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VIA EMAIL AND UPS
Information Quality Guidelines Staff
William Jefferson Clinton North
1301 Constitution Ave., NW
EPA OEI Quality Staff, Suite 5315
Washington, DC 20004
Attn: Kimberlie Orr

Re: RFC 14002; Supplemental Information in Support of Information Quality Act Request for Correction

Dear Sir or Madam:

We are writing to provide newly available materials in further support of the February 26, 2014 Information Quality Act ("IQA") Request for Correction ("Request") Regarding the Libby Amphibole Asbestos ("LAA") Integrated Risk Information System ("IRIS") Assessment ("Draft Assessment"). We are providing two types of information: 1) recent scientific studies that further demonstrate that the Draft Assessment's selection of the noncancer critical effect is not supported by the weight of evidence, and that illustrate the importance of identifying and correcting for confounders and bias when assessing scientific evidence; and 2) recommendations by the National Academy of Sciences ("NAS") Review of EPA's IRIS Process, dated May 6, 2014 ("NAS 2014 Report") that reinforce earlier NAS recommendations regarding transparency, systematic review of the literature and minimization of bias, all of which should be applied to the LAA assessment as best available science consistent with EPA's IQA Guidelines.

EPA has already been made aware of the recent scientific studies,[1] and we understand that EPA is already considering the NAS 2014 Report. Accordingly, we incorporate this letter by reference to the original Request and ask that EPA address the contents of this letter and its attachments when it responds to the Request and before it issues any further version of the LAA assessment.

[1] See attached letter from Keith N. Cole to Dr. Kenneth Olden, June 2, 2014.

I. Studies Regarding the Draft Assessment's Selection of the Noncancer Critical Effect

Several new studies further evidence that the Draft Assessment's noncancer critical effect (pleural plaques) has not been shown to cause impairment. This is important because, as set forth in the Request and EPA policy, a critical effect must be shown to be:

> likely to ***impair*** the performance or ***reduce the ability*** of an individual to function or to respond to additional challenge from the agent. Biological significance is also attributed to effects that are consistent with steps in a known mode of action. Statistical significance quantifies the likelihood that the observed effect is not due to chance alone. Precedence is given to biological significance, and a ***statistically significant change that lacks biological significance is not considered an adverse response.***[2]

Thus a physical change alone, without accompanying demonstrated functional impairment, cannot serve as a noncancer critical effect unless EPA were to transparently alter a fundamental element of the IRIS program and foundational scientific guidance.

Set forth below is a short summary of each of these additional studies. Each supplements Section III.A.1. of the Request, which seeks a reliable, accurate, and unbiased assessment under the base IQA standards, and requests that for the noncancer critical effect EPA: a) satisfy its own scientific criteria by showing an adverse effect; b) demonstrate causation of the selected critical effect; c) identify and adjust for confounders; and d) consider influential and relevant scientific literature. In order to comply with the IQA, EPA should evaluate and take these studies into account before disseminating further any version of the Draft Assessment. Doing so is mandated by EPA's IQA Guidelines, which require EPA to apply the best available science and to ensure that information EPA disseminates is complete, accurate, unbiased, and reflects a thorough weighing of all available scientific evidence.

1. Libby Miner Health Study

A new peer reviewed study published in *Chest*[3] analyzes historic health data from the Libby, Montana vermiculite miners and finds that plaques alone did not cause lung function deficits among miners exposed to LAA. No statistically significant difference in lung function was found between miners with pleural plaques alone and those with no radiography findings (using High Resolution Computed Tomography ("HRCT")).

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[2] Risk Assessment Guidance for Superfund, Volume I: Human Health Evaluation Manual (Part F, Supplemental Guidance for Inhalation Risk Assessment) Final ("EPA RAGS for Inhalation Risk Assessment"), EPA/540/R/070/002 Jan. 2009 at 9, fn.18 (Request, Exhibit 12).

[3] Clark, KA; Flynn, JJ III; Goodman, JE; Zu, K; Karmaus, WJ; Mohr, LC. 2014. "Pleural plaques and their effect on lung function in Libby vermiculite miners." Chest doi: 10.1378/chest.14-0043, http://journal.publications.chestnet.org/article.aspx?articleid=1868832.

EPA should evaluate and account for this study because it analyzes Libby-specific data, making it one of the most relevant studies for this LAA assessment to consider. Moreover, this study thoughtfully addresses bias and seeks to eliminate confounders present in many other studies. This study uses the most reliable diagnostic methods: HRCT and multiple pulmonary function test parameters. It is well accepted in the medical community that x-ray radiography is prone to misdiagnosis of pleural plaques (*e.g.,* extrapleural fat can be mistakenly identified as plaques) and underdiagnosis of other lung abnormalities (*e.g.,* fibrosis) that affect lung function. The HRCT data used in this study provide superior contrast sensitivity and cross-sectional imaging format, and thus minimize the potential for bias from relying upon x-rays. The study quality also is enhanced because it evaluates multiple pulmonary function test parameters to distinguish among different types of lung decrements (such as obstructive lung disease that is unlikely to be related to asbestos). In contrast to this new study, many other studies that EPA has relied on reflect bias from reliance upon less accurate x-rays and limited lung function testing.

2. Literature Review

A second peer reviewed study[4] rigorously assesses the body of literature that the Draft Assessment relies upon, and concludes that:

> . . . in light of the serious methodological limitations and inconsistent findings of these collective studies, ***the overall weight of evidence does not establish an independent adverse effect of pleural plaques on pulmonary function***.

This study quotes and then applies EPA-established criteria as follows: "***by the Agency's own definitions, for an effect to be considered adverse, the presence of biological or pathologic changes is not sufficient***. Rather, these changes must additionally affect the performance of the whole organism or compromise the organism's ability to respond to environmental changes."

EPA should evaluate and account for this study because it assesses sources of bias and confounders present in the body of literature that the LAA Draft Assessment relies upon. In addition to supplementing Section III.A.1 of the Request, the additional information and analysis of scientific methodology provided in this study further supports Sections III.A.2. (inadequate cohort strength), III.B (inadequate scientific methods), III.C (incompleteness, inaccuracy, lack of transparency and failure to identify the potential sources of error), IV.B (need for a rigorous weight of evidence analysis), and IV.C (failure to reflect the best available science) of the Request. This study supports the conclusion that the Draft Assessment is unduly biased, unreliable, and affected by confounders, thereby failing to satisfy applicable IQA standards.

3. HRCT Study Analysis

The third study[5] demonstrates that the Draft Assessment failed to assess relevant literature, and concludes that there is no reliable association between the presence of pleural plaques in

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[4] Moolgavkar, SH; Anderson, EL; Chang, ET; Lau, EC; Turnham, P; Hoel, DG. 2014. "A review and critique of U.S. EPA's risk assessments for asbestos." Crit. Rev Toxicol. doi: 10.31109/10408444.2014.902423. http://informahealthcare.com/doi/abs/10.3109/10408444.2014.902423.

[5] Kerper, et al 2014, presented at the Society of Toxicology (SOT) 53rd Annual Meeting, Phoenix, AZ (attached).

asbestos-exposed populations and lung function deficits. This study was included in the original Request (pp. 19, 35, Exhibit 23), but has since been revised for final presentation to the Society of Toxicology. Therefore, this letter transmits the final study in support of the Request.

This study should be considered because, by focusing only on literature that evaluates HRCT data, the researchers reveal the likelihood of significant and previously unanalyzed bias in studies that rely upon x-ray data and thus may have included inaccurate diagnoses. This study's analysis is transparent and systematic, and highlights the importance of a systematic approach. Accordingly, this study helps to fill a gap in the Draft Assessment's incomplete review of the literature concerning the noncancer critical effect. Like the previously referenced study, most of the literature assessed in this study was available at the time of the Draft Assessment.[6]

II. 2014 NAS Report

As explained in the Request, the August 2011 Draft Assessment fails to apply 2011 NAS recommendations regarding IRIS assessments, thereby failing to apply best available science. Some recommendations easily could have been implemented immediately in 2011, such as changes that could have improved the conduct of evidence-based review, inferences as to the strength of the evidence of association, and transparent assessment of causation.[7] Now NAS has spoken again regarding the IRIS program in its May 6, 2014 Review of EPA's IRIS Process ("2014 NAS Report"), building on its 2011 recommendations. The 2014 NAS Report again emphasizes some of the very issues that undermine the scientific integrity of the Draft LAA Assessment and squarely reflect IQA requirements. For the same reasons that the 2011 NAS recommendations reflect best available science, so does the 2014 NAS Report. As a result, EPA's IQA guidelines require that any final LAA assessment reflect the 2014 NAS report recommendations, in order to apply best available science and achieve an accurate, reliable and unbiased result.

Notably, the 2014 NAS Report emphasizes the importance of transparency and systematic reviews to minimize bias in evidence identification. The 2014 NAS Report found that the "concept of risk of bias is central to the evaluation of studies for systematic reviews of clinical evidence."[8] To address this central issue, among the 2014 NAS Report's highest priorities were the following strong recommendations for EPA to apply to IRIS assessments:

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[6] While EPA has identified "stopping rules" to minimize undue delay in finalizing IRIS assessments, those informal administrative guidelines cannot obviate requirements under binding OMB and EPA IQA Guidelines. Even under EPA's stopping rules, EPA should consider studies that impact the credibility of an assessment's conclusions, such as in this instance.

[7] NAS Formaldehyde Peer Review Report, Chapter 7, p. 164 (Request, Exhibit 5) ("Guidelines and protocols for the conduct of evidence-based reviews are available, as are guidelines for inference as to the strength of evidence of association and causation. Thus, EPA may be able to make changes in the assessment process relatively quickly by drawing on appropriate experts and selecting and adapting existing approaches").

[8] NAS 2014 Report, Chapter 5, p. 62.

- *When considering any method for evaluating individual studies, EPA should select a method that is transparent, reproducible, and scientifically defensible...*

- *. . . an IRIS assessment needs to include a transparent evaluation of the risk of bias of studies used by EPA as a primary source of data for the hazard assessment. EPA should specify the empirically based criteria it will use to assess risk of bias for each type of study design in each type of data stream.*

- *To maintain transparency, EPA should publish its risk-of-bias assessments as part of its IRIS assessments. It could add tables that describe the assessment of each risk-of-bias criterion for each study and provide a summary of the extent of the risk of bias in the descriptions of each study in the evidence tables.*

- *The risk-of-bias assessment of individual studies should be carried forward and incorporated into the evaluation of evidence among data streams.* [9]

In essence, the 2014 NAS Report provides EPA with IRIS-specific best available science for addressing concerns that are also central to the IQA: transparency, accuracy and lack of bias. As such, and as required by EPA's IQA Guidelines, EPA should apply the 2014 NAS Report recommendations as best available science.

Also, the 2014 NAS Report calls for transparent disclosure of the level-of-confidence needed before a critical effect can be used as the basis for a toxicity value,[10] transparency that the Draft Assessment lacks. This recommendation is particularly relevant to the Draft Assessment's controversial selection of the noncancer critical effect, where the underlying evidence is weak. In making such subjective judgments, the NAS recommended that EPA be "explicit and detailed" because of the potential for bias.[11] This recommendation supports Section III.A of the Request, which seeks transparent and detailed disclosure of the basis for the selection of a noncancer critical effect.

Finally, the NAS echoed an IQA requirement by recommending that IRIS assessments provide not only a lower bound estimate but also a central estimate. The Request asked EPA to address this issue (see Sections IV.F and G) and the 2014 NAS Report further supports the Request on these points.[12]

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[9] NAS 2014 Report, Box 8-1 (high priority recommendations)(italics added) and Chapter 5, p. 74 -75.

[10] NAS recommends conducting dose response assessment only when the "evidence is sufficient to derive toxicity values, such as when the "level of confidence" is at least "medium or high," or under another formulation it is "more likely than not likely that the hazard exists." NAS 2014 Report, Chapter 7, p. 124.

[11] NAS 2014 Report, Chapter 7, p. 112.

[12] NAS 2014 Report, Chapter 7, p. 124.

III. Conclusion

In conclusion, the three studies referenced in this letter further confirm that the best available science required by EPA's IQA Guidelines demonstrates that pleural plaques have not been shown either to cause functional impairment or to be a precursor in a continuum of effects leading to functional impairment. Therefore, use of pleural plaques as the critical effect does not comply with either EPA's own IRIS definition of "adverse effects" or the IQA Guidelines.

Given their important scientific content, these studies should be considered by EPA in evaluating the Request to correct the disseminated Draft Assessment, and also to ensure that future information EPA disseminates in connection with the LAA IRIS assessment is reliable, accurate, unbiased, and based upon the best available scientific methods. For example, EPA should thoroughly consider these new studies that evaluate the best scientific methods (i.e., HRCT instead of x-rays) and identify other sources of bias. In addition, in disseminating future LAA IRIS assessments, EPA should apply the above described 2014 NAS recommendations because they reflect best available science for IRIS assessments.

Thank you for your consideration of this supplemental information. Please contact us if you have any questions.

Sincerely yours,

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On behalf of Requester W.R. Grace & Co.-Conn.

Enclosures

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