MSHA 2023 Rule for Lowering Miners' Exposure to Respirable Crystalline Silica and Improving Respiratory Protection

Evaluation and comments on MSHA's literature review methodology

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Introduction

The comments below are provided at the request of and sponsored by the National Stone, Sand & Gravel Association (NSSGA) in response to MSHA's request for comments on the proposed rule, "Lowering Miners' Exposure to Respirable Crystalline Silica and Improving Respiratory Protection." Although requested and sponsored by NSSGA, the comments below represent my independent professional assessment and neither NSSGA nor any of its members played any role in my assessment. As a career epidemiologist and principal investigator on one of the largest epidemiological studies (reported in several peer-reviewed scientific publications) on quantified crystalline silica exposure and risk of silicosis and lung cancer published to date, I focused my comments on MSHA's Question 1 under "Health Effects" section of the proposed rule and as presented in the "Effects of Occupational Exposure to Respirable Crystalline Silica on the Health of Miners, Review of Health Effects Literature."[1]

Furthermore, I limited my responses to the epidemiological literature quantifying the risks of occupational crystalline silica exposure and silicosis and lung cancers, both of which – above respective exposure thresholds – are causally related to such crystalline silica exposure. This likely holds true for other forms of NMRD but is much less clear for renal disease.[2]

The comments are presented in three sections, the first addresses the review methodology overall, the second responds to specific statements presented by MSHA in the review document about their literature review, and the third highlights reported results from several studies that have quantified risks of silicosis and lung cancer by levels or categories of exposure to crystalline silica.

The first section additionally discusses the importance of conducting reviews of scientific evidence using systematic and transparent methods that can be documented and followed, as such reviews themselves are (and increasingly considered) scientific research. No credible scientific research study or experiment today could escape precise documentation of every method and source of data, their evaluation, synthesis, and interpretation. In other words, scientifically and societally important reviews also should follow basic principles of the scientific method (Lynch et al. 2022a).[3] Because much of my research and evaluation of epidemiological relationships has focused on research methods and study quality, my first set of comments address the apparently incomplete and possibly dated methodology that MSHA or the underlying work of OSHA may have followed (though the main problem is that this is not delineated). As "MSHA requests comments on this preliminary determination and its literature review, which draws

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[1] See US Department of Labor, Mine Safety and Health Administration. Effects of Occupational Exposure to Respirable Crystalline Silica on the Health of Miners, Docket ID No. MSHA-2023-0001. April 2023.

[2] In 2017 the German Federal Institute for Occupational Safety and Health (BAUA) published a systematic review and meta-analysis on respirable crystalline silica and non-malignant renal disease and concluded: "While the studies of cohorts exposed to silica found elevated SMRs for renal disease, no clear evidence of a dose–response relationship emerged. The elevated risk may be attributed to diagnostic and methodological issues."

[3] Lynch, H.N., K.A. Mundt, D. Pallapies, P.F. Ricci. 2022a. Lost in the woods: Finding our back to the scientific method in systematic review. Global Epidemiol. 4:100093. https://www.sciencedirect.com/science/article/pii/S2590113322000232

heavily from the review conducted by OSHA for its 2016 rulemaking," I did not attempt to isolate at what point of the evolution of MSHA's Review of the Health Effects Literature or by which Agency the methodological lapses occurred. Rather, it is more important that gaps and possible errors be identified and scientifically remedied according to current standards and guidelines for critically reviewing and synthesizing the epidemiological literature on any exposure-health outcome relationship and risk evaluation.

Key elements to the quality of a systematic review methodology include the comprehensiveness of the identification and inclusion of published studies, the metrics employed for assessing the quality of individual studies, the approach used to weighting evidence based on study quality, the methods used to synthesize the evidence and the validity of the interpretations and conclusions based on the systematic review – all common to most current guidance on performing systematic reviews of the human health literature. For an example (unrelated to crystalline silica) in which basic systematic review methods were drawn from multiple current frameworks, namely, those of the US EPA (TSCA) and the US NASEM, please see Lynch et al. (2022b).[4]

The second section highlights several ways in which the MSHA review – despite having claimed foundations in the OSHA review – appears to leave substantive gaps in the actual review process employed – or fails to document adequately all steps undertaken by OSHA or by MSHA, making it difficult for other scientists to replicate the process and identify specific aspects that give rise to unclear or misleading interpretations that might lead to clarification or correction. The magnitude of the unclear or missing documentation is sufficient to reduce methodological transparency to a point that it is difficult to fully assess where key data gaps or methods might have given rise to unrepresentativeness in the body of evidence reviewed, incomplete or unbalanced assessment of individual quality, which directly influence how any synthesis is performed (including greater weighting of evidence from higher-quality studies and discounting results from poor-quality studies) and ultimately, the validity of interpretations and conclusions.

The third section provides examples of published studies of good quality in which occupational crystalline silica exposures reasonably were quantified, allowing further assessment for exposure-response patterns including exposure thresholds for silicosis and lung cancers. Several of these were not addressed by MSHA, likely because they were performed on cohorts of workers exposed to crystalline silica but not from mining operations. While not comprehensive, these examples are provided as an epidemiological "reality check" regarding whether it is scientifically clear or not "miners' exposure to respirable crystalline silica [and presumably compliant under current exposure limits] presents a risk of material health impairment."

Section 1: MSHA's overall literature review approach

<u>What is a "Systematic Review"?</u>

"Systematic review" has become an important theme among human health scientists, especially epidemiologists and toxicologists, as it is widely recognized that traditional reviews, especially narrative reviews, are subjective at any of several steps (starting from methods for searching the literature), and that small differences in decisions and underlying assumptions often lead to disparate, including contradictory conclusions. If systematic review is viewed as a scientific research process, the review protocol must be defined, followed, and documented, allowing other scientists to evaluate the exact review methodology applied (as with any scientific experiment or study), to examine the data selected from published results, and to make transparent the scientific basis for any interpretations and

[4] Lynch HN, Kozal JS, Russell AJ, Thompson WJ, Divis HR, Freid RD, Calabrese EJ, Mundt KA. Systematic review of the scientific evidence on ethylene oxide as a human carcinogen. Chem Biol Interact. 2022 Sep 1;364:110031. doi: 10.1016/j.cbi.2022.110031. https://pubmed.ncbi.nlm.nih.gov/35779612/.

conclusions presented. For example, the [Cochrane Collaboration](), founded in 1992 to address evidence-based decision-making in health care, describes the systematic review process as an "explicit, systematic" method intended to minimize bias through "a clearly stated set of objectives with pre-defined eligibility criteria for the studies; an explicit, reproducible methodology; a systematic search that attempts to identify all the studies that would meet the eligibility criteria; an assessment of the validity of the findings of the included studies, for example through the assessment of the risk of bias; and a systematic presentation, and synthesis, of the characteristics and findings of the included studies" (Higgins et al. 2021).[5] Though Cochrane applies these principles for science-based health-care guidelines, they remain central to systematic reviews on human health risks and have been embraced by most state-of-the-art frameworks for performing systematic reviews on a wide range of human health risk evaluations.

The problem of failing to adhere to good systematic review practices is not limited to individual scientists or organizations with extreme views or biases, but too often falls at the center of important regulatory decision-making by major national and international Agencies. For example, as noted by Lynch et al. 2022a:

> One modern classic example may be the evaluation of glyphosate, which the International Agency for Research on Cancer (IARC) classified as "probably carcinogenic to humans" [16] whereas EPA's evaluation indicated that "glyphosate is not likely to be carcinogenic to humans" [10]. Similarly, the European Food Safety Authority (EFSA) concluded that glyphosate is "unlikely" to cause cancers in humans [5].[6]

Although all reviews were well-intended and reflected similar scientific objectives and principles for reviewing scientific evidence, they ultimately applied somewhat different review methods, and not all methods were adequately transparent to determine specifically why different conclusions were reached based on the same body of evidence. Ultimately, while some assumptions and subjective decisions inevitably are necessary at several steps in conducting systematic reviews, these simply need to be stated and explained to maintain transparency, acknowledging that others may not agree. However, such transparency provides an essential starting point for productive, focused dialogue on such differences of opinion so that they may be adjudicated, preferably based more on science than bias or opinion.

<u>MSHA's literature review appears not to have been systematic</u>

MSHA's description of the methods used in conducting the literature review appears either to have omitted several important steps that might have been performed in conducting a scientifically sound and transparent systematic review or failed to clearly document the steps. Nevertheless, as in any peer-review of a scientific study (e.g., as in the role of a medical or health journal editor or peer-reviewer), the identification of major gaps and areas of ambiguity in the study (in this case review) methods and materials (in this case the body of studies included for review, as well as those specifically excluded) generally results in constructive recommendations for substantive revision but sometimes, in the interest of upholding scientific standards, rejection.

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[5] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions version 6.2 (updated February 2021). Cochrane 2021:2021. Available from, www.training.cochrane.org/handbook

[6] Lynch, H.N., K.A. Mundt, D. Pallapies, P.F. Ricci. 2022a. Lost in the woods: Finding our back to the scientific method in systematic review. Global Epidemiol. 4:100093. https://www.sciencedirect.com/science/article/pii/S2590113322000232

To assist MSHA in identifying and remedying these gaps, I provide the following list, which I do not claim to be comprehensive. Based on my review, I find the following to be missing, incomplete or ambiguously addressed in the proposed MSHA rule:

- One or more clearly formulated and articulated research questions and associated hypotheses;
- Explicit criteria for individual study inclusion or eligibility and exclusion, as well as the rationale for both;
- Definition or roadmap for the literature search methodology, i.e., the search engines or databases used; additional manual searches if any; search terms and keywords used, etc. The results of searches usually are presented graphically to demonstrate at each step of the search and selection process the counts of paper retained for the next step(s) and often identify specific papers excluded, especially those excluded toward the end of the screening process;
- Methods used as quality checks to verify the completeness and accuracy of study inclusion and exclusion decisions;
- Identification and definition of the metrics employed for assessing individual study quality and validity of the results reported for informing each specific review hypothesis;
- Methods used as quality checks to verify the quality ratings assigned to various aspects of individual studies, e.g., engaging two or more independent reviewers and means by which disagreements are adjudicated;
- Summary table of key results from original studies that inform each specific review hypothesis (as separate hypotheses require exposure-disease specific study results);
- Definition of and criteria for applying quality ratings and weighting prior to synthesizing study results across studies);
- Approach and specific methods used to synthesize, summarize, and interpret the body of evidence;
- Clear statement of conclusions, substantiated by the integration of evidence;
- Discussion of the strengths and weaknesses of the review (including the source data, e.g., most studies were based on small numbers, study results were too heterogeneous to combine, etc.) including some indication of the strength, precision, and confidence in the stated conclusions; and
- Descriptions of any independent expert or peer-review of the draft review (internally and externally to the Agency) prior to publication.

To the extent that any of the identified gaps or omissions actually had been addressed as part of the MSHA review (including by OSHA in the review MSHA relies upon), it is recommended and requested that MSHA make them available and transparent as part of this proposed rule, so that differences in interpretations and conclusions might be understood and possibly explained (at least in part) by differences in review methods used, facilitating scientific discussion and remediation. If key methodological steps had not been performed or incompletely performed, a major revision of the literature review portion of the proposed MSHA rule may be warranted.

MSHA's proposed rule may have over-relied on OSHA's 2013 literature review

Although utilizing a prior review to help inform and shape an updated review is commonly done and often acceptable, it does not completely satisfy the scientific standard of describing and documenting in sufficient detail all methods and materials used in the research effort, especially when the parent review is old and possibly obsolete – both methodologically and with respect to the data that have been generated (in this case, in the decade) since. Much of my commentary in the previous section highlighting state-of-the-art perspectives and methods for conducting systematic reviews reflects major developments achieved only in the last decade. Relying on a previous review also does not preclude the need to define the review methods and document transparently that the methodology (or at least some methodology) was followed from the inception of the original review through the updated review.

MSHA acknowledged that it relied heavily on the review conducted by OSHA: "To develop this literature review, MSHA expanded upon OSHA's (2013b) review of the health effects literature to support its final respirable crystalline silica rule" (RIN 1219-AB36 document p. 60). This also would have provided an opportunity to justify using a more dated methodology, or at least describing the decision to do so a possible weakness of the current review. Nevertheless, the detailed methods used in the OSHA review at least should be summarized, referenced, or explained, as well as all methods used by MSHA to "develop" and "expand upon OSHA's review" added to the documentation of methods.

The following table summarizes general systematic review principles and a summary assessment of the degree each was addressed by MSHA in its proposed rule:

Summary of Systematic Review Principles and Areas addressed in the 2023 proposed MSHA Rule

Systematic Review Principles	**Addressed in 2023 proposed MSHA Rule?**
Early assessment planning and problem formulation	Partially
Standardization of review and evaluation approaches across reviewers	No
Transparent and well documented methods	No
Comprehensive and well documented literature review and article selection process	No
Incorporation of Mode of Action (MOA) into hazard assessment approach (e.g., selection of outcomes of concern)	Partially
Standardized approach to data abstraction/tabular summary	No
Standardized study quality evaluation approach	No
Clear and consistent evidence synthesis method and narrative	No
Clear evidence integration using Bradford Hill or similar causal approach	Partially
If conducting quantitative dose-response analysis, consider quality and limitations of studies	No
Clear guidelines for selection of studies and derivation of toxicity values/ data pooling approaches	No
Well described and justified use of dose-response models	No
Thorough discussion of uncertainty and variability in all steps of review	No

From the summary table, even assuming that some of the specific summary assessments are incorrect, the overall impression is that the methods used to critically review and synthesize the epidemiological literature and body of evidence regarding occupational crystalline silica exposure and risk of silicosis and lung cancer fall short of current standards for performing systematic reviews, as advocated by numerous other Agencies in the US and worldwide (Lynch et al. 2022a).[7]

Because of these substantive limitations, the MSHA literature review scientifically cannot be replicated, verified, or confirmed. This does not necessarily mean that all conclusions therefore are incorrect or invalid, as some might be correct, e.g., proper methods were used but not described; because the evidence is so strong, any method leads to a valid conclusion; the correct conclusion was reached by chance (good luck), etc. However, it does underscore that the quality of review methods cannot be verified directly due to the lack of proper documentation of the methods used. Unless documented, it would be inappropriate scientifically to assume that current systematic review methods were employed and that the interpretations and conclusions are necessarily valid. This is akin to accepting and relying on the results of a scientific experiment without any knowledge of how the experiment was conducted.

[7] Lynch, H.N., K.A. Mundt, D. Pallapies, P.F. Ricci. 2022a. Lost in the woods: Finding our back to the scientific method in systematic review. Global Epidemiol. 4:100093. https://www.sciencedirect.com/science/article/pii/S2590113322000232

Therefore, I strongly recommend that MSHA either demonstrate that some acceptable framework for conducting systematic reviews was followed (both by OSHA and MSHA in updating and expanding the 2013 OSHA review) or conduct a new review of the literature that approaches if not meets or exceeds modern standards.

Section 2: Comments on specific statements from MSHA's literature review

In this section, I provide specific comments in response to specific statements made by MSHA discussing the literature review. Statements derived verbatim from the proposed MSHA rule document or review of health effects literature document are ***presented in bold italics below***, followed by my response and commentary:

MSHA Statement

> ***MSHA also drew upon numerous studies conducted by NIOSH, the International Agency for Research on Cancer (IARC), the National Toxicology Program (NTP), and other researchers. These studies provided epidemiological data, morbidity (having a disease or a symptom of disease) and mortality (disease resulting in death) analyses, progression and pathology evaluations, death certificate and autopsy reviews, medical surveillance data, health hazard assessments, in vivo (animal) and in vitro toxicity data, and other toxicological reviews." (pg. 60, MHSA proposed rule - Lowering Miners' Exposure to Respirable Crystalline Silica and Improving Respiratory Protection****)*

Response

MSHA is not explicit and does not specifically identify the "numerous" studies mentioned. It is not surprising that a body of studies conducted by several Agencies – and "other researchers" (which is unlimited) would provide data on the entire range of possible types of studies from various fields. While it is somewhat reassuring that MSHA recognizes that the totality of the (presumably peer-reviewed published) collection of "studies" is vast and diverse, it does not assist the reader of the MSHA review in narrowing that universe to the subsets of studies from each line of scientific inquiry that are of adequate design and quality to address if not inform specific scientific (in this case review) research questions and associated hypotheses.

For example, how was evidence from different types of epidemiological studies and reviews evaluated on the basis of scientific quality, and how was underlying quality of evidence weighed in the synthesis of evidence leading to evidence-based conclusions? As discussed in more detail above, MSHA appears not to have identified or employed (or failed to document its use of) any study quality assessment framework or tool consistent with current standards for conducting systematic reviews. Most importantly, how did the literature review and its direct conclusions translate into and help substantiate the conclusions stated in the proposed MSHA rule?

MSHA Statement

> ***To examine the health effects of respirable crystalline silica, MSHA reviewed a wide range of health research literature that included more than 600 studies that explore the relationship between respirable crystalline silica exposure and the resulting health effects for miners in multiple mining industries within the MNM and coal mining sectors. (pg. 1 "Effects of Occupational Exposure to Respirable Crystalline Silica on the Health of Miner – Review of health effects Literature - Docket ID No. MSHA–2023–0001")***

Response

As with the previous highlighted statement and my response to it, having "reviewed a wide range of health research literature that included more than 600 studies" sounds impressive (and represents a lot of work!) but if such review is not done in a systematic way using transparent and documented methods, the effort may not necessarily be scientifically rigorous or balanced. Again, what were the search parameters and databases (PubMed; Web of Science etc.) used to identify candidate studies, and what inclusion/exclusion criteria were applied? Where is the documentation identifying each of these 600+ studies? How many of the 600+ studies were irrelevant to the specific hypothesis in hand (as each hypothesis likely has its own universe of relevant papers), or were repeat or overlapping publications, or were of such poor quality that they were uninformative? How many studies remained after such basic screening methods were applied? How many "key" studies were identified as meeting at least minimal (preferably stated) quality criteria for inclusion in considering each scientific review hypothesis? For these key studies, what was the study design, study population size, source of the study population participants and/or data, potential confounding factors and whether they were adequately controlled, source and likely validity of health outcome data, source and quality of exposure measurement data (if any) or exposure surrogates used, study results selected for consideration in the literature review – and rationale for selecting these and excluding others, etc.?

The complete list of what could or should have been done (and not assuming that they were not performed, but if so, they were not documented) would be quite long; however, it is clear that even the most basic description of the methods used (again, assuming that standard methods were used) to search for and to evaluate for quality the individual studies or the "data" used in the review have not been documented adequately to allow the review to be replicated independently. Therefore, as a peer-reviewer, I consider the literature review on which important scientific and occupational health decisions regarding crystalline silica exposure will be based appears to be of questionable scientific methodological quality.

MSHA Statement

> ***MSHA's literature analysis is based on a weight-of-evidence approach, in which studies (both positive and negative) are evaluated for their overall quality. (pg. 1 "Effects of Occupational Exposure to Respirable Crystalline Silica on the Health of Miner – Review of health effects Literature - Docket ID No. MSHA–2023–0001")***

Response

"Weight of evidence" has become cliché, and now is used in many different contexts with different intention and meaning. If as literally implied, MSHA "weighted" studies based on their "overall quality," then one major problem immediately arises: for what research question or hypothesis was any study selected? This is not trivial. Epidemiological studies, for example, might be designed specifically to address a central research question such as, at what cumulative exposure levels does occupational exposure to crystalline silica increase the risk of silicosis (defined by radiological surveillance and confirmed ILO score of 1/1 or higher based on three independent B-readings)? Other studies might be interested in documenting the mortality patterns including silicosis mortality demonstrated after following cohorts of workers highly exposed to crystalline silica for decades. While both studies might be evaluated for overall quality and classified as even "high quality," they clearly are not of comparable quality with respect to the question of silicosis morbidity – a far more sensitive indicator of silicosis than silicosis mortality. Based on my own experience with the German Porcelain Workers Study, we identified a total of 40 silicosis cases based on an independent double-blind re-reading all x-rays of workers with at least one original x-ray from the medical surveillance program with a B-reading of 1/0 or higher by trained B-readers; however, based on standard mortality records, we identified only five silicosis deaths.[8] Had these two sets of results been published as separate studies (based on the same cohort but using different methods for ascertaining silicosis outcome – x-ray surveillance vs. mortality), they both might have been classified as "high" quality, but for the specific stated hypotheses, one was far superior than the other. Thus, the basic approach to "weighting" studies based on their "overall quality" does not necessarily lend itself to a valid weight-of-evidence synthesis and can be quite misleading.

Unfortunately, the MSHA literature review and synthesis – including methods for performing a "weight-of-evidence" synthesis – remains too incomplete and vague to be certain of what was done and if done properly, whether any conclusions can be substantiated transparently and scientifically. Furthermore, if such "weight-of-evidence" was based solely on overall study quality and not grounded in any specific scientific review hypothesis, the methodology may not be of adequate quality, and any conclusions based on it may not be reliable for purposes such as policy- or rule-making or even legal decision-making.

<u>MSHA Statement</u>

> ***Factors MSHA considered in this weight-of-evidence analysis included: size of the cohort studied and power of the study to detect a sufficiently low level of disease risk, duration of follow-up of the study population, potential for study bias (such as selection bias or healthy survivor effects), and adequacy of underlying exposure information for examining exposure-response relationships. (pg. 2 "Effects of Occupational Exposure to Respirable Crystalline Silica on the Health of Miner – Review of health effects Literature - Docket ID No. MSHA–2023–0001")***

<u>Response</u>

As discussed in the previous response, an adequate description of the "weight of evidence" approach and methods used by MSHA was not provided and should be included and documented specifically as to what it was, how it was applied in the literature review and how it was used to substantiate scientifically the conclusions in the final rule.

The general factors listed in the statement do reflect an appreciation of some of the key characteristics of epidemiological studies that affect study quality and therefore the quality of the evidence reported and used in the MSHA literature review. The importance of not only acknowledging these aspects but also in fact transparently documenting the methods and how they were applied specifically in a systematic review has been discussed in several places above and need not be repeated.

Additionally, however, when such methods are transparently reported, more explicit definitions also should be noted. For example, from the statement above, "size of the cohort studied and power of the study to detect a sufficiently low level of disease risk" is not sufficiently clear. At the most basic level, what does "sufficiently low level of disease risk" exactly mean? Silicosis in the general population is extremely rare, therefore a doubling of this is not particularly difficult in any setting where occupational respirable crystalline silica exposure is intense, and as few as three observed cases of silicosis would not be surprising and possibly even statistically significant. Is this hypothetical study of adequate statistical power to detect a low level of disease risk? It appears that it actually was, by detecting a statistically significant elevated risk. By conventional statistical power calculations performed prior to a study, however, the study sample size calculation unlikely would have indicated sufficient statistical power.

On the other hand, in the German Porcelain Workers Study, we reported 94 lung cancer deaths, a number that appears to satisfy most expectations for adequate statistical power. However, and even focusing on the 74 lung cancers occurring among men only, we reported an SMR of 0.71 with a 95%

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[8] Mundt KA, Birk T, Parsons W, Borsch-Galetke E, Siegmund K, Heavner K, Guldner K. Respirable crystalline silica exposure-response evaluation of silicosis morbidity and lung cancer mortality in the German porcelain industry cohort. J Occup Environ Med. 2011 Mar;53(3):282-9. doi: 10.1097/JOM.0b013e31820c2bff. .]

confidence interval (CI) of 0.56–0.89.[9] While this was unexpected, this study demonstrated adequate statistical power to detect a 29% deficit risk of lung cancers (at face value a 'protective' vs. 'risk' factor), and this SMR is highly statistically significant. This also means that our study was adequately statistically powered to detect a 29% excess risk of lung cancers (but obviously did not). This illustrates just how important a simple statement about statistical power can be misunderstood (or meaningless) without any context, i.e., based on any specific research question or hypothesis, as well as explicit statements regarding the size of effect one wishes to identify with sufficient statistical power to reasonably rule out chance occurrence.

Much more difficult to understand without detailed information and well-stated definitions is what specifically meets the expectation of "adequacy of underlying exposure information for examining exposure-response relationships." Ultimately, each of the study characteristics listed would benefit not only from more explicit definitions, but also doing so in the context of specific scientific review questions. Using the "duration of follow-up of the study population" as an additional example (also a surrogate for exposure), and again using the German Porcelain Workers Study to illustrate, our follow-up of 21 years identified 40 verified silicosis cases (Birk et al. 2009). Ironically, in updating this cohort an additional 15 years with follow-up through 2020 (work in progress), we anticipate far fewer new silicosis cases, suggesting that the original follow-up was "adequate" to identify a large majority of the silicosis cases to arise from this cohort. However, and although we reported 94 lung cancer deaths in the cohort, IARC dismissed the study and its findings on the basis of what they largely considered to be too short a follow-up period to accommodate the long latency period associated with lung cancers.

Similar questions arise regarding review methods used to identify the potential for study biases. There are many different types of study bias – some more common for certain types of epidemiological studies than others. For example, in the category of "underlying exposure information for examining exposure-response relationships exposure," self-reporting of historical exposures as commonly relied upon in case-control studies is far more susceptible to recall, rumination and reporting biases than the detailed job exposure matrices constructed using historical industrial hygiene monitoring data and precise personnel employment history records.

Although the number of additional illustrations of the criticality of clear documentation of methods could be very long; however, in each case the underlying message remains the same: methods used to evaluate individual published studies for quality and synthesis for literature reviews conducted today should be systematic, transparently reported and followed for each hypothesis being evaluated.

MSHA Statement

> ***Causal inferences are drawn based on a determination of whether there is substantial evidence that exposure increases the risk of a particular adverse health effect. In making this determination, MSHA used conventional criteria for evaluating epidemiology studies, including: the strength of the association between exposure and outcome, consistency with other findings, specificity, evidence on whether exposure preceded outcome, biological plausibility, coherence, degree of support by experimental findings, and reasoning by analogy. (pg. 31 "Effects of Occupational Exposure to Respirable Crystalline Silica on the Health of Miner – Review of health effects Literature - Docket ID No. MSHA–2023–0001")***

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[9] Birk T, Mundt KA, Guldner K, Parsons W, Luippold RS. Mortality in the German porcelain industry 1985-2005: first results of an epidemiological cohort study. J Occup Environ Med. 2009 Mar;51(3):373-85. doi: 10.1097/JOM.0b013e3181973e19. .]

Response

The MSHA statement appears to be referring to some of the nine "viewpoints" posed by Sir Austin (Bradford Hill) nearly 60 years ago, from which he claimed one should examine the evidence before crying causation.[10] Interestingly, although advanced in his appreciation of what epidemiology might have to offer in the objective consideration of causality – in contrast to his occupational medical colleagues whom he was admonishing for scientific consideration in assessing observed associations, Sir Austin unlikely considered the viewpoints criteria for evaluating individual epidemiological studies (or even "causal" criteria as commonly held). This is consistent with modern understanding and convention that causality likely never can be based validly on the reported associations seen in any one epidemiological study. Nevertheless, "strength of association" clearly applies to the magnitude and precision of epidemiological relative risk estimates, and temporal sequence of exposure relative to outcome is just logical – not necessarily epidemiological. Another of Sir Austin's viewpoints that has great epidemiological relevance is biological gradient, or more specifically exposure-response in epidemiological studies. <u>It in fact is considered the single most important of the nine viewpoints in supporting causal inference based on experimental and observational data of high quality. Surprisingly, it appears that MSHAs evaluation omitted this critical element, again, perhaps unsurprisingly, without explanation or justification.</u>

The remaining viewpoints claimed by MSHA to have been used in their review and assessment of epidemiological studies are not particularly relevant to epidemiological studies. For example, how does a study – say, a case-control study, of reported statistical associations between some cancer and dozens of self-reported historical exposures and behaviors elucidate "biological plausibility"? As a side note, this is not exactly one of Sir Austin's nine viewpoints – he identified "plausibility" and "biological gradient" (see above) separately. Plausibility (or believability) could be relevant for sorting out (especially implausible) observed epidemiological associations, but observing random associations in an epidemiological study likely does nothing to improve our understanding of biology.

Ultimately the MSHA statement suggests to me that a modern framework for conducting a systematic review was either not followed or not transparently documented. Also, the attempt to claim that some – but not all, and not the most important – of Sir Austin's viewpoints were incorporated into the literature review methodology must be described, if possible.

MSHA Statement

> ***Where MSHA identified studies that did not demonstrate a statistically significant relationship between respirable crystalline silica exposures and cancer, MSHA considered potential deficiencies in the study (e.g., study size, limited periods of follow-up, confounding factors) and whether additional evidence was available (pg. 220 "Effects of Occupational Exposure to Respirable Crystalline Silica on the Health of Miner – Review of health effects Literature - Docket ID No. MSHA–2023–0001")***

Response

There appears to be a conflation of two discrete concepts here. First, and as I have focused my comments above on the importance of objectively evaluating individual studies for quality (for each scientific review hypothesis that the study might inform), standard systematic review methods and guidance consistently recommend that individual study quality be assessed first, independently of what that study's results might indicate. For example, the best study ever published on a given topic and that provides quality evidence informing a key hypothesis might not report a statistically significant relationship between the exposure and outcome of interest. However, if a reviewer has a preconceived notion of what a study <u>should have reported and expends additional effort to discredit it</u>, this might

[10] Hill AB. Inaugural Meeting. *Proc R Soc Med.* (1965) 58:289.

indicate a lack of reviewer objectivity or bias. Much of the underlying purpose of conducting systematic reviews is to support the reviewer in avoiding such potential biases (akin to double blinding in clinical trials) and following the most transparent and objective methods (again, well formulated research questions and detailed descriptions of data and methods are critical). Trying to "explain away" or make a special effort to identify weaknesses late in the systematic review largely defeats some of the central objectives of the process, and invites subjectivity.

When sound systematic review methods are faithfully followed, heterogeneity in the results or even outliers across (or even within) studies will be no surprise. However, the systematic reviewer strives to assess objectively and transparently, and to synthesize the data (i.e., relevant results reported in studies of adequate or higher quality) to determine what the collective body of evidence indicates – including its strengths and consistency as well as inconsistencies and limitations. If a sound systematic review fails to reject a null hypothesis (that the evidence is insufficient to reject the primary hypothesis), scientifically, one must accept and report that finding. If some high-quality study generates results that are contrary to the broader body of evidence generated by studies of comparable quality, it would be reasonable for the reviewer to consider that result an outliner. As science is dynamic, one also must be open to the possibility that yesterday's conclusion – or even today's conclusion – may be found to be incorrect tomorrow.

Section 3: Examples of epidemiological studies potentially informative in evaluating whether miners' current exposure to respirable crystalline silica presents a risk of material health impairment (limited to silicosis and lung cancers)

It is well established that at relatively high concentrations and over long exposure periods, respirable crystalline silica presents "a risk of material health impairment," for, i.e., cause, silicosis and lung cancer. Several epidemiological investigations have confirmed a causal relationship between workers in industries such as mining, potteries and quarrying historically exposed to large amounts of respirable crystalline silica and are at increased risk of silicosis and possibly lung cancer. However, it also has become clearer over time and with stronger studies that quantify crystalline silica exposure and rely on more sensitive diagnostic technologies than death certificates to quantify risk that silicosis and lung cancer risks increase significantly after some exposure thresholds are exceeded. As exposures that increase silicosis risk are believed to be lower than those that likely increase lung cancer risks (though this is not entirely clear) it often is stated in the scientific and occupational medical literature that preventing silicosis should also prevent crystalline-silica-related lung cancers. Silicosis appears not to occur among workers exposed only to low-to-ambient concentrations of respirable crystalline silica; however, the amount of exposure (in terms of intensity, duration, or cumulative exposure) that increases risks of these remains an important research topic. One aspect that complicates identification of exposure thresholds for lung cancers is the powerful potential confounding effects of cigarette smoking. Nevertheless, studies that quantify crystalline silica exposures and (for lung cancers) have individual smoking history data provide the greatest potential for improving estimates of exposure thresholds for these diseases.

A recent cohort study by Lenander-Ramirez et al. (2022) of 1,752 Swedish foundry workers with quantitative estimates of silica exposure and 26,218 person-years at risk reported a high and statistically significantly increased risk (SIR=45.87) of silicosis among the "high respirable silica exposure" group with

>0.39 mg/m^3-years. This result was based on six silicosis cases with zero cases reported in the lower exposure groups.[11] (NOTE: this appears not to have been considered in the MSHA literature review)[12]

Similarly, Zhang et al. (2010) identified 48 silicosis cases in a 29-year cohort study of 2,009 Chinese automobile foundry workers with 31,751 person-years of follow-up (NOTE: this appears not to have been considered in the MSHA literature review). The authors reported that “Incidence of silicosis was expected to be 44.6 per thousand with average daily exposure to 4.18 mg/m^3 of silica for 30 years, and if incidence of silicosis was expected to be less than 1 per thousand, their daily average exposure to silica should be controlled below 0.2 mg/m^3 for 20 years of employment, or below 0.1 mg/m^3 for 30 or 40 years of employment (Fig. 3).” (p. 126)[13]

Mundt et al. (2011) quantified the silicosis and lung cancer risks among a cohort of 18,000 German porcelain workers occupationally exposed to respirable crystalline silica. The authors concluded that a cumulative respirable crystalline silica exposure of more than 4 mg/m^3-years or average respirable crystalline silica exposure and more than 0.15 mg/m^3 were strongly associated with the development of silicosis but the same exposures were not related to risks for the development of lung cancer.[14]

The MSHA review did address this study:

> *Of interest in this cohort was that workers exposed to cumulative respirable crystalline silica exposures of greater than 3,000 µg/m3-years (> 3.0 mg/m3-years) had significant silicosis HRs (i.e., approximations of RR). This was true: 1) for the full cohort (HR: 3.1; 95 percent CI: 1.1 – 9.3), 2) if exposures lagged for 10 years (HR: 3.7; 95 percent CI: 1.4 – 9.9), or 3) if analyses were limited to those workers hired since 1960 (HR: 4.2; 95 percent CI: 1.2 – 15.1). This exposure equates to a 45-year working lifetime annual exposure of 70 µg/m3 (0.07 mg/m3) respirable crystalline silica. The results for lung cancer were equivocal, with some elevated risks that were not statistically significant.” (p. 206)*

Had most or all of our silicosis cases worked as long as 45 years in exposed jobs, the MSHA calculation would be more reasonable (but not necessarily correct, as exposures in the German porcelain industry declined precipitously over the last several decades). However, based on the data we present in Table 3 of our publication, it appears that half of the cases diagnosed with silicosis had worked less than 30 years and half had worked more than 30 years at the time of their silicosis diagnosis. Therefore few, if any, of these cases likely worked as much as 45 years. If we divide the 4 mg/m^3-yrs (the threshold above which we demonstrate elevated risks) by 30 years (rough but conservative estimate of average duration of exposure) we get 0.13 mg/m^3- this is nearly 2-fold higher than the number presented in the literature review for our paper - and more consistent with our findings presented as average exposure (risk elevated above 0.15 mg/m^3).[15] Also apparent from Table 3 in the publication is that duration of employment was nearly unrelated to silicosis risk in the study population, and that those employed

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[11] Lenander-Ramirez A, Bryngelsson IL, Vihlborg P, Westberg H, Andersson L. Respirable Dust and Silica: Respiratory Diseases Among Swedish Iron Foundry Workers. J Occup Environ Med. 2022 Jul 1;64(7):593-598. doi: 10.1097/JOM.0000000000002533.

[12] MSHA regularly notes its preference for studies of miners, but this and other studies below that were not considered in the MSHA review are examples of studies that provide insights as well as data that might help the specific hypotheses being evaluated.

[13] Zhang M, Zheng YD, Du XY, et al. Silicosis in automobile foundry workers: a 29-year cohort study. Biomed Environ Sci. 2010;23(2):121-129. doi: 10.1016/S0895-3988(10)60041-4.

[14] Mundt KA, Birk T, Parsons W, Borsch-Galetke E, Siegmund K, Heavner K, Guldner K. Respirable crystalline silica exposure-response evaluation of silicosis morbidity and lung cancer mortality in the German porcelain industry cohort. J Occup Environ Med. 2011 Mar;53(3):282-9. doi: 10.1097/JOM.0b013e31820c2bff.

[15] Mundt KA, Birk T, Parsons W, Borsch-Galetke E, Siegmund K, Heavner K, Guldner K. Respirable crystalline silica exposure-response evaluation of silicosis morbidity and lung cancer mortality in the German porcelain industry cohort. J Occup Environ Med. 2011 Mar;53(3):282-9. doi: 10.1097/JOM.0b013e31820c2bff.

more than 30 years were somewhat less likely to develop silicosis than those employed for less than 30 years (Mundt et al. 2011).

Another study (Morfeld et al 2013) using the German Porcelain Workers Study data estimated an exposure threshold value of 0.25 mg/m^3 (95% CI: 0.15 -0.30 mg/m^3) for respirable quartz dust concentration and silicosis incidence. [16] (NOTE: this appears not to have been considered in the MSHA literature review)[17]

In an extended follow-up of lung cancer and non-malignant respiratory disease mortality among California diatomaceous earth workers, the authors provided an updated mortality analysis among 2343 California diatomaceous earth (DE) workers, concluding, "For lung cancer, only the highest exposure category (>5.6 mg/m3-years), lagged by 15 years, produced a statistically significant hazards ratio (HR) (2.2, 95% CI 1.07 to 4.5). HRs for non-malignant respiratory disease (NMRD) mortality, regardless of lagging, exceeded 4.0 for the highest exposure categories (3.0 to <6.9 and >6.9 mg/m3-years). These results, taken together, are consistent with the hypothesis of a threshold in the effect of crystalline silica exposure on lung cancer and NMRD." (Mundt and Boffetta 2016)[18] (NOTE: this appears not to have been considered in the MSHA literature review)[17]

A recent modeling study (Cox LA 2019) confirmed the existence of exposure concentration threshold and duration threshold for respirable crystalline silica exposures below which it does not increase the risk of chronic inflammation or inflammation mediated lung diseases such as silicosis, or lung cancer. In other words, mathematical computer modeling studies re-emphasize the findings of several epidemiological studies that only respirable crystalline silica exposure concentrations in excess of a certain threshold, maintained for at least a certain minimum duration, can cause chronic inflammation eventually leading to silicosis and/or lung cancer.[19]

Thus, properly conducted epidemiological studies provide a critical "reality check" as to what can be linked with "material health impairment." While the examples provided above are not comprehensive, and are not meant to be representative, they are provided to demonstrate that the scientific questions underlying the proposed MSHA rule can be informed by studies conducted outside of the mining industry. Furthermore, the "determination" of any adverse health effect presumed to be caused by respirable crystalline silica must be placed into some valid context (i.e., exposure scenario) in which the health effects reasonably causally can be linked with such exposure, and the quality of the studies and the evidence on which such determinations are based is objective and transparent.

Conclusion

MHSA appears either not to have conducted a systematic review of the published epidemiological evidence addressing quantified levels (using one or more logical exposure metrics) of occupational crystalline silica exposure and risks of silicosis and lung cancers that aligns with current standards and frameworks for performing objective and transparent systematic reviews or did but failed to document it as one would document the methods in any scientific research effort. Therefore, the review, as

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[16] Morfeld P, Mundt KA, Taeger D, Guldner K, Steinig O, Miller BG. Threshold value estimation for respirable quartz dust exposure and silicosis incidence among workers in the german porcelain industry. J Occup Environ Med. 2013 Sep;55(9):1027-34.

[17] MSHA regularly notes its preference for studies of miners, but this and other studies below that were not considered in the MSHA review are examples of studies that provide insights as well as data that might help the specific hypotheses being evaluated.

[18] Mundt KA, Boffetta P. Extended follow-up of lung cancer and non-malignant respiratory disease mortality among California diatomaceous earth workers. Occup Environ Med. 2016 Jan;73(1):71-2.

[19] Cox LAT Jr. Risk Analysis Implications of Dose-Response Thresholds for NLRP3 Inflammasome-Mediated Diseases: Respirable Crystalline Silica and Lung Cancer as an Example. Dose Response. 2019 Apr 2;17(2):1559325819836900.

presented, cannot be replicated, or fully evaluated for its scientific validity and therefore it is unclear whether any of its interpretations of the literature and the conclusions and inferences are sufficiently reliable as a basis for rules, policies or other decision-making purposes.

I recommend that before the final rule is promulgated, MSHA revisit the methodology used by OSHA and by them in updating and expanding the decade-old OSHA review and more fully and transparently report the exact methods that were used to produce the literature review. If MSHA learns that current standard methods for conducting systematic reviews were not adequately employed in its literature review, it might be prudent to revise the literature review and all interpretations and conclusions drawn from or based on it.

Respectfully submitted,

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