ALPHA FOUNDATION FOR THE IMPROVEMENT OF MINE SAFETY AND HEALTH

Final Technical Report

Project Title: A Translation Project: How Best to Communicate Epidemiology to Improve Protection of Miners Health

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Organization: The Regents of the University of California

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Executive Summary (recommended length 1 page):

Epidemiologic studies of miners have historically underestimated the risks of chronic respiratory and cardiovascular effects from occupational exposures due to bias from the Healthy Worker Survivor Effect (HWSE). Familiar methods such as Standardized Mortality Ratios (SMRs) and hazard ratios from Cox proportional hazards models often yield counterintuitive results. For example, SMRs frequently indicate that a known hazard is not harmful and Cox models can produce nonmonotonic exposure-response patterns. Analytic approaches known as g-methods are available to correct for underlying biases, but these methods are complex to implement and difficult to describe, even for many epidemiologists. It is no surprise then that policy makers neither find the counterintuitive SMRs or hazard ratios persuasive, nor understand the results from g-methods.

Our goal is to reduce the risks of chronic disease from mining by developing and communicating educational materials responsive to the needs and interests of people in a position to modify mining methods or improve workplace and public policies. We relied on key informants and an advisory board knowledgeable and experienced in the mining industry to assist the investigator team with identifying best practice communication methods (both messages and messengers) for communicating the concepts of HWSE and Risk Assessment based on g-methods. We then developed, designed, and assessed a suite of educational material. This material has undergone several iterations incorporating feedback from stakeholders including our advisory board, key informants, the Alpha Foundation, and participants at the Annual Health and Safety Breakfast at the Society for Mining, Metallurgy, and Exploration (SME) in February 2023.

We developed a suite of educational materials for translating scientific information into understandable and actionable terms. Product #1 stands alone and is intended for readers with less time to absorb the material. Products #2 and #3 are longer and intended for readers with more time to engage with the material.

- Product #1: Healthy Worker Survivor Effect (HWSE) and Silica Exposure Infographics
- Product #2: Why Most Worker Studies Underestimate Health Risks of Long-Term Exposure
- Product #3: Excess Risk of Lung Cancer due to Silica Exposure in the Workplace

The educational material is ready for dissemination, and we have created a dissemination plan with several options. In addition to developing the final material and giving oral presentations based on this material to diverse audiences, we have influenced the addition of language about the impact of HWSE into the proposed MSHA silica standard. We are finalizing a paper for a peer review journal aimed at the critical reader of occupational health literature.

2.0 Problem Statement and Objective:

Studies of miners have historically underestimated the chronic health effects related to occupational exposures due to bias from Healthy Worker Survivor Effect (HWSE). Without correcting for this bias, results of epidemiologic studies can suggest that toxic exposures are only minimally hazardous - or even protective. When studies lead to such counter-intuitive results, people do not take the findings seriously – nor should they. Analytic methods, known as g-methods, are available to correct the bias. These methods, however, are complex, both to describe and to implement. For this reason, manuscripts applying g-methods have been published only in academic journals with a statistically-inclined readership. Most mining professionals have been unaware of literature relating to the Healthy Worker Survivor Effect in general and the complicated g methodology. We developed a suite of educational material translating HWSE, Excess Risk and G-methods to a policy-maker audience to aid in their interpretation of the occupational health literature. Our multi-step process included the following aims:

Aim 1: Develop an understanding of the stakeholders' informational needs and interests at baseline and then iteratively with drafts of the material.

Aim 2: Based on iterative feedback in Aim 1, develop a suite of educational material.

Aim 3: Prepare a dissemination strategy and/or disseminate this material.

3.0 Research Approach: The strategy and study design used to solve the problem should be clearly described. The specific tasks that were used to address the research objectives are to be identified and described to a level of detail that would allow another researcher to understand the methodology and experimental design used to achieve the research objectives.

We adopted an iterative and multidisciplinary approach for identifying which communication methods and channels are most effective to use in the translation of HWSE and g-methods. Audience-based interviews informed the strategy, content, messaging, and diffusion of the material directed to occupational health policy makers. The material further explains why failure to account for this bias leads to substantially underestimated risks and, ultimately, to practices and policies that may fail to provide adequate protections. The project was focused on effective communication, with modules designed to grab – and sustain – the attention of the key stakeholders using design and infographics. They are technically accurate (although less complete or nuanced than the literature) and communicated in a clear and engaging way.

Aim 1:
First, we engaged in a series of cross-cutting interviews with stakeholders in the mining community and the policy/regulatory arena. These interviews began early in the first year and continued, iteratively, throughout the project period to keep us on track and ensure that the materials we develop are useful for the targeted audiences. Additionally, we formed an advisory board comprising an industry representative, a former miner and labor organizer, and

a federal researcher, and met periodically to review the material, testing, and dissemination plan.

1a. In initial interviews we sought guidance on how best to communicate the translational material from members of the mining community as well as occupational health policy makers, union leaders, and occupational health and safety professionals. We also consulted with MSHA district managers and practitioners who provide technical assistance to MSHA, as well as representatives of NIOSH, trade associations, and the mining academy, who are in positions to move the translational information to actions designed to reduce health risks, such as silicosis, COPD, and lung cancer, arising from mining exposures.

1b. We then circled back to stakeholders at regular intervals during the project to present updated drafts of the written modules (developed in Aim 2) for their further input. Ongoing content/message testing helped to ensure communication was comprehensible, personally relevant, compelling, and motivated action (behavior) among the key stakeholder groups, both internal and external. Frequent input from stakeholders also helped identify areas for improvement or mid-course adjustments in the communication strategy, product development, and implementation.

Aim 2:
Develop the educational material.
2a. Explain basic concepts and how and why "traditional" epidemiologic methods fail to address HWSE, why the more sophisticated g-methods do better, and why they provide a sound basis for policy decisions. We explain how to interpret results from g-methods and how those results are different from, and potentially more useful than, results from traditional methods.

2b. Apply guidelines for using g-method results to quantify risk and provide the basis for intervention using silica exposure as the motivating example. The guidelines begin with a rejection of the standard approach and continue with translation of findings based on g-methods into intuitive language that can guide potential workplace interventions.

2c. In the late phase of the development, we beta tested the educational material by presenting the material to small groups, representative of the intended audience, but who were not involved in the earlier outreach interviews.

Aim 3: We prepared a dissemination strategy and partly disseminated this material. First, using an omni-channel approach, project milestones and accomplishments were disseminated via: Events – we attended an annual meeting of the Society for Mining, Metallurgy, and Exploration (SME) conference; and Media – targeted outreach to mining-specific trade and professional associations. As described in Aim 1, we engaged in a series of cross-cutting interviews with stakeholders in the mining community, policy/regulatory and practitioner arenas. Second, we are finalizing a pedagogical paper for a peer-reviewed trade journal using the material developed for the primary suite of material. Third, we influenced the inclusion of a section on HWSE into the MSHA Proposed Rule for Silica – the first time such material has appeared in any OSHA or MSHA Standard.

4.0 Research Findings and Accomplishments: The highlight of the report should be a detailed documentation and discussion of the research findings and accomplishments. The presentation of this material should be organized in a manner that clearly relates to the specific aims and research objectives for the project. Data and information developed from the project efforts should be presented with sufficient detail, analysis, and interpretation to support a clear and full understanding of the research conclusions derived from the project.

We conducted several in-depth, semi-structured interviews with members of the mining and regulatory community. The key informants included members of the following groups: industry leaders, senior regulatory officials, federal and academic researchers, union representatives, health and safety officers, communications experts, and retired miners. We extracted several themes from these initial interviews which we used to refine our target audience and develop the first draft of the material.

Motivating factors for voluntary adoption of improved mining practices

1) The key informants all agreed that changing exposure control practices in a mine setting involved a complicated calculation based on economic and legal considerations as well as scientific findings.
2) There was agreement that the threat of a lawsuit, potential for a monetary fine, or the threat of a new occupational standard - were motivating factors for adoption of improved practices. Short of these external motivations, the informants demonstrated little confidence that scientific results alone would tip the scales.

Preferred formats and sources for scientific information

3) Trustworthy sources of information include trade associations and government agencies.
4) There was a strong preference for material that summarized published literature.
5) There was a strong preference for results that were definitively stated and used regulatory language.

Based on this information, we narrowed our target audience to occupational policy makers. Our original goal was to try to promote voluntary change, but we heard that the scientific information we had to offer would have the most impact on policy makers who were interpreting occupational health research.

For our first round of material, we adopted a story framework– presenting the material from the viewpoint of an epidemiologist named Mary and introducing four potential miners, Jim, Sam, Rick, and Marvin. However, we received feedback from our advisory board that the story framework was not the right approach. Another pivot point occurred when we were advised to avoid the polarizing topic of diesel exhaust in our worked examples and concentrate our examples on silica dust exposure. Although we shifted tone/frameworks, we continued to intentionally avoid scientific jargon (e.g. “counterfactual” or “simulation”), words with different lay meanings (e.g. “bias” or “truth”), and the use of any formulas or causal diagrams. Finally, we were strongly advised to avoid the term “Risk Assessment”, because it is perceived as a

management strategy used to avoid actual risk reduction. We reframed this material as "Excess Risk Calculations".

We then concentrated on developing short infographics or handouts with just the main points. We presented a draft of the handouts at the Annual Health and Safety Breakfast at the Society for Mining, Metallurgy, and Exploration (SME). The overall project and draft handouts were well received, although it was not clear how many of the attendees deeply engaged with the material in the breakfast setting. The major lesson learned was that this group was very focused on the health of the individual worker, thus we needed to do a better job framing HWSE as a population-level problem that impacts studies of workers. Overall, there was a desire for more facts and examples regarding HWSE and Excess Risk Calculation. As a "teaser", the handouts seemed to do their job.

We then turned our attention to the longer explanations of HWSE and excess risk using g-methods in plain language for an audience without training in epidemiology. We developed figures and tables to illustrate our points and engaged with a designer to make the material more attractive. The feedback from stakeholders was uniformly positive regarding the explanation of the HWSE, although some still did not understand why they should care. Thus, we iteratively refined this section to highlight the key message. We received mixed feedback regarding the depth of the material for risk assessment and explanation of g-methods. Most stakeholders were not interested in engaging with the material in that much depth and advised us to cut dramatically; however, some wanted even more detail. We compromised by including a technical appendix for the explanation of the g-method for those who are interested.

5.0 Publication Record and Dissemination Efforts:

The products for this project include 1) the suite of educational materials, 2) incorporation of HWSE into the MSHA proposed silica rule, 3) talks on HWSE, and 4) a paper explaining HWSE for peer-review. We discuss each below and describe dissemination possibilities for the suite of educational materials.

The suite of educational materials for translating scientific information into understandable and actionable terms is attached to this final report. Product #1 stands alone and is intended for readers with less time to absorb the material. Products #2 and #3 are longer and intended for readers with more time to engage with the material.

- Product #1: Healthy Worker Survivor Effect (HWSE) and Silica Exposure Infographics
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This product has undergone several rounds of edits and refinements, including the incorporation of feedback from the Alpha Foundation in October 2023 which resulted in a major revision of Appendix 2.

Once the material has been approved by the Alpha Foundation, we will distribute it through our known networks including the Northern California Center for Occupational and Environmental Health Newsletter, the NIOSH Education and Research Centers director email list, and the Berkeley School of Public Health.

Depending on the time required and/or financial resources for travel and a small amount of salary support, other dissemination opportunities include:

- Incorporating this material into the Health and Safety book for SME, which targets mining professionals (Advisory board member Emily Hass is an editor).
- Approaching the editor of *Rock Products* publication for potential interest in publishing the material.
- Approaching the NIOSH Science Blog editors for potential interest in publishing the material.
- Presenting the material at the AIHA annual conference in their educational section.
- Approaching the National Stone Sand and Gravel Association about their interest in hosting a webinar or presentation at their annual convention.

Incorporation of HWSE into the MSHA proposed silica rule

By providing a less technical description of the bias, our translation material enabled policy makers at MSHA to take HWSE more seriously than they would otherwise have been able to do. Unlike any previous OSHA or MSHA Standard, the recently proposed MSHA silica standard (2023) describes, and explicitly incorporates, the healthy worker survivor effect (HWSE) into their risk estimates.[1]

Section VI.E (p150), "Healthy Worker Bias", in the Preliminary Risk Assessment of the proposed silica standard, describes the bias as follows:

> "The healthy worker survivor bias causes epidemiological studies to underestimate excess risks associated with occupational exposures. As with most worker populations, miners are composed of heterogeneous groups that possess varying levels of background health. Over the course of miners' careers, illness tends to remove the most at-risk workers from the workforce prematurely, thus causing the highest cumulative exposures to be experienced by the healthiest workers who are most immune to risk. Failing to account for this imbalance of cumulative exposure across workers negatively biases risk estimates, thereby underestimating true risks in the population."

It then goes on to describe results from a reanalysis of a pooled cohort study of silica and lung cancer[2] where it was estimated that the lifetime risk of lung cancer mortality was underestimated by 28% due to HWSE.[3] After adjusting the MSHA risk estimates for HWSE by increasing them 28%, however, they then step back from incorporating a specific % reduction into their final risk estimates. Instead, they state:

"MSHA believes adjusted estimates for the healthy worker survivor bias are more reliable than unadjusted estimates. However, given that the literature does not support specific scaling factors for *each of the health endpoints* analyzed, these adjustments for the healthy worker survivor bias have not been incorporated into the final lifetime excess risk estimates that served as the basis for monetizing benefits."

The concept of HWSE has not been incorporated into any occupational standard nor has it been explicitly incorporated into an IARC monograph which have a large influence on standards. The discussion of HWSE in the MSHA silica proposed rule is an important and meaningful step. The proposed rule can be found online:

Talks given to diverse audiences

Dr. Costello was invited to provide an overview of HWSE and g-methods to two groups during the period of this project. The material developed as part of this project was featured in these talks and the project fund number was credited.

1) "Healthy Worker Survivor Effect" Annual Danish Ramazzini Center Seminar, Aarhus Universitet, Denmark, October 3, 2023

2) *"Healthy Worker Survivor Bias"* Occupational and Environmental Health Interdisciplinary Grand Rounds, University of California, San Francisco, San Francisco, CA. October 27, 2022.

Peer-reviewed paper

We are finalizing a commentary in which we provide our explanation and graphics to an audience that accesses the peer-review literature. Our primary target audience for this paper include academics and other instructors who can use the material as a teaching guide.

6.0 Conclusions and Impact Assessment:

We have developed a unique and impactful suite of educational material to translate occupational health research concepts for people in a position to influence policy. These materials are responsive to the interests and needs of stakeholders from industry and government. We believe that this material solves the problem posed in our research proposal, has already had a positive influence on a MSHA standard, and has the potential to improve understanding of these complicated concepts if they are further disseminated.

7.0 Recommendations for Future Work:

Future work includes finalizing the peer-review paper and disseminating the final suite of educational products. The dissemination plan will utilize our current resources and networks, at the very least. A more extensive dissemination plan may require additional financial resources for travel and/or a small amount of salary to support ongoing efforts.

8.0 References

1. https://www.msha.gov/sites/default/files/Regulations/Proposed%20Rule.pdf

2. Steenland K, Mannetje A, Boffetta P, Stayner L, Attfield M, Chen J, Dosemeci M, DeKlerk N, Hnizdo E, Koskela R, Checkoway H. Pooled exposure–response analyses and risk assessment for lung cancer in 10 cohorts of silica-exposed workers: an IARC multicentre study. Cancer Causes & Control. 2001 Nov;12:773-84.

3. Keil AP, Richardson DB, Westreich D, Steenland K. Estimating the impact of changes to occupational standards for silica exposure on lung cancer mortality. Epidemiology (Cambridge, Mass.). 2018 Sep;29(5):658.

9.0 Appendices:

We are attaching our final suite of material.

Alpha Translation Project: Healthy Worker Survivor Effect and Excess Risk

An Example Based on Silica and Lung Cancer in Miners

ALPHA FOUNDATION
for the Improvement of Mine Safety and Health, Inc.

October 2023

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PRODUCT #1

Healthy Worker Survivor Effect (HWSE) and Excess Risk Summary

The longer people work in hazardous jobs, the more they are exposed to hazards. We expect more exposure to lead to greater risk of disease.

But exposure can make some workers ill quickly, and those workers change jobs or quit. The healthier workers stay at work longer and remain exposed. **The workers who accumulate the most exposure are also the healthiest, making toxic exposures appear less harmful or even beneficial-- a misleading conclusion.**

Studies of workers often underestimate risks of death or chronic illness because of this problem, called the Healthy Worker Survivor Effect--**HWSE.**

HWSE creates the appearance that hazards are safer than they actually are. If a study underestimates risk, then regulations that limit exposure based on the study will be too high to protect workers adequately.

Modern data analysis methods for studies that follow groups of workers over time can account for this underestimation. Rather than estimating risk from cumulative exposure over many years, these modern methods estimate the risk of disease from exposure in each year and then sum up the risks of disease over time. By avoiding HWSE, these studies can provide evidence to support more protective exposure limits.

An example of accounting for HWSE when calculating Excess Risk for Lung Cancer and Silica Exposure

Long term exposure to silica dust at work can increase risk of dying from lung cancer. Many factors in the general environment contribute to risk of lung cancer. The amount of **additional** risk **due** to workplace exposure is called “excess risk”.

To protect miners from excess risk, the government establishes regulations to limit exposure based on scientific studies and employers control the exposures at mines.

To do this, the government needs to know how much risk is caused by different levels of silica exposure, including the risk of lung cancer without exposure to silica. They then need to know the risks to miners exposed to silica at the current and proposed regulated limits. Excess Risk is the difference in risk between workers who are unexposed and workers exposed at different levels.

Calculating Excess Risk of Lung Cancer due to Silica Exposure Accounting for HWSE

- Scientists observe groups of miners exposed to silica over time to estimate the risk of lung cancer. They can use the observed data to answer causal questions about what the cancer risk would be under different exposure limits, accounting for HWSE.
- The government can then set a regulation that protects miners and is also technically and economically feasible for mine operators to achieve.
- The Table shows the results of a recent research study that pooled 10 different worker groups and estimated the causal effects of 45 years of silica exposure under different exposure limits on lung cancer risk.
- The MSHA PEL substantially reduces excess risk but the OSHA PEL would protect miners even more.

Excess Risk for Lung Cancer due to Silica Exposure in Miners*

Exposure Limit	Silica ($\mu g/m^3$)	Risk*** (per 1000)	Excess Risk (per 1000) due to Silica
Observed data**	>100	30.3	3.9
MSHA PEL	100	28.6	2.2
OSHA PEL & Proposed MSHA PEL	50	27.8	1.4
Unexposed Miners	0	26.4	-

*Keil AP, Richardson DB, Westreich D, Steenland K. Estimating the impact of changes to occupational standards for silica exposure on lung cancer mortality. Epidemiology (Cambridge, Mass.). 2018 Sep;29(5):658.
**Pooled data from 10 cohorts in several countries with no known exposure limits for silica
***Risk at age 80 based on a working lifetime of 45 years of exposure

PRODUCT #2

Why Most Worker Studies Underestimate Health Risks of Long-Term Exposure

Exposures at work that can make people sick include anything potentially toxic, such as diesel exhaust, silica particles, or radon gas. Studies can lead to better protection for workers by characterizing hazards which can, and should, be reduced. Silica exposure and lung cancer among miners provides a good example.

A well-designed and conducted study tries to answer basic questions to determine if there is a health risk to exposed workers, and, if so, how much?

No Increased Risk – If a specific substance is truly safe for humans, then a high-quality study will show that there is no increased risk of disease among workers who are exposed to that substance compared to workers who aren't.

Increased Risk – If the substance is truly hazardous for humans, a good study will demonstrate that people who are exposed to the substance are more likely to get a disease than those who aren't exposed.

Level of Risk – The most useful studies accurately estimate the level of risk resulting from different levels of hazardous exposure. Estimating risk at different levels of exposure requires first figuring out how much of a substance each worker has been exposed to, and for how long. Correctly specifying exposure levels is important because people who are exposed to more of a dangerous substance over their lifetime are more likely to experience health effects compared to people who are exposed to less, or none, of the substance.

Exposure-Response from Silica

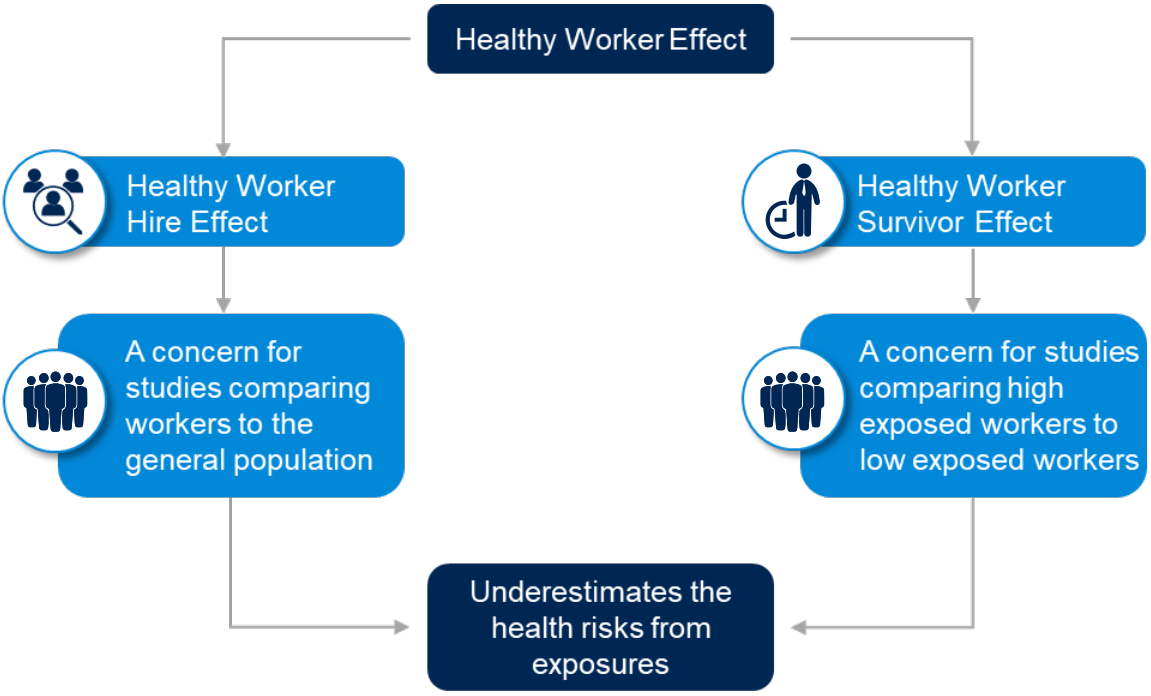
Miners exposed to high levels of silica are more likely to get a silica-related disease, such as silicosis or lung cancer, than miners with lower exposures. In addition, miners exposed to silica for many years are more likely to get sick than people who work with silica for only one year. These concepts are called "exposure-response": the more exposure a group of people have the more disease, or response, they will have.

Healthy Worker Effect

There are some problems that affect almost every occupational study of long-term exposure. One common problem is called the **Healthy Worker Effect;** it has two parts and can distort study results.

1. **Healthy Worker *Hire* Effect:** healthier people are hired in the first place.
2. **Healthy Worker *Survivor* Effect (HWSE):** healthier people stay longer at work.

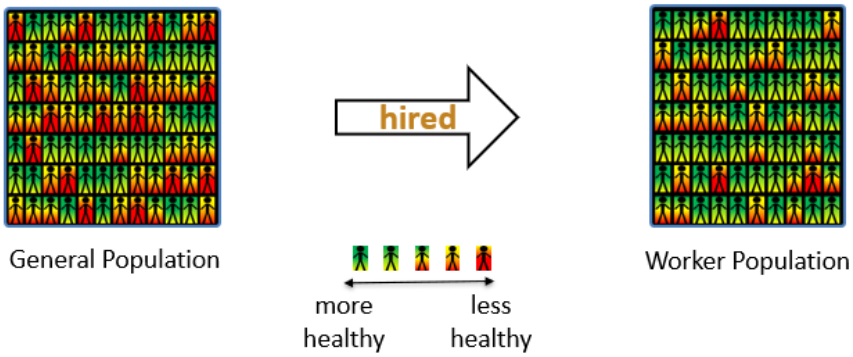
Both types of problems lead to underestimated results, which are a concern because they may lead people to conclude that a hazardous substance is less harmful than it really is. Falsely concluding that the substance is safe, or even "protective" against chronic heart or lung disease or cancer, will ultimately harm exposed workers because it will discourage control of the exposure.



Healthy Worker Hire Effect

Healthy Worker Hire Effect arises most clearly when jobs have physical demands or require a pre-placement medical evaluation; for example, prior to respirator use. As a result, healthier people tend to be hired into jobs like mining. The Healthy Worker Hire Effect is not a judgment on hiring or employment practices, but rather is a fact about working populations that can lead to underestimation in some types of studies.

Some occupational studies compare the health of a group of workers to the general public. When workers are compared to the general public, work like mining might appear to protect people from disease, but that's because it is not a fair comparison. One would expect a healthy group of young workers to live longer than a group that includes less healthy young adults, some too sick to be employed! As the figure below demonstrates, the general population includes a mix of people, some who are more healthy (green) and others who are less healthy (red). Those who are healthier (green) are more likely to be hired, on average, so that the hired population is healthier than the general public.



Healthy Worker Hire Effect

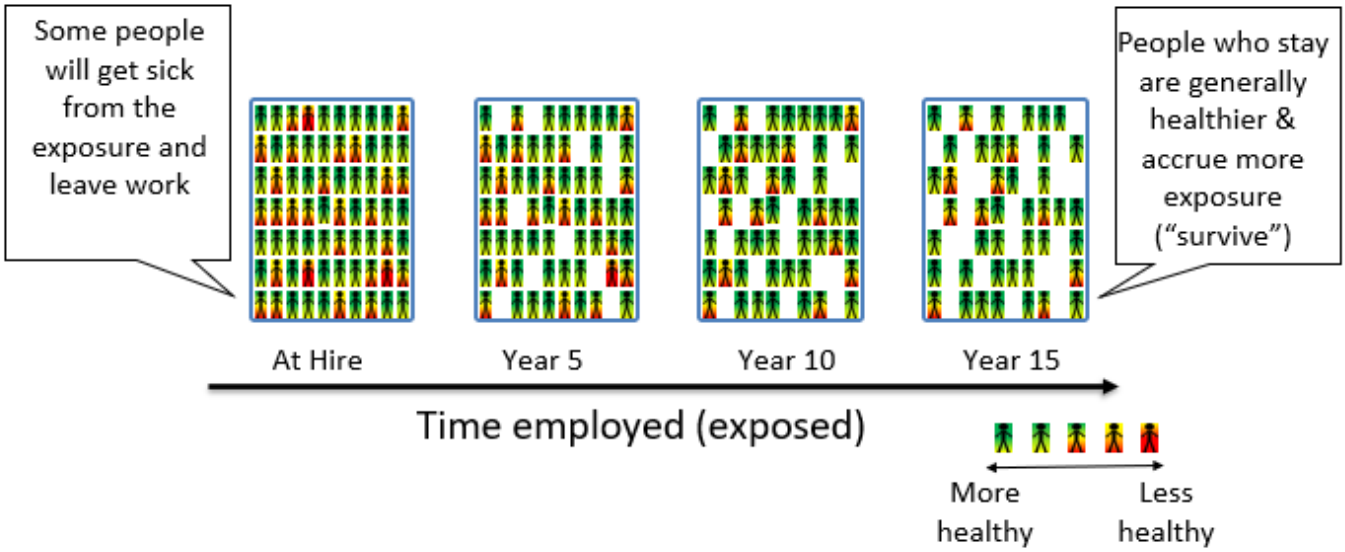
If researchers wants to know if high levels of silica exposure cause lung cancer, they might compare coal miners, who experience a lot of silica exposure, to the general population that doesn't work in mines. They expect that miners will be more likely to die from lung cancer than other people. However, the general population includes a greater proportion of people with poor baseline health that puts them at greater risk of cancer. Results from studies that compare workers to the general population usually result in work exposures paradoxically appearing "protective" against many chronic diseases.

Healthy Worker Survivor Effect (HWSE)

The most useful type of study compares miners with high exposure to miners with lower exposure. That way, researchers know that everyone was equally likely to be healthy when they were hired and share a lot of similarities with respect to work, so that any disease differences that occur are likely due to differences in their specific work exposures.

However, people leave work at different times and for different reasons. Some leave work because the exposure is making them sick. Therefore, the people who stay at work the longest are also, on average, the healthiest of the group that was originally hired. The Healthy Worker Survivor Effect (HWSE) simply refers to the fact that the workers who "survive" long tenures at work are healthier, on average, than their co-workers who left earlier for exposure-related reasons. Again, this isn't a judgment on retention practices or employee health programs, HWSE is just a reflection of the variation in biology among any group of people.

The figure below illustrates HWSE: as time goes by, people leave work and those who leave sometimes leave because of exposure-related health problems. On average, the people who leave work are more likely to be unhealthy (red) and so a greater proportion of healthier people (green) remain employed longer. Comparing the people who stay at work longer, thus acquiring the most exposure, with people who were at work for a shorter period of time may seem like a reasonable contrast. And in fact, such comparisons based on duration of employment are common in studies of workplace exposures--but it is not a fair comparison. As illustrated below, such unfair comparisons often lead to underestimates of risk.



It stands to reason that people who work with hazardous chemicals longer are more likely to get sick than shorter term workers. This is usually true, but because of HWSE, it often isn't clear in occupational studies. In large studies, we usually see an increased estimate of exposure-response when there is a hazardous chemical, but this may just be a signal -- only the tip of the iceberg. The fact that the workers who "survive" longest at work are a healthier subset of those hired leads to underestimation in studies that evaluate risk related to the duration of employment or cumulative exposure (exposure added up over a working life).

Healthy Worker Survivor Effect

We might expect that workers who had moderate levels of silica exposure for 40 years will be more likely to get lung cancer than workers with only 10 years of moderate exposure. However, workers who begin to develop silicosis or other lung problems may leave work after 10 years. So, comparing workers who stayed at work for 40 years to workers who stayed for only 10 years is not a fair comparison. It may look like working additional years is protective against developing disease – when really, it was a lack of silica-related lung disease that allows some workers to stay at work longer than others.

Conclusion

To summarize, the Healthy Worker Effect is a problem in occupational epidemiology studies because it can lead to underestimation of the health risks from hazardous exposures. There are two parts to the Healthy Worker Effect: 1) the Healthy Worker Hire Effect and 2) the Healthy Worker Survivor Effect. Both components lead to underestimation, but in different ways.

So, what should we take away from this? Understanding why many occupational studies underestimate the risk of exposure is a good start. A study that compares low exposed workers to high exposed workers avoids the healthy worker hire effect, which is a step in the right direction. However, even the best studies that compare high to low exposed workers can also underestimate exposure-related risk of disease. Duration of exposure (years) is often an aspect of how exposure is measured, either on its own or combined with daily exposure intensity (mg/m^3) into a “cumulative exposure” metric (mg/m^3-years). It is the necessary, but problematic, consideration of duration of exposure that gives rise to the heathy worker survivor effect.

There are ways to analyze data that side-step the HWSE and avoid underestimates of risk. These methods, known as g-methods, analyze the observed data to figure out what **would** have happened to those people who left work had they stayed and continued to be exposed. G-methods have been applied to estimate the exposure-response for several occupational hazards in relation to chronic disease and cancer, including silica. By paying attention to the Healthy Worker Effect when reading papers and relying on results from papers that apply g-methods to estimate the health risks from potential hazards, we can inform health standards to better protect workers.

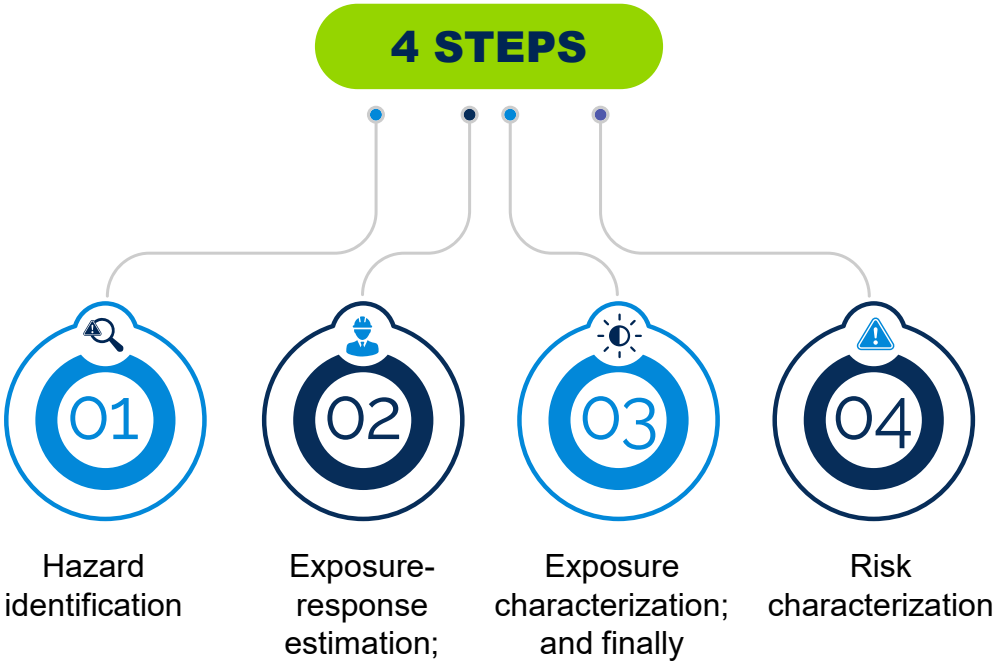
PRODUCT #3

Excess Risk of Lung Cancer due to Silica Exposure in the Workplace

Exposure to certain materials, such as silica, increases the risk of cancer in miners, construction workers, and others who are exposed to silica at work. But lung cancer can also result from other environmental exposures such as tobacco smoke, asbestos, or diesel exhaust or can occur for unknown reasons in people with no known hazardous exposure. Excess Risk is the additional risk of lung cancer for workers who are exposed to silica in the workplace above what it would be if unexposed. Both the government and employers have responsibilities to protect workers from excess risk. The government establishes and enforces regulations for better protection, and employers are responsible for following the regulations to protect their employees from excess risk.

To protect miners, the federal Mine Safety and Health Administration (MSHA) establishes permissible exposure limits based on scientific studies that answer questions about silica exposure and lung cancer risk, such as: What is the excess risk of lung cancer for miners exposed to silica at the current regulated limit? Are there feasible changes to the exposure limit that would reduce that risk?

To answer these questions about excess risk of lung cancer due to silica exposure, scientists and policy makers go through a sequence of four steps:



Step 1: Hazard identification

Silica has long been recognized as the cause of silicosis, a chronic deadly lung disease. In 1971, the OSHA Permissible Exposure Limit (PEL) of 100 μg/m^3 for silica was based on the risk of silicosis. (The PEL refers to the maximum level of exposure allowed under OSHA regulations.) However, in 1996, the International Agency for Research on Cancer (IARC) reviewed the science and classified occupational exposure to silica as a definite human carcinogen. In response to mounting evidence that silica also causes lung cancer, the Occupational Safety and Health Administration (OSHA) issued a new Silica Standard that reduce the PEL from 100 to 50 μg/m^3 in 2016. In 2023, MSHA issued a proposed Silica Standard reducing the PEL to 50 μg/m^3 in all mines. Both OSHA and MSHA relied on calculations of excess risk based on epidemiologic studies of workers exposed to silica to support reducing the PEL.

Step 2: Exposure-Response Estimation

For hazardous exposures such as silica, we expect that higher total exposure increases the chances of being diagnosed with disease. Total workplace exposure depends on how long someone is exposed and how much silica was in the air on the job. Silica exposure in air is measured by the concentration of respirable silica particles in a cubic meter—a bit bigger than a cubic yard—of air (μg/m^3). Policy makers want to know how much miners' risk of lung cancer would decrease if the permissible exposure limit (PEL) for silica were reduced to a lower concentration.

To answer this question, epidemiologists use observational data to compare lung cancer risk between groups of workers exposed to different amounts of silica and estimate the exposure-response. But because individuals are not randomly assigned to different exposure levels, it may be challenging to know how to interpret results accurately. For example, we might observe that individuals with greater total exposure to silica do not have higher rates of lung cancer. Although this may be surprising, it is not an unusual result. It can happen if people who are especially vulnerable to the respiratory effects of silica leave work after a few years, and those who stay at work are less susceptible to getting lung cancer from silica exposure.

Step 2: Exposure-Response Estimation, continued

If less healthy workers who are more susceptible to exposure tend to leave work sooner than healthier coworkers, those remaining at work longer are a healthy survivor subset of the original workforce. This is known as the healthy worker survivor effect (HWSE)**.** HWSE is a problem in occupational epidemiology studies because it can lead to underestimation of health risks due to hazardous exposures.

To estimate the exposure-response for lung cancer and silica, OSHA and MSHA both rely on high-quality studies of workers. One key study was based on combining 10 different cohorts of miners and other workers in China, South Africa, Finland, Australia and the U.S..[1] The results, based on several different measures of respirable silica exposure (cumulative exposure, intensity of exposure, logged exposure, and lagged exposure) provided quantitative estimates of lung cancer rate ratios associated with different levels of exposure. **This study, however, did not account for the healthy worker survivor effect.**

Several methods have been proposed over the years to account for the HWSE. These methods are straight forward to understand and implement and have been widely applied (See Appendix 1). However, despite their appeal, none of these methods work very well to avoid underestimating risks related to workplace exposure. It wasn't until the recent development of the more complex g-formula, that occupational epidemiologists were finally able to account for HWSE and accurately estimate exposure-response.

Step 2: Exposure-Response Estimation, continued

The g-formula was designed precisely to handle the challenge posed by HWSE to the accurate estimation of exposure-response in worker studies. The g-formula accounts for factors that vary over time, like employment status, that influence future exposure and the outcome (See Appendix 2 for an explanation of how and why the method works).

In a recent reanalysis of the same data from the combined study of lung cancer in 10 different populations of silica exposed workers, the g-formula was applied to account for the HWSE.[2] Results are presented in the first row of Table 1. Lifetime risk was then estimated in the same study under several interventions to limit respirable silica exposure. Respirable silica exposure limits of 100 (current MSHA PEL), 50 (proposed MSHA PEL) and 0 μg/m^3 were applied. Altogether, the lifetime risk of lung cancer estimated at each of the silica exposure limits in Table 1 presents the type of exposure-response information policy makers need to decide where to set the PEL. **By accounting for HWSE, the lung cancer risk estimates in Table 1 are 28% higher than they would be if HWSE was ignored.**

Table 1: Risk of lung cancer in a study of silica exposure in miners and other workers estimated under different exposure interventions[2]

Exposure Limit	Silica (μg/m^3)	Risk of lung cancer (per 1000)**
Observed data (No intervention)	>100*	30.3
MSHA PEL	100	28.6
OSHA & Proposed MSHA PEL	50	27.8
Unexposed	0	26.4

* The range of exposure extended to well above 100 μg/m^3 in the observed data from the study of 10 cohorts in several countries, some with no reported silica exposure limits.
**Risk at age 80 based on a working lifetime of 45 years of exposure

Step 3: Exposure Characterization

The next step needed to calculate excess risk is to characterize the total silica exposure of all workers by describing the duration and the daily intensity of exposure. The approach used at OSHA and MSHA to evaluate risk under a proposed PEL assumes that all workers are exposed at the proposed exposure limit for a working lifetime of 45 years. Many miners, however, would actually be exposed at concentrations below the proposed PEL and most would work less than 45 years in the mines. OSHA and MSHA's approach provides estimates of lung cancer risk that would be expected if all workers were to remain at work in the mines for their entire working life and be exposed at the limit.

In contrast with that approach, the cancer risks in Table 1 relied on the actual duration of employment observed for the miners in the pooled study. The range of exposures based on observed data and capped by each of limits considered above can be assumed to be representative of the silica exposures all miners.

Overall, risk estimates are more realistic if they both account for the healthy worker survivor effect and allow for real world variation in workplace exposure.

Step 4: Excess Risk Characterization

There are many different causes of lung cancer that contribute to the lifetime risk in miners, and only a portion of that total risk--called “excess risk”--is actually due to silica exposure. Evidence of the many other causes of lung cancer can be seen in the last row of the Table, where a high risk of lung cancer exists even when there is **no** silica exposure. **Excess risk** can be simply measured as the difference between the risk in the miner population under an intervention at a selected exposure limit compared to what the risk would have been if there had been no exposure to silica at all.

Table 2 below adds a final column for **excess risk** of lung cancer for each of the exposure limits considered, based on the research study.[1] Excess risk is the number of lung cancer deaths attributable to silica for every 1000 workers exposed. It is estimated as the difference between the lifetime risk (%) under each exposure limit and the lifetime risk if miners had not been exposed to silica at work at all. Lifetime risk is converted from a percent, N/100 (%), into N/1000 workers–the standard form for excess risk.

Table 2: Excess risk of lung cancer due to silica exposure in a combined cohort of miners and other workers [2]

Exposure Limit	Silica (ug/m^3)	Lung cancer risk (per 1000)	Excess Risk of Lung Cancer (per 1000) due to Silica Exposure**
Observed data*	>100	30.3	3.9
MSHA PEL	100	28.6	2.2
OSHA and Proposed MSHA PEL	50	27.8	1.4
Unexposed	0	26.4	-

*The range of exposure extended to well above 100 ug/m3 in the observed data from the study of 10 cohorts in several countries, some with no reported silica exposure limits.
**Risk at age 80 based on a working lifetime of 45 years of exposure

Compared to unexposed miners, as the exposure limit for silica decreases from well above100 in the observed data to 100 µg/m^3 and then to 50 µg/m^3, the excess risk decreases from 3.9/1000 to 2.2/1000 to 1.4/1000.

Applying lessons learned in this Excess Risk Calculation

Worker protection agencies were set up by Congress and told by the courts to protect workers so that they would not suffer serious disease or death as a result of their lifetime of exposures at work. The assessment of excess risk helps the government agencies set standards that protect miners and are also technically and economically feasible for miner operators to achieve. We have emphasized that excess risk may be under-estimated if the healthy worker survivor effect is ignored in the epidemiology studies that form the basis of occupational risk assessment.

The goal of zero risk is usually not feasible. Instead, the agencies try to identify an exposure limit that would result in less than 1/1000, or one excess death per 1000 workers. Based on the analysis above, taking account of the healthy worker survivor effect, the excess risk of lung cancer expected at the OSHA PEL of 50 $\mu g/m^3$ is higher than 1/1000, thus does not meet that goal.

1 Steenland K, Mannetje A, Boffetts P, Stayner L, Attfield M, Chen J, Doscemeci M, DeKlerk N, Hnizdo E, Koskela R, Checkoway H. Pooled exposure-reponse analysis and risk assessment for lung cancer in 10 cohorts of silic-exposed workers: an IARC multicentre study. Cancer Causes and Controls 12; 2001.

2 Keil AP, Richardson DB, Westreich D, Steenland K. Estimating the impact of changes to occupational standards for silica exposure on lung cancer mortality. Epidemiology (Cambridge, Mass.). 2018 Sep;29(5):658.

Appendix 1- Alternative analytic approaches to estimate exposure-response relationships for long term workplace exposures that address the healthy worker survivor effect

The Healthy Worker Effect has long been a well-known problem. Researchers have proposed different strategies to reduce the problem over the years. Today the g-formula is considered the best approach, but it requires longitudinal data with time-varying data on exposure and employment status as well as sophisticated analytic capabilities. Below we highlight other methods that researchers sometimes use, why they are used, and what their limitations are. The other methods (See Table below) are much simpler to use than g-methods and frequently show up in the literature; however, they are not very effective at reducing the problem of the Healthy Worker Effect.

Strategy	Rationale/ Advantage	Limitation
#1: Adjust cause-specific SMR* by the SMR for all-causes-of-death-combined to identify a hazard	All-cause SMRs* are generally < 1.00 because healthier people get hired and the adjustment will offset that healthy hire effect	Does not address HWSE and does not estimate an exposure-response
#2: Use workers as the reference group instead of the general population	Avoids healthy hire effect	Does not address HWSE
#3: Ignore recent exposure by lagging cumulative exposure	Down-weights recent time to offset leaving work	Does not make biologic sense for outcomes with short latency
#4: Adjust for employment status/duration of employment in regression model for the outcome	Only compares individuals who have been employed the same amount of time	Blocks effect of past exposure if employment status/duration is a mediator and further distorts results

*SMR = Standardized Mortality Ratio, a common measure of association when comparing exposed workers to the general population.

Appendix 2
Application of the parametric g-formula: The How and the Why

For this technical Appendix, we assume some familiarity with epidemiologic terms such as regression models and cumulative exposure that varies over time.

As we described earlier, exposure to workplace toxins may make some people leave work early. One of the common methods researchers have used to try to correct for HWSE is a regression model to estimate the impact of cumulative exposure on a health outcome adjusting for an annual indicator of leaving work or duration of employment (#4 in the Table in Appendix 1). In some ways, this method makes sense--leaving work predicts future exposure and the health outcome, so it is an important variable to adjust for. **However, this method fails because regression models will produce the wrong answer when adjusted for a variable that comes after exposure.** In this case, years of active work exposure contributes to the cumulative exposure that occurs prior to people leaving work. Therefore, adjusting for whether someone was still at work is adjusting for a variable that **comes after** exposure. Adjusting for a variable that **comes after** exposure can distort the results by masking, or hiding, part of the effect of exposure. Thus, although this is a common and accessible method, it does not solve the problem of obtaining results that are underestimated by HWSE.

So, researchers should not adjust for a variable that comes after exposure - and yet this is exactly the variable that one needs to adjust for to avoid HWSE. Thus, the solution requires a fundamentally new way of exposure-response modeling. G-methods solve the problem because they allow researchers to estimate the impact of exposure on the outcome without adjusting for important variables that come after exposure. There are a handful of g-methods that are appropriate for specific study designs and research questions. We will describe g-formula, which is an appropriate method for most occupational cohorts that are followed for mortality.

G-formula approaches the analysis in a novel manner. Standard methods use the observed data to compare the disease risk in people with high cumulative exposure to disease risk in people with low cumulative exposure and adjust for differences between these two groups of people. G-formula essentially allows researchers to generate a dataset that simulates, or mimics, the observed data. Since the simulated dataset is made by the researcher, the researcher can then change aspects of the data to create a contrast (risk for high versus low exposed) similar to the contrast estimated by standard regression but with no need to adjust for problematic variables.

How G-formula works in 5 steps:

Step 1

A series of regression models are used to simulate a dataset that mimics the observed data.

Step 2

Checks are made to make sure that the simulated dataset is similar to the observed. This simulated dataset is called the “natural course” since it mimics what occurred naturally in the observed data, including exposure levels, health outcomes, and all other covariates.

Step 3

Risk of disease in each year is then estimated in the natural course dataset and summed to produce the cumulative risk of disease up until a specific age (~~ie~~ e.g., the lifetime risk of lung cancer by age 80).

Steps 1-3 represent the work needed to create an estimate of risk by creating a mimicked dataset using regression models. In subsequent steps, the researcher can then change the regression models and estimate what the disease risk would be if model changed.

Step 4

The exposure is changed in each year and the risk of disease in each year is estimated given this revised exposure. Usually, the researcher will change the exposure so that it is capped at a potential regulatory limit so that they can estimate what would have happened in this cohort if no worker had been exposed above that limit. Frequently, they also estimate the risk after setting the exposure to zero.

Step 5

The risks can then be compared between the risks from the different datasets. For example, researchers can compare the risk at one exposure limit to the risk when exposure was set to zero.

Why does G-formula correct for HWSE?

There are two key reasons why g-formula allows researchers to account for people leaving work without having to adjust for it in a regression model.

Reason 1

Cumulative exposure is not the exposure metric. Instead, researchers estimate risk in each year based on the exposure in that year (adjusted for past exposure), thus sidestepping the need to adjust for variables that **come after the exposure** of interest. Risk, rather than exposure, is cumulated.

Reason 2

Researchers do not compare the risk of disease as it was observed in two (or more) groups of workers. Instead, they estimate the risk that would have occurred in the whole population under different exposure circumstances based on the collected data.