. The National Academy of Sciences addressed a parallel issue when it reviewed biomonitoring for chemicals detected in humans (NRC 2006):

“The ability to generate new biomonitoring data often exceeds the ability to evaluate whether and how a chemical measured in an individual or population may cause a health risk or to evaluate its sources and pathways for exposure. As CDC states in its National Reports on Human Exposure to Environmental Chemicals, the presence of a chemical in a blood or urine specimen does not mean that the chemical causes a health risk or disease. The challenge for public-health officials is to understand the health implications of the biomonitoring data, to provide the public with appropriate information, and to craft appropriate public-health policy responses.” (p. 2)

Similar to pleural plaques, many of the chemical markers of exposure detected in humans are not reversible, in that they might persist in the body indefinitely—for example, persistent lipophilic organic compounds such as organochlorine pesticides.

**Dose-Response Model for RfC**

EPA presents its dose-response model compared to the raw results in the restricted Rohs et al. (2008) data set in Figure E-1 (reprinted below as Figure 1). The model estimates a relationship between cumulative exposure and the prevalence of localized pleural thickening (pleural plaques) based on a data set of 108 subjects with 12 cases (7 unilateral, 5 bilateral). EPA determined that the best-fitting model was a Michaelis-Menten form, assuming a 1% background rate. By choosing the sub-cohort for this non-cancer evaluation, large amounts of data are discarded.
It is peculiar that a Michaelis-Menten model was even attempted, given that this type of model is based on receptor binding in enzyme kinetics, and the development of plural plaques, while not well understood biologically, probably has little to do with enzyme kinetics. Also, the 1% background rate is an arbitrary selection that may have a significant effect on the model result. Because the background rate is not estimated directly from the data, the AIC value for the Michaelis-Menten model will be artificially lower, which gives it an unfair advantage in competing with the other models. The fitted Michaelis-Menten model limits the maximum prevalence of pleural thickening (56%), which has been exceeded in cohorts of very highly exposed insulation workers.

EPA’s model fit shows a maximum slope at zero exposure (characteristic of a Michaelis-Menten model), which results in increasing risks with exposure, even for tiny exposures. EPA’s model predicts a doubling of the assumed background rate of 1% at only 0.023 f/cc-yr. However, a review of the raw data shows that the dose-response at the lower doses is far less clear than might be concluded from EPA’s figure.

To plot the raw data (and possibly in the dose-response modeling itself), EPA apparently divided the data into quartiles by the cases. In other words, EPA ordered the data by exposure and then divided the data set to make groups with three cases in each of four quartiles. This raises the question of whether or not the “independent x-value” in the regression is dependent on the outcome values. At the least, we can approximately reproduce the quartiles with this method.
The common way to divide the data into quartiles is to order the data by exposure, select an even number of subjects for each quartile, and calculate the prevalence in each quartile, such as was done in the Rohs et al. study. Table 1 shows the result when using this approach. When the quartiles are assembled with an approximately even number of subjects, the dose-response pattern looks very different. There is no discernible effect in the first three quartiles. In fact, the second quartile has no cases, compared to two in the first quartile, and the three cases in the third quartile are not statistically higher than the two cases in the first quartile.

<table>
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<th>Subjects</th>
<th>Prevalence</th>
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</thead>
<tbody>
<tr>
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<td>2</td>
<td>29</td>
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<tr>
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<td>30</td>
<td>0.233</td>
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</table>

Table 1. Rohs restricted data set divided into quartiles with even numbers of subjects

One can also divide the data into deciles with approximately equal numbers of subjects, as shown in Table 2. In this case, there is no clear effect for 9/10ths of the exposure distribution. There is one case in both the first and ninth deciles where the difference in exposure is 100-fold. Only in the 10th decile is a statistically elevated incidence clear (4 cases for 11 subjects).

<table>
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Table 2. Rohs restricted data set divided into deciles with even numbers of subjects

Given the extremely small number of cases (12) and the fact that 4 of these cases are in the top decile of exposure, reliable conclusions about the dose-response relationship at low doses (far above the reference concentration estimate) cannot be made.
The fit in EPA’s model is dominated by the response at the highest dose, which is undesirable in BMD modeling. EPA states in its benchmark dose guidance document (U.S. EPA 2000):

“In the absence of a mechanistic understanding of the biological response to a toxic agent, data from exposures that give responses much more extreme than the BMR do not really tell us very much about the shape of the response in the region of the BMR” (emphasis added).

In summary, EPA’s modeling appears to be a case where the prevalence rates at the highest doses dominate the model fit, whereas the key interest is at lower doses. The available data appear to be extremely limited for characterizing effects at lower doses.

**Metric for the Derived RfC: Division of POD by 60 years**

The real-world use of the proposed RfC in the Draft Toxicological Review, $2 \times 10^{-5}$ f/cc, can result in a finding of an unacceptable non-cancer hazard for exposures that do not exceed the POD adjusted by uncertainty factors. This dichotomous arises because the RfC has been derived for a lifetime of exposure, and in standard risk assessment practice, the RfC is not prorated for less than lifetime chronic exposure durations.

Asbestos exposures are evaluated in a different way from exposures to other toxic substances. The concentration metric is in fibers per volume of air, rather than the mass-based concentration used for other toxic substances. The use of lifetime cumulative exposure (f/cc-years) as the POD is also uncommon; typically, the POD is expressed in concentration terms.

The Draft Toxicological Review’s proposed RfC can be split into three elements: the POD (fibers/cc-year), the combined uncertainty factors (UFs) (unitless), and the lifetime exposure duration (ED) (years). Using the values presented in the Draft Toxicological Review, the calculation of the proposed RfC can be broken down as follows:

1. POD = 0.1177 f/cc-years
2. UF = 10 and 10 = 100
3. POD/UF = 0.001177 f/cc-years
4. ED = 70 years (lifetime) – 10 years (lag) = 60 years
5. RfC = POD/UF/ED = 0.0000196 f/cc (rounds to 0.00002 f/cc).

The RfC is the POD divided by 6000, representing the air concentration that equates to the POD/UF for an exposure scenario that involves a lifetime of exposure. These adjustment factors

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1 The order of these steps is presented slightly differently in the Draft Toxicological Review, in which the POD is initially divided by 60 years and then by the uncertainty factors.
are highly conservative, and the lifetime adjustment factor of 60 presents a dilemma for asbestos risk assessors, as explained below.²

The standard human health risk assessment practice, such as that applied by EPA for Superfund, uses the RfC as a benchmark for deriving the hazard quotient (HQ), the measure of non-cancer risk.³ For any chronic exposure scenario (by convention, an exposure occurring over 7 or more years) the HQ is the ratio of the average daily exposure concentration (EC) to the RfC; accordingly, if the EC exceeds the RfC, the HQ will exceed 1. Although an HQ exceeding 1 does not necessarily indicate there is an actual health risk, typically action is required to reduce the exposure.⁴ Unlike the flexibility of accepting risk for management purposes that span a range of 10⁻⁶ to 10⁻⁴, there are no ranges of acceptability for the non-cancer endpoint around the hazard index of 1. An exceedance of the hazard index of 1 requires risk management.

The EC is defined as the time-weighted concentration over the exposure duration in years; thus, for an exposure lasting 30 years, the EC is the average concentration over those 30 years, not a lifetime.⁵ For example, using the 30-year exposure as an example, the HQ for an EC of 2.1×10⁻⁵ f/cc (a concentration that is just above the draft RfC value) exceeds 1, which would potentially result in a conclusion that further action is required. However, the cumulative exposure for this example would be approximately 0.0006 f/cc-years (2.1×10⁻⁵ f/cc × 30 years), which is only about ½ of the POD/UF (0.001177 f/cc-years). Therefore, an exposure concentration less than the “safe” level would trigger an “unacceptable risk” conclusion. Three approaches are suggested to resolve this contradiction:

1. Require the EC to reflect the lifetime average concentration.
2. Express the RfC in units of cumulative exposure (i.e., f/cc-years, made equivalent to the POD/UF).
3. Base the POD itself on exposure concentrations rather than cumulative exposure. This was done in the Draft Toxicological Review but only as a sensitivity analysis (see Section 5.3.7 of the Draft Toxicological Review). It is unclear whether that analysis was rigorous; for example, it is not clear whether the BMD model selected was based on the best fit to the

² EPA’s IRIS glossary (http://www.epa.gov/iris/help_gloss.htm) defines the RfC as follows: “Chronic Reference Concentration (RfC): An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure for a chronic duration (up to a lifetime) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark concentration, with uncertainty factors generally applied to reflect limitations of the data used. Generally used in EPA’s noncancer health assessments.”
⁵ 30 years is selected for this example, because it is the typical assumption for upper-bound residential exposure duration.
concentration data or if it was adopted from the main analysis using cumulative exposure.

Option 1 is problematic, because it redefines the EC. Option 2 is viable, because the conversion of the EC to a cumulative exposure is a trivial matter. Option 3 should be considered further.

In addition, as described above, the proposed RfC is currently equal to the POD divided by 6000. Although this factor includes both uncertainty and adjustment for lifetime exposure, it essentially provides a margin of exposure on the POD. EPA has placed a cap of 3,000 on the upper end of the safety factors, with the notation that uncertainties exceeding this level make the resulting guidance levels too uncertain to be of use (U.S. EPA 2002). We agree with several members of the SAB that the database deficiency factor of 10 could be reduced to 3, based on the available literature regarding other asbestos exposures.

**Implications of the Proposed RfC**

In my (Dr. Anderson’s) initial comments and addendum provided to the SAB, I stressed the wide-ranging implications that the proposed RfC would have on past and future sampling efforts using EPA’s activity-based sampling program for Libby as an example. I demonstrated that the proposed RfC, in most cases, would likely drive any risk assessment, because in most cases, the non-cancer hazard would eclipse the cancer risk targets of one in one million to one in ten thousand. I also pointed out the disparity between current analytical targets and those that would be associated with the draft RfC, and the increased time and cost that may be involved with achieving the “new” data quality objectives.

With respect to costs, I noted that per-sample costs would likely range in the low thousands of dollars to tens of thousands of dollars, and I provided some figures based on information provided to me by a single lab. Since then, we have talked with another lab, and although the above ranges still hold true, the second lab’s costs were somewhat lower. We therefore have included these additional cost estimates as a low end of the cost range and provide a revised Table 1-2 (originally provided in my addendum comments) below. With respect to time to analyze samples, this will depend on the materials collected on the filters (non-asbestos mineral structures on the filter would significantly increase the time) and the staffing capabilities of the lab. The new sensitivities would require examining on the order of 100 to 500 grid openings. My understanding is that this level of effort will require days or weeks, rather than hours, of a microscopist’s time, which is the primary determinant of time and cost (U.S. EPA 2008).

In my (Dr. Anderson’s) addendum comments, I provided a graph that shows the tendency of the proposed RfC to drive risk assessment. We have performed a similar analysis for dioxin (2,3,7,8-TCDD) using the new oral reference dose (RfD). The LAA and dioxin figures are compared below. In contrast to LAA, where the non-cancer hazard will drive risk at about the 1-in-1,000,000 level, the new dioxin RfD will drive risk only if the target risk is above 1 in 100,000, approaching 1 in 10,000 for longer exposures. We present this information here to confirm the importance of this RfC decision and the need to meet the challenge to confirm a solid scientific foundation to support this decision.
Although the EPA draft assessment is focused on LAA, for the novel non-cancer proposed RfC, there is no convincing literature that would preclude application of these results to all types of asbestos exposures, including past and present exposures that are occupational, indoor residential, or ambient exposures. These forms of asbestos are widespread and well known.
### Table 1-1: Calculation of Required Analytical Sensitivity for Noncancer Health Endpoint Based on Draft RFC

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Exposure Time (hrs)</th>
<th>Exposure Frequency (days/year)</th>
<th>Target Analytical Sensitivity (f/cc)</th>
<th>note</th>
<th>Draft RFC (f/cc)</th>
<th>Time Weighting Factor, TWF (3)</th>
<th>Required target sensitivity for noncancer Hazard Quotient (HQ) = 1 (4)</th>
<th>Required target sensitivity for noncancer target Hazard Quotient = 0.2 (1 of 5 scenarios)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residents in yards</td>
<td>8</td>
<td>60</td>
<td>0.002</td>
<td>(1)</td>
<td>2.0E-05</td>
<td>0.055</td>
<td>0.00012</td>
<td>0.000024</td>
</tr>
<tr>
<td>Residents in gardens</td>
<td>4</td>
<td>60</td>
<td>0.003</td>
<td>(1)</td>
<td>2.0E-05</td>
<td>0.027</td>
<td>0.00024</td>
<td>0.000049</td>
</tr>
<tr>
<td>Child playing on driveway</td>
<td>2</td>
<td>120</td>
<td>0.004</td>
<td>(1)</td>
<td>2.0E-05</td>
<td>0.027</td>
<td>0.00024</td>
<td>0.000049</td>
</tr>
<tr>
<td>Driving on Libby roads</td>
<td>4</td>
<td>180</td>
<td>0.001</td>
<td>(1)</td>
<td>2.0E-05</td>
<td>0.082</td>
<td>0.00008</td>
<td>0.000016</td>
</tr>
<tr>
<td>Biking in Libby (adult)</td>
<td>2</td>
<td>90</td>
<td>0.005</td>
<td>(1)</td>
<td>2.0E-05</td>
<td>0.021</td>
<td>0.00032</td>
<td>0.000065</td>
</tr>
<tr>
<td>Breathing ambient air</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0000395</td>
<td>2.0E-05</td>
<td>1.0</td>
<td>0.00002</td>
</tr>
</tbody>
</table>

Notes:
1. Scenario, exposure and target sensitivity values taken from Table 3-3 of EPA Sampling and Analysis Plan (EPA 2010)
   Supplemental Activity-based Sampling Libby Asbestos Site, Operable Unit 4, June 2010.
   http://www.epa.gov/region8/superfund/libby/OU4_SupplementalABS_SAP.pdf
2. Typical Sensitivity from EPA Libby sampling “Ambient Air Sampling Results for Operable Unit 4, Libby asbestos Site, Libby, Montana 2010-2011”
   http://www.epa.gov/region8/superfund/libby/OU4_AmbientAirSamplingResults2010-2011.pdf
3. Time Weighting Factor (fraction of time exposed) = exposure duration x exposure frequency / (24 x 365)
4. = RFC/TWF/3 for activity based scenarios (EPA 2010) and =RFC for ambient
5. High end of range is based on discussions with an analytical asbestos laboratory the cost for TEM analysis can be approximated by the following formula
   Cost = (RFC/Required sensitivity) x (5.66 x 10^7/Volume sampled in Liters)
   Low end assumes $135 per sample including 10 grid openings plus $5 per grid opening thereafter

### Table 1-2: Calculation of Per Sample Costs of Laboratory Analysis to Meet Draft RFC-Required Analytical Sensitivities

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Required Sensitivity for noncancer (Target Hazard Quotient = 1) (4)</th>
<th>Assumed Typical Sampling Duration (min)</th>
<th>Assumed flow rate of sampling pump (Liters/min)</th>
<th>Volume of Air Sampled (Liters)</th>
<th>Cost to Analyze Volume to Required Sensitivity for HQ=1 (5)</th>
<th>Cost to Analyze for HQ=0.2 (1 of 5 scenarios)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residents in yards</td>
<td>1.22E-04</td>
<td>120</td>
<td>5</td>
<td>600</td>
<td>$ 2,700 - $ 15,500</td>
<td>$ 13,500 - $ 77,500</td>
</tr>
<tr>
<td>Residents in gardens</td>
<td>2.43E-04</td>
<td>120</td>
<td>5</td>
<td>600</td>
<td>$ 1,400 - $ 7,800</td>
<td>$ 7,000 - $ 39,000</td>
</tr>
<tr>
<td>Child playing on driveway</td>
<td>2.43E-04</td>
<td>120</td>
<td>5</td>
<td>600</td>
<td>$ 1,400 - $ 7,800</td>
<td>$ 7,000 - $ 39,000</td>
</tr>
<tr>
<td>Driving on Libby roads</td>
<td>8.11E-05</td>
<td>240</td>
<td>10</td>
<td>2400</td>
<td>$ 1,100 - $ 5,800</td>
<td>$ 5,500 - $ 29,000</td>
</tr>
<tr>
<td>Biking in Libby (adult)</td>
<td>3.24E-04</td>
<td>120</td>
<td>5</td>
<td>600</td>
<td>$ 1,100 - $ 5,800</td>
<td>$ 5,500 - $ 29,000</td>
</tr>
<tr>
<td>Breathing ambient air</td>
<td>2.00E-05</td>
<td>7200</td>
<td>2</td>
<td>14400</td>
<td>$ 800 - $ 3,900</td>
<td>$ 3,900</td>
</tr>
</tbody>
</table>

Notes:
1. Scenario, exposure and target sensitivity values taken from Table 3-3 of EPA Sampling and Analysis Plan (EPA 2010)
   Supplemental Activity-based Sampling Libby Asbestos Site, Operable Unit 4, June 2010.
   http://www.epa.gov/region8/superfund/libby/OU4_SupplementalABS_SAP.pdf
2. Typical Sensitivity from EPA Libby sampling “Ambient Air Sampling Results for Operable Unit 4, Libby asbestos Site, Libby, Montana 2010-2011”
   http://www.epa.gov/region8/superfund/libby/OU4_AmbientAirSamplingResults2010-2011.pdf
3. Time Weighting Factor (fraction of time exposed) = exposure duration x exposure frequency / (24 x 365)
4. = RFC/TWF/3 for activity based scenarios (EPA 2010) and =RFC for ambient
5. High end of range is based on discussions with an analytical asbestos laboratory the cost for TEM analysis can be approximated by the following formula
   Cost = (RFC/Required sensitivity) x (5.66 x 10^7/Volume sampled in Liters)
   Low end assumes $135 per sample including 10 grid openings plus $5 per grid opening thereafter
Libby Amphibole Risk Driver: Cancer versus Noncancer w/ proposed RfC

Cancer risk based concentration:

\[ C = \text{Risk} \times \frac{\text{EXR} \times \text{years}}{70} \]

(not adjusted for age of first exposure, assumes continuous exposure

Noncancer Hazard-based Concentration (RfC) for chronic exposure (exceeding ~7 years):
\[ C = \text{Target} \times \text{RfC} \]
\[ = 0.01 \text{mg/L} \]
\[ = 0.00002 \text{mg/L} \]

assumes continuous, 24/7

A. Cancer risk based exposure concentration exceeds concentration for a noncancer hazard of 1; the noncancer health endpoint will drive risk assessment and data quality objectives (analytical sensitivity)

B. Cancer risk based exposure concentration is lower than concentration for a noncancer hazard of 1; the cancer health endpoint will drive risk assessment and data quality objectives (analytical sensitivity)

2,3,7,8-TCDD Risk Driver: Cancer versus Non-Cancer

Non-cancer Hazard-Based Intake, I:
\[ I = \text{Target} \times \text{HD} \]
\[ = 1 \times 7.3 \]

Cancer risk based intake:
\[ I = \text{Risk} \times \text{SF} \times \text{mg/L} \]
\[ = 1.36 \text{ mg/L} \]

A. Cancer risk based intake exceeds intake for a non-cancer hazard of 1; the non-cancer health endpoint will drive risk assessment

B. Cancer risk based intake is lower than intake for a non-cancer hazard of 1; the cancer health endpoint will drive risk assessment
References


**Background and Qualifications: Dr. David G. Hoel**

Dr. David G. Hoel is a Distinguished University Professor in the Department of Medicine at the Medical University of South Carolina in Charleston, and is a Principal Scientist at Exponent, Inc. He received an A.B. in mathematics and statistics from the University of California at Berkeley and a PhD in mathematical statistics from University of North Carolina in Chapel Hill, and was a post-doctoral fellow in preventive medicine at Stanford University. Prior to joining the Medical University of South Carolina, Dr. Hoel was Division Director for Risk Assessment at the NIEHS in North Carolina. Dr. Hoel is a Fellow of the AAAS, a member of the Institute of Medicine of the National Academies, and a National Associate of the National Academies. His awards include the Spiegelman Gold Medal in Public Health and the Ramazzini Award in Environmental and Occupational Health. He has served on numerous governmental and National Academy committees, including the EHC and RAC of EPA’s Science Advisory Board and the BEIR V committee of the National Academy of Sciences. He was a member of IARC’s committee on ionizing radiation (report 100D) and contributed to the United Nations’ UNSCEAR report 2006. Dr. Hoel’s research has focused on risk assessment methods with particular interest in low-dose radiation exposures and cancer. This work has included stays in Hiroshima as a Director at the Radiation Effects Research Foundation, and he currently is a RERF Scientific Counselor. Until this year, he was a member of National Academies’ Board on Nuclear and Radiation Studies. Finally, he has testified several times in both the House and Senate on human health issues.