Critique of

Health Effects Institute Special Report 19, "Diesel Emissions and Lung Cancer: An Evaluation of Recent Epidemiological Evidence for Quantitative Risk Assessment"

(November 2015)

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July 26, 2016

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I. Abstract

The International Agency for Research on Cancer (IARC) in 2012 upgraded its cancer hazard classification of diesel engine exhaust exposure to Category 1 of "carcinogenic to humans" based on what IARC asserted was adequate or sufficient epidemiological evidence.[1] Its 1988 classification of "probably carcinogenic to humans" was based on limited epidemiological evidence.[2]

The new epidemiological evidence of an association between diesel exhaust exposure and lung cancer viewed as sufficient epidemiological evidence in the 2012 IARC review came primarily from a diesel exhaust in miners study (DEMS) published in 2012 by investigators from the National Institute for Occupational Safety and Health (NIOSH) and the National Cancer Institute (NCI). The DEMS investigation followed 12,315 workers in eight nonmetal mining operations (one limestone, one salt, three potash and three trona) from the beginning of dieselization (as early as 1947 in the limestone mine) through December 31, 1997 by which time there were 2,185 deaths in the study population with 198 lung cancers. IARC also relied on new evidence from a study published in 2012 of 31,135 U.S. truckers using diesel-powered trucks followed from 1985 through December 31, 2000, (the U.S. Truckers' Study), which included 4,306 deaths with 779 lung cancers.

Neither study actually measured diesel exhaust exposures for the individuals that were studied, resulting in the need to retrospectively estimate exposures to diesel exhaust. In the U.S. Truckers' study, the original investigators used Submicron Elemental Carbon (SEC), particles below one micron in aerodynamic diameter, as the exposure metric for diesel exhaust.

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[1] *See* IARC Monographs, Diesel and Gasoline Engine Exhausts and Some Nitroarenes (Vol. 105 2013), *available at* http://monographs.iarc.fr/ENG/Monographs/vol105/mono105.pdf.

[2] Epidemiology is the study of the distribution and determinants of health related status or events, including overt disease and related problems. Each epidemiological study may be viewed as analogous to a three-legged stool. The three legs being: (1) a defined population and related vital health data for the population such as morbidity (sickness) and mortality (deaths by cancer) for a defined period of time; (2) the exposure assessment for members of the population being studied, including the agent of interest (in this case, diesel engine exhaust) and any other agents such as cigarette smoke, radon, asbestos, etc. that may also cause the endpoint of interest; and (3) the analytical methods used to analyze for a relationship between exposure, in this case to diesel exhaust, and health outcome, in this case, lung cancer deaths. The overall strength of a study is dependent on the strengths and weaknesses of each component. Uncertainties in one component, such as in the exposure assessment or assessment of vital statistics, cannot be offset by superior quality or certainty of other components.

Estimates of SEC exposure were projected retrospectively from measurements made near the end of the study. In the DEMS investigations, Respirable Elemental Carbon (REC) was used as the metric for diesel exhaust exposure. REC is characterized with a sampling technique that collects particles less than 3.5 microns in aerodynamic size. The original NCI/NIOSH investigators retrospectively estimated REC using knowledge of diesel equipment horsepower (HP), mine ventilation in cubic feet per minute (CFM), past measurements of CO and assumed relationships among HP, CO and REC pre-1998 and measurements made in 1998-2000. This approach assumed that CO emissions and CO mine concentrations were reasonable surrogates for REC.

Following publication of DEMS, independent investigators used DEMS data to develop alternative REC estimates using CO as a surrogate for REC and most importantly, estimate REC based on HP-CFM, without using CO as a surrogate for REC.[3]

The initial analyses of the entire DEMS cohort, including both surface and underground workers, did not show a clear association between diesel exhaust exposure and lung cancer. However, analyses conducted with workers grouped as only (a) surface workers versus (b) ever-underground workers, (about one-half of the ever-underground workers had always worked underground and the other half of the ever-underground workers had spent time both on the surface and underground) revealed a modest increase in the standardized mortality rate ratio for diesel exhaust exposure (1.26, 95% Confidence Interval of 1.09 to 1.44) when adjustment was made for worker location. This standard mortality rate ratio translates to an attributable risk for diesel exhaust exposure of 0.21. Thus, the majority of the lung cancer deaths were attributable to other risk factors, including cigarette smoking, the dominant cause of lung cancer in the United States.

A group of independent investigators, funded by a coalition of private industry organizations organized by the Engine Manufacturers Association were provided access (under carefully controlled conditions) to the DEMS data via NIOSH/NCI and other official channels of the Department of Health and Human Services. The independent investigators replicated the original NIOSH/NCI investigators' analyses demonstrating that the independent investigators were using the same basic DEMS data sets. However, the independent investigators, using an alternative biologically based model found a somewhat reduced association between diesel

[3] As an aside, neither the REC metric in the DEMS or SEC metric exactly coincide with the Diesel Particulate Matter (DPM) metric used in the current Mine Safety and Health Administration regulations for diesel exhaust which is based on total carbon, including both elemental carbon and organic carbon.

exposure and lung cancer, and, most importantly, identified a strong influence from the workers in one mining operation, the limestone mine.

The original NIOSH/NCI investigators also conducted a nested lung cancer case-control study in which they obtained smoking data on the 198 lung cancer cases and 562 incidence density-sampled control subjects. As expected, they found a very strong association between cigarette smoking and lung cancer. This included an unexplained markedly stronger association between smoking and lung cancer for surface-only workers versus ever-underground workers. The original investigators observed a statistically significant increasing trend in lung cancer risk with increasing cumulative REC and average REC Intensity. They also observed an interaction between smoking and cumulative REC such that the effects of each of those exposures was attenuated in the presence of high levels of the other, an unexpected and not explained finding.

The independent investigators' analyses of the DEMS nested case-control data replicated the results of the original investigators. However, when the independent analysts used REC exposure estimates based on HP-CFM (without assuming CO was a surrogate for REC), none of the trend slopes for (a) all subjects, (b) all subjects who ever worked underground, or (c) subjects who worked only underground were statistically significant. Moreover, these trend slopes calculated using the new REC estimates based on HP-CFM were smaller by a factor of five without control for radon, and a factor of 12 smaller with control for radon exposure compared to those reported in the original DEMS analysis. Also, the 95% confidence intervals for the trend slopes with the HP-CFM based REC had minimal overlap with those for the slopes in the original analyses.

The original analysis of the U.S. Truckers' Study cohort data revealed a weak association between SEC and lung cancer and, even then, only when mechanics were excluded from the analyses. There have apparently been no analyses of the U.S. Truckers data set other than those published by the original investigators. One published paper has joined the U.S. Truckers' study results with the DEMS results in an attempt to show consistency between the results of studies of the two populations.

The Health Effects Institute (HEI), at the request of HEI's sponsors (both the U.S. Environmental Protection Agency and the engine manufacturers), convened an independent panel (HEI Epidemiology Panel) of nine scientists to evaluate use of the results of the U.S. Truckers' study and DEMS whether those studies could provide the basis for a future quantitative risk assessment. Most of the Panel members were experienced in epidemiology, biostatistics, and/or industrial hygiene. One member is well known for his expertise in diesel

engine technology. None of the Panel members were experienced in underground mining operations using diesel equipment. The HEI Epidemiology Panel declined an invitation to visit one of the mines that was studied in DEMS.

Such a quantitative risk assessment, if conducted, could establish a quantitative estimate of the potency of diesel exhaust exposure for causing lung cancer. Such potency estimates could be used to estimate, for a specified level of exposure, the estimated excess risk of lung cancer attributable to measured or estimated levels of diesel exposure. The results of such calculations are frequently reported as avoidable deaths and these numerical estimates used as evidence of the need for more stringent regulation.

In Special Report 19: Diesel Emissions and Lung Cancer: An Evaluation of Recent Epidemiological Evidence for Quantitative Risk Assessment (Nov. 2015) (HEI Report), the HEI Panel concluded, "the DEMS and the Truckers' Study provided results and data that provide a useful basis for quantitative risk assessment of exposure in particular to older diesel engine exhaust."[4] "However, "the uncertainties within each study should be considered in any attempt to derive an exposure response relationship" for diesel exhaust particulate matter."[5]

In my opinion, even this qualified endorsement of the two studies is not consistent with the substantial uncertainties in estimates of REC exposure and the association between diesel exhaust exposure and lung cancer made by the original NIOSH/NCI investigators and those of the independent analysts using alternative estimates of REC exposure, control for radon exposure, and alternative REC exposure-response models.

As expected, analysis of the DEMS nested case-control data reveals a strong influence of cigarette smoking on lung cancer, an influence that makes it challenging to tease out the effects of other risk factors, including diesel exhaust exposure and radon exposure. The new analyses of the DEMS data by independent analysts using new estimates of REC exposure based on HP-CFM showed a reduced risk of REC-associated lung cancer compared to those of the original investigators. Moreover, the new analyses using limited radon measurement in the mines show a clear influence of radon exposure. Based on all of the analyses conducted to date by either the original investigators or independent analysts, it is likely that any estimates of the potency of diesel exhaust from old traditional technology diesel engines (pre-1990) will be bounded on the upper bound by the results of the original analyses of the DEMS nested case-

[4] HEI Report at 1 (*available at* http://pubs.healtheffects.org/view.php?id=446).

[5] *Id.* at 7.

control data and on the lower bound by limited excess risk, as revealed by the independent analyses using the HP-CFM based REC estimates and control for radon exposure.

The multiple analyses performed to date using the DEMS data set serve as an example of the value of making epidemiological data sets available for replicative and new extended analyses by multiple teams of scientific investigators. Moreover, the results of the multiple analyses emphasize the importance of considering the complete constellation of results to inform public policy decisions on the risks of exposure to diesel exhaust without excessive reliance on the original analyses.

Any use of the DEMS results for either cancer hazard characterization or quantitative risk assessment also needs to recognize the results of such assessments are most relevant to old traditional diesel technology (pre-1990). This is especially the case since the strongest influence of REC on the relationship between REC and excess lung cancer was found when a 15 year lag was used in the models. With mortality followed through December 31, 1997, this meant the exposures of greatest influence occurred in 1982 and earlier. Substantial changes in diesel technology (engine technology, exhaust after-treatment and ultra-low sulfur fuel) have been made in recent decades such that new technology diesel engines have extraordinarily low emissions of particulate matter and nitrogen oxides. The results of the analyses of DEMS data based on exposure to exhaust from old technology engines have limited relevance to evaluating the health risks of exhaust from the new technology diesel engines.

The cancer hazard findings from analysis of the DEMS data, even if uncertain, underscore the value of past and continuing efforts to reduce the exposure of workers to exhaust from traditional diesel engines. Moreover, the results emphasize the benefits of shifting to new technology diesel engines using ultra-low sulfur fuel with low emissions of particulate matter and oxides of nitrogen.

II. Introduction

This critique of the Health Effects Institute Special Report 19 – “Diesel Emissions and Lung Cancer: An Evaluation of Recent Epidemiological Evidence for Quantitative Risk Assessment” (HEI, 2015) addresses an issue of substantial importance to many different audiences, including the mining industry. It is also a topic with a rich history. The author of this critique, Roger O. McClellan, has over four decades of experience investigating the potential health effects of diesel exhaust as detailed in Section XIV.

To provide context, this critique starts with a brief review of concerns for the health effects of exposure to diesel engine exhaust emphasizing lung cancer as the primary health endpoint of concern. It then proceeds to provide a brief description of the Health Effects Institute and its 35-year history of involvement in the broad issue of diesel engine exhaust exposure and potential health effects.

The critique then describes the DEMS and U.S. Truckers' studies of the association between diesel exhaust exposure and excess risk of death from lung cancer. This section starts with a discussion of the design of the epidemiological studies and proceeds to a discussion of the findings published by the original NIOSH/NCI investigators, and then the findings obtained by a group of independent analysts funded by a coalition of private industry organizations organized by the Engine Manufacturer's Association (EMA).

The evaluation conducted by the HEI Epidemiology Panel, the authors of HEI Special Report 19, is then discussed.

The critique concludes with summary conclusions on the utility of the range of findings, especially those from analyses using the DEMS data, for conducting quantitative risk assessment of the lung cancer risk to miners from exposure to diesel exhaust.

This critique is not intended to address the broader issue of the applicability of the findings of the DEMS and U.S. Truckers' Study for evaluating the lung cancer risks to the general population of exposure to ambient $PM_{2.5}$ containing diesel exhaust particulate matter. Obviously, many of the issues raised in this critique are also applicable to any use of results of analyses of the DEMS data, irrespective of the population under consideration.

III. Historical Concerns for Potential Health Effects of Exposure to Diesel Engine Emissions

Diesel compression ignition engines named for the inventor, Rudolph Diesel, were introduced into commerce in the early 20th century and soon became the major power source used in a wide range of industrial settings and in transportation. The power, durability and fuel efficiency of diesel engines have made them attractive in heavy duty applications such as trucks, buses, construction, farming and mining equipment, locomotives and in marine shipping. The low emission rate of carbon monoxide from diesel engines, as contrasted with emissions from gasoline-fueled spark ignition engines, has been viewed as a plus for many applications, including use of diesel engines in mines. Early in the commercialization and use of diesel engines, concerns developed for their conspicuous black carbon soot emissions and the odor of diesel exhaust. Concern for the emissions initially focused on their impact on visibility. With

increasing use of diesel-powered equipment, concern developed for the potential impact of exposure to diesel exhaust emissions on lung disease and especially lung cancer in workers and the general population.

In the 1960s and 1970s, numerous new techniques were developed and introduced for evaluating the function of living cells in humans and laboratory animals, including the development of tests for evaluating the potential for a range of agents to cause genetic alterations, i.e., mutation in cells. One of the most popular of these tests, utilizing special strains of bacteria, was developed by Professor Bruce Ames of the University of California, Berkeley, and used to test a wide range of agents for mutagenicity. The use of the Ames test was based on the presumption that detection of mutagenic potential served as a surrogate measure of the potential of the agent to cause cancer in humans. This presumptive evidence of human carcinogenic potential could then be used to limit exposure to the mutagenic agent even in the absence of laboratory animal or epidemiological evidence of carcinogenic potential for the agent.

It is not surprising that soon after the Ames test was developed and introduced for widespread use, the test was used by EPA scientists and others to test organic solvent extracts of diesel exhaust soot particles (McClellan, et al., 2012). As an aside, the organic solvent extracts were already presumed to be carcinogenic since the extracts contained high concentrations of polycyclic aromatic hydrocarbons and nitroarenes. Some of these compounds had already been identified individually as having cancer-causing potential. The results of the Ames tests of the organic solvent extracts of diesel soot particles were clearly positive, immediately resulting in heightened concern for exposure to diesel engine exhaust causing cancer and, especially, lung cancer. Ironically, decades earlier scientists had collected large samples of airborne particles near freeways in Los Angeles and demonstrated that organic extracts of the collected particles applied to the skin of mice caused skin tumors.

The positive mutagenicity findings with organic solvent extracts of diesel exhaust particles also served as a stimulus for additional research on the potential health effects of exposure to diesel exhaust. This included the conduct of new epidemiological studies of workers previously exposed to diesel exhaust. In addition, in four countries around the globe, controlled exposure studies were initiated using laboratory animals. In these studies, multiple species of laboratory animals were exposed, in many studies over their lifetime, to various low dilutions (and thus, high concentrations) of whole diesel engine exhaust. Other research studies sought to characterize the fate of inhaled diesel soot particles and their organic

constituents and identify the mechanisms by which cancer might presumably be produced by exposure to diesel exhaust.

To some extent, concern over the new findings on the potential cancer hazard of diesel exhaust exposures served to stimulate the creation of a new non-profit entity, the Health Effects Institute (HEI). HEI was created in 1981 as a "good intentions" approach to meeting the requirements of the Clean Air Act that required combustion engine manufacturers to "certify" that over and above meeting all applicable health-related regulation, use of the engines did not pose any health risks. Moreover, the Act required the EPA Administrator to certify that the manufacturers' certification was correct. Creation of HEI to conduct research on the health effects of engine emissions, with joint funding from the engine manufacturers and the EPA, was viewed as an alternative to the impossible to meet "certification requirements."

By the late 1980s, a substantial body of scientific information had been developed indicating that protracted exposure to high concentrations of diesel soot particles could cause lung cancer in rats at incidences over and above the background rate. The primary studies in the United States were conducted by Mauderly, et al. (1987) at the Lovelace Institute in Albuquerque, NM with support from the U.S. Department of Energy. A typical study involved exposures of 7,000 µg diesel exhaust particles/ m^3 for 7 hours/day for 5 days/week for up to 2½ years. To provide perspective, these exposures represented about a 1 to 10 dilution of whole exhaust from diesel engines typical of the 1980s. Similar results were obtained in studies conducted in laboratories in Germany, Switzerland, and Japan. Ironically, mice exposed under identical conditions at the Lovelace Institute did not develop an increased incidence of lung cancers (Mauderly et al., 1996).

During this same time period, it was discovered that exposure of rats to the high concentrations of other poorly soluble particles, such as titanium dioxide, over their lifespan caused an increased incidence of lung cancer (Lee, et al., 1985). This raised the possibility that the association between long-term high concentration exposure to diesel exhaust and lung cancer in rats might be due to the carbonaceous diesel soot particles alone or in combination with organic constituents. A paper by Wolff, et al. (1987), now viewed as a classic, revealed that the rats exposed to the highest concentrations of diesel particulate matter had impaired lung clearance and lung burdens of particles that were disproportionately higher than at low concentration exposures. Later it would be demonstrated that prolonged high concentration exposure of rats to pure carbon black particles, absent any organic compounds, would cause an increase in lung cancer (Nikula, et. al., 1995). These findings supported the view that the

findings of lung cancer in diesel exhaust exposed rats were a species-specific, high exposure phenomena that was not relevant to assessing human risks.

Debate over the relevance of the findings in cell assays and laboratory animal bioassays for predicting human cancer causation placed even more emphasis on the need to conduct epidemiological studies of diesel exhaust exposed workers. This included studies on worker populations using diesel-powered equipment, including bus drivers, railroad workers, truckers and underground miners. The results of the epidemiological studies were viewed, and continue to be viewed, as the "gold standard" for evaluation of the human carcinogenic hazard of specific chemicals and occupational and environmental exposure circumstances. A major challenge in all of the epidemiological studies has been uncertainties in the estimates of diesel exhaust exposure.

IV. The Risk Assessment Paradigm

The dominant paradigm for evaluating the safety of drugs, food additives, work place exposures and other situations pre-World War II, was to assume that any adverse health effects observed with long duration, high concentration exposure could be reduced and, indeed, eliminated if the exposure duration and concentration were reduced below some threshold concentration. In short, there were thresholds above which health effects were observed and below which exposures were considered to be safe. This approach began to be questioned in the 1930s as concern increased for genetic effects and cancer being caused by exposure to radiation and other agents. Debate began, and continues today, over whether exposure-response relations for particular agents and a range of health endpoints are best described by (a) an exposure-response function with a threshold, or (b) a linear, no threshold exposure-response function.

A new paradigm for evaluating and regulating safety began to emerge during World War II and intensified in the 1950s and 1960s (McClellan, 1999). This new paradigm was clearly evident in new legislation and organization of new regulatory agencies in the 1970s. This was the era of the influential book – "Silent Spring," the passage of the Clean Air Act Amendments of 1970 and the creation of numerous new environmental and occupational health agencies such as the EPA, NIOSH, the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA).

The new paradigm that emerged was multi-faceted (McClellan, 1999; NRC, 1983, 1993, 1994, 1996, 2009). The paradigm recognized that exposure-response relationships for some

agents might show thresholds but also assumed that for some agents and health endpoints such as cancer, the relationship may be linear and not have a threshold.

The basic risk or, conversely, safety paradigm that emerged in the 1960s and 1970s is illustrated in Figure 1. This figure summarizes the basic paradigm as advocated by the National Research Council (2014) and used by the EPA and most federal agencies. The paradigm has four components: (a) hazard identification (Does an agent have potential to produce and adverse outcome such as cancer?); (b) exposure characterization (What are the exposures encountered or estimated to be encountered?) (c) exposure-response characterization (What are the observed or estimated exposure-response relationships?); and (d) risk characterization (What is the estimated or predicted outcome when the exposure and potency are both taken into account?). The history of development of the risk assessment paradigm and its application has been reviewed by McClellan (1999).

It may be noted that in Figure 1, the phrase, dose-response, is used. For consistency it should have been exposure-response. However, the two words, exposure and dose, are often used interchangeably although they have very different meanings. Exposure refers to the concentration present in the air, water or food and available for intake. Dose is a more restrictive term relating to the quantity of an agent that enters the body and may reach various organs and tissues. Two other words, hazard and risk, deserve comment. Within this paradigm, the word hazard is used as a descriptor of potential harm without consideration of the level of exposure or dose required to produce an effect, such as cancer. Risk, on the other hand, takes account of the likelihood of a hazardous agent causing harm, i.e. its potency and the level of exposure or dose to yield a probability that harm can occur, i.e. cancer incidence, over and above that arising from other factors.

The hazard identification component of this paradigm soon gave rise to development of qualitative assessments of causality for specific agents. This approach under-girds the IARC monograph program initiated in the early 1970s that has evaluated over 1000 agents or exposure circumstances with regard to human carcinogenic hazard, i.e., does the agent or exposure have the potential to cause cancer. The IARC program conducts periodic reviews utilizing expert panels that place agents in five categories: 1 – human carcinogens; 2a – likely human carcinogens; 2b – possible human carcinogens 3 – not likely to be a human carcinogen; and 4 – insufficient information for classification. Decisions on which cancer hazard characterization is appropriate are made by a panel of some 20 scientific experts and consideration of three types of data: (a) epidemiological; (b) animal; and (c) mechanistic evidence. The IARC Monograph Reports also contain information on sources of the agent and

exposure circumstances. The EPA and the National Toxicology Program (NTP) in the United States have developed and used similar schemes. More recently, this approach has been extended by multiple agencies to other health endpoints, including non-cancer effects. It is important to note that IARC and the NTP only address whether the agent or exposure pose a carcinogenic hazard, they do not provide estimates of carcinogenic potency.

As public concern increased for the exhaust emissions of diesel engines, a number of U.S. and International agencies conducted reviews of the health hazards of exposure to diesel exhaust with an emphasis on human carcinogenic hazard (Table 1). Not shown in Table 1 is an independent review of emissions, exposures, and health effects of diesel exhaust conducted by HEI (1995). The table includes columns summarizing the conclusion drawn based on animal data and human data. As discussed earlier, interpretation of the animal evidence, especially the results of lifespan studies of diesel exhaust exposure with lung cancer as a health outcome in rats, has been complicated by questions as to the relevance of the findings in laboratory animals to humans.

The same situation exists with regard to interpreting the relevance of mechanistic findings from studies conducted with *in vitro* systems or animals injected with diesel soot particles typically at high concentrations. Alternatively, particles can be collected, extracted with a strong organic solvent and the extracts containing organic constituents of the particles studied. Findings from such studies have been published in more than a thousand papers in the peer-reviewed literature (Hesterberg, et al., 2005, 2006, 2012). It is noteworthy that diesel soot particles are relatively easy to collect and study in cell assays or by injection into laboratory animals. Thus, the studies are relatively easy and inexpensive to conduct with a wide array of different assay systems. In this reviewer's opinion, these results are of limited value in most cases for better understanding the human hazards of exposure to diesel exhaust because of the substantial uncertainties in extrapolating from: (a) cells to intact mammalian organisms; (b) laboratory animal species to humans; (c) extraordinarily high exposures *in vitro* to *in vivo*; and (d) the use of non-physiological modes of exposure, such as intra-tracheal injection, to inhalation exposure. Nonetheless, the results of these assays continue to heighten the concern of scientists and, in turn, concern by the public for the health hazards of diesel exhaust emissions and a multitude of other materials.

The last entry in Table 1 shows the IARC 2012 categorization of exposure to diesel exhaust as "carcinogenic to humans (Group 1)" based on sufficient evidence from epidemiological studies (Benbrahim-Talla, et al., 2012; IARC, 2013). That landmark decision was followed the next year by IARC categorizing "ambient air pollution" and "particulate matter

in ambient air" as "carcinogenic to humans" (Loomis, et al., 2013; IARC, 2015). In view of the significance of these findings, the background to these decisions is reviewed in the next section of this critique.

V. History of Assessing Carcinogenic Hazards of Diesel Technology

All of the assessment reviews in Table 1 have been comprehensive, utilizing scientific evidence from epidemiological studies on occupationally exposed populations, a small number of controlled exposure studies conducted with human volunteers, long-term inhalation bioassays of diluted diesel exhaust conducted with laboratory animals, and a broad array of studies with cells and laboratory animals directed toward understanding mechanisms by which diesel exhaust could potentially cause cancer and other diseases. It is generally recognized that diesel exhaust is among the most studied agents that human populations routinely encounter.

It is also noteworthy that of the assessments shown in Table 1, only the assessment conducted by the California EPA in 1998 included quantitative characterizations of the cancer risk of exposure to diesel exhaust based on human data (Dawson and Alexeeff, 2001). That quantitative assessment was based on an epidemiological study of railroad workers (Garshick, et al., 1988). As an aside, in 1999 an HEI Panel had recommended against the use of the 1988 railroad workers study results for quantitative risk assessment (HEI, 1999).

IARC first qualitatively evaluated the carcinogenic hazard potential of exposure to diesel exhaust in 1988 (reported in IARC, 1989). This review was updated in 2012 (Benbrahim-TL, et al., 2012; IARC, 2013). The 1988 evaluation concluded that data from chronic exposure studies with diesel exhaust conducted in rats provided "sufficient" positive evidence of lung cancer induction. Ironically, as noted earlier, later studies would reveal that the same effects were produced by chronic exposure to pure carbon black particles and other poorly soluble particles such as TiO_2. Pure carbon black particles do not contain polycyclic aromatic hydrocarbons that are found as components of exhaust particles from traditional diesel technology engines and are known to be carcinogenic. In the 1980s, it was commonly assumed that carbonaceous diesel soot particles containing polycyclic aromatic hydrocarbons, when inhaled, could initiate the carcinogenic process. Thus, the findings of lung cancer in the diesel exposed rats were expected. However, by the mid-1990s, the picture had changed and it was generally accepted that the lung cancers observed in rats exposed in lifespan studies to high concentrations of poorly soluble particles such as diesel soot, titanium dioxide, and carbon black resulted from a

species-specific, prolonged high concentration exposure mode of action that did not involve the hydrocarbons. This led to the conclusion that these findings should not be used as evidence of a cancer causing potential for humans, especially at the modest air concentrations found in ambient air or most work place environments.

A key finding in the 1988 IARC evaluation was that the human epidemiological evidence for diesel exhaust exposure causing cancer in humans was judged to be "limited." This IARC evaluation included consideration of the data from the Garshick, et al. (1987) study on railroad workers used by CARB to develop quantitative estimates of the potency of exhaust from old technology diesel engines to cause lung cancer. A major criticism of the Garshick, et al. (1987) railroad workers study was the uncertainty in the retrospective exposure assessment.

Not shown in Table 1 is an evaluation conducted by HEI (1999), noted earlier, which concluded that the epidemiological findings available at that time were not suitable for qualitative risk assessments.

In the early 1990s, the EPA, anticipating development of regulations for diesel engine exhaust emissions and diesel fuel quality, initiated a comprehensive assessment of the health effects of exposure to diesel exhaust. This review, as is customary within EPA, was conducted by the EPA's Office of Research and Development as part of its risk assessment activities. It was anticipated that this assessment would inform the EPA's regulatory decisions on diesel technology developed and issued by EPA's Office of Air and Radiation. Ultimately, the EPA evaluation would involve preparation and external review of five draft reports before a report was finally endorsed by the external advisory committee, a panel of the EPA Clean Air Scientific Advisory Committee on which this author served in 2002 (EPA, 2002).

The major contentious issue that delayed preparation and endorsement of the final report on the health effects of diesel exhaust was whether either the epidemiological or animal evidence were sufficient for conducting a quantitative cancer risk assessment. The final report published in 2002 concluded that exposure to diesel exhaust posed a health hazard; however, the data were not sufficient for developing a quantitative cancer risk assessment. As it turned out, EPA in 1998 (while development of the health hazard report was still underway) set very stringent exhaust emission regulations for diesel engines and the sulfur content of diesel fuel. These regulations were based on the qualitative assessment of hazards for cancer and other health endpoints reviewed in the earlier draft reports. This is an excellent example illustrating that quantitative assessments of cancer risk or other health endpoints are not always essential for regulatory agencies to take action.

It is noteworthy that the controversy in the late 1980s and early 1990s over the adequacy of the epidemiological evidence for diesel exhaust causing cancer served as a major impetus for the conduct of new epidemiological studies. A key consideration in the design of the new studies was increased attention to developing quantitative estimates of historical exposure to diesel exhaust (HEI, 1999, 2002). That issue will be considered in detail later in this critique.

Two of the new studies initiated in the 1990s yielded results that were evaluated by IARC in 2012 and were the focus of the HEI evaluation (HEI, 2015) and this critique: the U.S. Truckers' Study and the Diesel Exhaust in Miners Study (DEMS). These studies will be reviewed in detail later in this critique.

For now, it is sufficient to note that the 2012 IARC evaluation of diesel exhaust exposure concluded diesel engine exhaust exposure should be placed in Category 1, "carcinogenic to humans." That conclusion was based on a key finding of "sufficient" epidemiological evidence largely based on the positive findings reported for the original analysis of the DEMS data set by Attfield. et al. (2012) and Silverman, et al. (2012) and, to a lesser extent, the results of the U.S. Truckers' Study (Garshick, et al., 2012a). A review by Gamble, et al. (2012) provides an independent perspective on the literature used in the 2012 IARC review on occupational exposures to diesel exhaust and lung cancer.[6]

In 2013, another IARC Panel (Loomis, et al., 2013; IARC, 2015) concluded that exposure to (a) outdoor air pollution, and (b) particulate matter in outdoor air pollution is "carcinogenic to humans." Both evaluations made reference to the earlier IARC (2012) conclusion that diesel exhaust particulate matter was carcinogenic to humans and was an important component of ambient air pollution and of particulate matter in ambient air. Thus, the conclusions rather automatically followed that "outdoor air pollution" and "ambient particulate matter in outdoor air" were carcinogenic to humans (IARC, 2015).

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[6] As an aside, both the 1988 and 2012 IARC Panels also evaluated gasoline engine exhaust and concluded in both reviews that it was "possibly carcinogenic to humans." The finding for gasoline engine exhaust deserves comment. It was based on much more limited experimental and epidemiological research. Diesel exhaust is much easier to study than is exhaust from gasoline-fueled spark ignition engines and the epidemiological findings were characterized as "limited evidence" of human carcinogenicity. Moreover, by the 1980s major changes had been made in gasoline engines and fuels, including removal of lead from gasoline enabling the use of catalyst-based exhaust treatment systems resulting in reduced emissions of hydrocarbons, CO and NO_x.

EPA officials have regularly referred to removal of lead from gasoline as a major success story for the Agency. More recently, senior EPA officials have commented on development of clean diesels as a success story.

IARC's classifications in 2012 and 2013 seem to have motivated EPA to ask HEI to determine whether the new epidemiological studies could be used in a quantitative risk assessment. Motivation for EPA to develop an updated cancer risk assessment for exposure to diesel exhaust could also have come from the Mobile Source Office within the EPA's Office of Air and Radiation Programs that issued EPA's previous diesel engine emission and diesel fuel regulations. A quantitative cancer risk assessment for diesel exhaust would strengthen the evidence used to justify past actions and also lay the groundwork for more aggressively replacing old technology diesel engines with new technology diesel engines. The EPA already has in place a very popular, but modestly funded, program to subsidize the purchase of new technology diesel equipment by state and local agencies. In considering this myriad of options, it is important to recognize EPA is not a monolithic agency, it has multiple offices competing for resources and attention,

At an early stage in its evaluation process, the HEI Epidemiology Panel held a workshop on "Diesel Exhaust, Lung Cancer and Quantitative Risk Assessment" on March 6, 2014 for multiple interested parties. At that workshop, one of the participants, Robert Park from NIOSH, announced the intention of his agency to develop a quantitative risk assessment on diesel exhaust. That work is apparently proceeding, as evidenced by Park submitting an abstract on his preliminary work with the DEMS data for presentation at an international exposure assessment and occupational epidemiology meeting in Barcelona, Spain in September 2016. Encouragement to complete the NIOSH quantitative risk assessment on diesel exhaust could come from NIOSH's partner agencies, OSHA and MSHA, which would use a NIOSH prepared risk assessment to under-gird any new regulations related to diesel exhaust emissions. This would include any updates to the MSHA 2005 regulations (DOL/MSHA, 2005).

It is important to recognize that any future regulatory actions on occupational exposure to diesel exhaust particulate matter as well as occupational exposure to other kinds of airborne particulate matter will occur within a broader arena than just occupational exposures to the agents. It is my opinion that the boundaries between different kinds of particulate matter exposures in the work place will become less distinct. Moreover, the scientific and policy boundaries between occupational and environmental health are becoming increasingly blurred, as are the boundaries between air quality and climate change.

VI. Epidemiological Studies

Epidemiology is the study of the distribution and determinants of health-related status or events, including overt disease and related problems. An epidemiological study may be viewed as analogous to a three-legged stool. The three legs being: (1) a defined population and related vital health data for the population such as morbidity (sickness) and mortality (deaths by causes) for a defined period of time; (2) the exposure assessment for the population being studied, including the agent of interest (in this case, diesel engine exhaust) and other agents such as cigarette smoke, asbestos, radon, etc.; and (3) the analytical methods used to analyze relationships between exposure and health outcome, for example, lung cancer. Today, these analytical procedures routinely include complex computer-based statistical programs that typically use conditional logistic regression models to evaluate the risk of dying of disease, in this case, lung cancer, from the putative carcinogenic agent, in this case, diesel exhaust exposure, relative to a base line situation without exposure to the putative agent, diesel exhaust. A well-conducted epidemiological study is dependent on all three components of the study being solid. Uncertainties in one component, such as the exposure assessment or the assessment of vital statistics cannot be offset by the superior quality or certainty of other components. In my opinion, the weakest component of DEMS is the retrospective exposure assessment.

As already noted, the original NIOSH/NCI DEMS investigators used Respirable Elemental Carbon (REC) concentrations as the metric for diesel exhaust exposure. However, REC measurements do not exist for any of the workers from the beginning of dieselization of the mines through December 31,1997; the end of the mortality follow up for the DEMS workers. Hence, all REC concentrations used in the original epidemiological analyses (Attfield, et al., 2012; Silverman, et al., 2012) were developed from an elaborate retrospective exposure assessment. That original DEMS exposure assessment was done largely by NCI personnel and was reported in a series of peer-reviewed publications (Stewart, 2010, 2012; Coble, et al., 2010; Vermeulen, et al., 2010a, 2010b).[7] The follow-up epidemiological analyses by the independent investigators (Moolgavkar,et al., 2015; Crump, et al., 2015; Crump, et al., 2016;

[7] As an aside, the leader of the DEMS exposure assessment was Patricia Stewart, a long time NCI employee who is now retired and works as a private consultant. A second lead in the DEMS exposure assessment effort was Roel Vermeulen, a citizen of The Netherlands, who has since returned to Utrecht University and remains very active in the exposure assessment and occupational epidemiology fields.

Neophytou, et al., 2016) also used the estimates of REC exposure developed by the original DEMS team.

The independent investigators also developed alternative estimates of REC exposure. The first set were developed based on the analysis in Crump and Van Landingham (2012) and used in the Crump, et al (2015) extended analysis of the lung cancer case-control DEMS data. Another alternative REC exposure estimate followed the lead suggested in Appendix F of the HEI Report (2015) and was based on HP and CFM in each mine each year beginning with dieselization through 1997. This REC estimate based on HP-CFM was used in analyses reported by Crump, et al. (2016).

Thus, various methods of extrapolation have been used to estimate the exposure of miners to REC from the times the mines dieselized (as early as 1947 for the limestone mine) and extending through December 31, 1997. All of these REC estimates have substantial uncertainty, especially recognizing that some of the estimated REC exposures extend back 45 years to as early as 1947.

One special feature of many epidemiological studies, especially those involving cancer as a health endpoint, is the evaluation of various lag periods between when exposures occur and deaths from the health endpoint, in this case, cancer occurs. The use of various lag periods, typically 5, 10, or 15 years, recognizes that the development of cancer is complex and cancers typically occur years after an extended period of exposure. Indeed, the cancer may occur years after the exposure has been discontinued, recognizing that most lung cancers occur relatively late in life. While the time of death from cancer is precisely known, the time of various events in the initiation and progression of the cancer, including specific exposures such as diesel exhaust are not known with certainty. This becomes a matter of statistical estimation. In the analyses of the DEMS data, the use of a 15-year lag yielded the most consistent results. Hence, for a DEMS worker dying in 1997, the exposures of interest were those that occurred 15 years previously and earlier, i.e., in 1982 and earlier.

VII. Overview of U.S. Truckers' Study and Summary of Results

An overview of the U.S. Truckers' Study as developed by the HEI Panel is provided in Table 2. The original cohort included 58,326 unionized trucking industry workers who worked one day or more in 1985 and were followed through 2000. The original analysis of this cohort was reported by Laden, et al. (2007) and included 769 lung cancer cases. The Standardized

Mortality Rate Ratio for lung cancer was SMR = 1.04, 95% CI = 0.97-1.12. This indicates a very weak signal for diesel-related lung cancer, a signal that was not statistically significant.

Garshick et al. (2008, 2012a) reported a more detailed analysis of the Trucker cohort using an elaborate retrospective exposure assessment based on Submicron Environmental Carbon (SEC), elemental carbon less than 1.0 micron in diameter (Davis et al., 2007, 2009). Over 4,000 personal and area monitoring measurements were made in 2001-2006 and retrospectively modeled to earlier time periods (Davis, et al., 2006, 2011; Smith, et al., 2006).[8]

A total of 31,135 male workers who were over 40 years of age in 1985 with at least one year of work were included in Garshick, et al. (2008, 2012a,b). The workers were followed through 2000, by which time 4,306 deaths with 779 lung cancers had occurred. The 18% crude incidence of lung cancer is quite high and, is no doubt reflective of the smoking history of the population although the actual smoking history of the population was not ascertained. Thus, none of the analyses of the U.S. Truckers cohort could rigorously control for smoking despite strong evidence that smoking was the major cause of lung cancer in the cohort.

Key analyses reported by Garshick, et al. (2012a), excluding mechanics, yielded statistically significant elevated Hazard Ratios (HRs) for a 5-year lag, for example, HR = 1.48, CI = 1.05 – 2.10, for a cumulative SEC of ≥ 1803 $\mu g/m^3$ –months. For comparison purposes, this is equal to 150 $\mu g/m^3$–years. The results without a lag and for a 10-year lag were not statistically significant nor were analyses of the mechanics alone. There were no results presented for a 15-year lag; it is not known if such analyses were or were not done. It is not known if any analysts, other than the Garshick team, have analyzed the U.S. Truckers' Study data. Vermeulen, et al. (2014b) did use the U.S. Truckers' results in an aggregate analysis that also included the DEMS findings. Crump (2014) has noted the shortcomings of that analysis using the results of several studies with a mix of different lag periods. Morfeld and Spallek (2015) have also noted serious reservations with the approach of Vermeulen, et al. (2014a), especially for estimating lung cancer risks at low exposure levels, below 150 $\mu g/m^3$-years and Vermeulen, et al. (2014b) has responded.

The IARC Panel (Benbrahim-Talla, et al., 2012; IARC 2013), in concluding that diesel exhaust exposure was carcinogenic to humans, relied most heavily on the DEMS results.

[8] As an aside, the SEC metric is different than the Diesel Particulate Matter (DPM) metric used by Mine Safety and Health Administration (MSHA) in controlling exposures to DPM. The MSHA permissible Exposure Limit (PEL) of 100 $\mu g/m^3$ is based on Total Carbon which includes both EC and Organic Carbon (OC).

However, the U.S. Truckers' Study results were also used as supporting evidence along with results from a number of other less conclusive studies.

The HEI Special Report 19 contains a brief review of the U.S. Truckers' Study; however, like IARC, the HEI evaluation focused primarily on the DEMS study. In my opinion, the HEI Panel's evaluation of the U.S. Truckers' Study was rather superficial. It could have explored in greater depth the weaknesses in the U.S. Truckers' Study related to: (a) the retrospective exposure assessment; (b) the need to exclude mechanics to obtain positive results; and (c) the lack of smoking histories on any members of the cohort. In this reviewer's opinion, findings from the U.S. Truckers' Study, as reported to date, are not likely to be used as a primary source of information in any quantitative risk assessment, an opinion also shared by the HEI Epidemiology Panel. It is not apparent that the findings reported to date from the U.S. Truckers' Study provide any unique insights into the potential lung cancer hazards of diesel exhaust exposure of underground miners.

VIII. Overview of Diesel Exhaust in Miners Study (DEMS)

As noted earlier, the 1988 IARC evaluation published in 1989 concluded that exposure to diesel engine exhaust was "probably carcinogenic to humans," a conclusion largely driven by the characterization of the animal evidence as being "sufficient" tempered by the human epidemiological evidence at that time being viewed as "limited." This uncertain characterization in 1988 of the epidemiological evidence and the overall classification served as a major stimulus for the design and conduct of epidemiological studies with improved design and statistical power for detecting a carcinogenic hazard.

In the United States, NIOSH has the primary federal government responsibility for developing information on occupationally related diseases, including lung cancer. In this role, NIOSH serves as an advisor to MSHA and OSHA for the regulations those agencies develop. NCI is the primary U.S. federal agency responsible for funding and conducting research on the etiology, diagnosis, and treatment of cancer. Thus, it was natural for these two agencies, NIOSH and NCI, to jointly fund, design and conduct the DEMS project, initiated in 1992. The non-metal mining industry was selected for study because monitoring reports indicated this industry had high levels and a wider range of diesel exhaust (DE) exposure than other industries (NCI/NIOSH 1997; Stewart, et al., 2010)

A summary overview of the DEMS project as developed by the HEI Panel is provided in Table 3. Some important details for each of the mining operations are given in Table 4. Table 5 provides a summary of the data available for estimating REC exposure. Note that very limited

REC data are available except for post-1997 and the relative abundant CO data, especially from MSHA Mine Information Data System (MIDAS) historical area CO compliance data (1976-2001). This was a key factor in the NIOSH/NCI decision to use CO as a surrogate for REC. Summary data on the populations studied are provided in Table 6.

After an extensive feasibility effort, 10 mining facilities in the USA [four potash in New Mexico, three trona (trisodium hydrogen dicarbonate dehydrate) in Wyoming, two rock salt mines in Ohio and Louisiana, and one limestone mine in Missouri] were selected for further evaluation. These particular mining operations were selected because they had a long history of using diesel-powered equipment underground and were thought to have low concentrations of other potential airborne agents, such as radon, silica and asbestos known to cause lung cancer. (NCI/NIOSH, 1997) Two of the 10 facilities, a potash facility in New Mexico and a salt mine in Louisiana, were later excluded from the DEMS due to incomplete personnel records. One of the potash mines in New Mexico closed before the DEMS research was concluded. Thus, for exposure assessment purposes one of the other potash mines in New Mexico served as a surrogate for the closed mine located in the same area.

The mines selected had started using diesel equipment in 1947 through 1967, dependent upon the mine (Table 4). Ultimately, 12,315 workers in all eight mining and associated operations would be studied through December 31, 1997, by which time 2,185 deaths had occurred among the study population with 193 lung cancers.

The first actual air contaminant monitoring measurements made specifically for DEMS were not made until 1998-2001 (Table 5). Thus, it was necessary to retrospectively estimate the DE exposures using REC as the exposure metric for the DEMS participants from the dieselization of each mine through December 31, 1997. Recall that mortality of the participants in DEMS was followed through December 31, 1997. The DEMS exposure assessment process has been documented in five detailed peer-reviewed papers: Stewart, et al., 2010; Coble, et al., 2010; Vermeulen, et al., 2010a; Vermeulen, et al., 2010b; and Stewart, et al., 2012.

At the core of the DEMS exposure assessment process was the decision to use Respirable Elemental Carbon (REC) as the indicator for DE exposure. REC is characterized with a sampling technique that collects airborne particles less than 3.5 microns in size. This size cut off is slightly above the 2.5 micron cut off used for the NAAQS $PM_{2.5}$ standard. The REC metric is different than the DPM metric used by MSHA to regulate and control exposures to diesel exhaust. MSHA uses a PEL of 160 $\mu m/m^3$. In the absence of measurements of REC, another diesel exhaust constituent, carbon monoxide (CO), was selected for use in DEMS as a surrogate for REC. This was done because it was one of the airborne agents for which there

were measurements available dating to 1976 (Table 5). It is noteworthy that for all mines for all years, approximately 50 percent of the CO measurements used were below the limits of detection. In the absence of measured CO concentrations, the CO values used in the exposure assessments had to be imputed. This added uncertainty for estimating CO concentrations and, most importantly, also added to the uncertainty to the REC estimates that were retrospectively estimated from the CO concentrations.

The basic approach of the DEMS team to retrospectively estimate REC involved measurement of REC on personal monitoring samples collected on individual workers in seven of the eight DEMS mines in 1998-2001. Recall one potash mine had closed in 1993 and, thus, was not available. Arithmetic means of the DEMS REC measurements in 1998-2001 were considered to be reference values. Temporal trends in CO measurements based primarily on MSHA Mine Information Data System (MIDAS) historical area CO compliance data were modeled using diesel exhaust related determinants, i.e., diesel engine horse power (HP) and ventilation rates (CFM). The modeled trends in CO concentrations were then used to adjust the 1998-2001 REC reference values to obtain historic annual REC concentrations for each job in each prior year in each mine. Central to this approach is the assumption that CO is a suitable surrogate for REC.

The estimated primary REC concentrations used by Attfield, et al. (2012) and Silverman, et al. (2012) to conduct their epidemiological analyses are shown graphically in Figure 2. As discussed in Crump, et al. (2015), the NIOSH/NCI investigators also developed three other REC estimates.

A total of 12,315 workers, with 2,185 deaths, in the eight mining operations were included in DEMS (Table 6). This included all workers who were employed in blue-collar jobs for at least one year after dieselization of the study facilities. Individuals who held only administrative or management positions during their employment were excluded. Mortality of the workers was followed through December 31, 1997. The cohort was matched with the National Death Index (NDI-plus) and Social Security Death files to identify individuals who died and the cause of death (Attfield, et al., 2012).

Within the DEMS cohort, 207 deaths were identified as being caused by lung cancer (Attfield, et al., 2012). For a variety of reasons, nine cases were excluded from the nested lung cancer case-control study (Silverman, et al., 2012). The remaining 198 lung cancer case deaths were matched with 562 incidence density-sampled control subjects. As an aside, about 10% of the deaths in the DEMS cohort were associated with lung cancer, substantially less than the 18% reported for the U.S. Truckers' Study. This substantial difference could be related to

many factors, including the age distribution of the population and differences in smoking history in the population.

The epidemiological analyses of the total DEMS cohort directed at identifying an association between exposure to diesel exhaust using REC as the metric were reported in Attfield, et al. (2012). Those analyses did not consider cigarette smoking since it was not possible to ascertain the smoking history of all 12,315 individuals in this cohort or even the 2,185 individuals who died prior to December 31, 1997.

To ascertain, and potentially to adjust for, the effects of cigarette smoking, a nested lung cancer case-control study was conducted as part of DEMS (Silverman, et al., 2012). In this study, information on cigarette smoking was ascertained from next-of-kin interviews for the 198 lung cancer cases and for the 562 incidence density-sampled control subjects.

It is noteworthy that in the analyses conducted by Attfield, et al. (2012) and Silverman, et al. (2012), workers were categorized in binary fashion either as *surface-only workers* or as *ever-underground workers* (Table 6). The ever-underground category includes both (a) underground-only workers, and (b) individuals who, at different times, worked on the surface and underground. From Table 6 it is apparent that about one third (approximately 4000 workers) of the total cohort is included in each of the three subgroups, the surface-only, underground only, and mixed (sometimes underground and sometimes on the surface). The number of lung cancer cases is not proportional to the population sizes, presumably related to differences in the age distribution of the individuals in each group and, most importantly, their smoking history. The older the population studied, the higher the incidence of lung cancer and the higher the portion of the population smoking, the higher the incidence of lung cancer.

IX. Results for DEMS Data Analysis

The primary results of the analysis of the DEMS data by the original NIOSH/NCI investigators have been summarized by the HEI Panel and are shown in Table 3. As noted earlier, the DEMS cohort study did not include collection of smoking history data. Attfield, et al. (2012) did a Standardized Mortality Rate (SMR) ratio analysis with rates externally standardized to state-, age-, gender- and ethnic group-, specific death rates for each mine. This was necessary because rates vary substantially for different populations, especially state specific death rates. Recall the mines were located in four different states. They found statistically significant effects for the (a) complete cohort – SMR = 1.26, CI = 1.09-1.44; (b) ever-underground – SMR = 1.21, CI = 1.01=1.45; and (c) surface-only – SMR = 1.33, CI = 1.06-1.66.

These results can be interpreted as indicating about 21% of the lung cancers in the DEMS cohort are attributable to diesel exhaust exposure or a closely correlated risk factor such as radon exposure. A key consideration in interpreting these findings is that the cigarette smoking history of the workers is assumed to be similar to that of the populations of the states in which the mines are located. The results can be interpreted as indicating that for the DEMS population, just as for the general population, the vast majority of the lung cancers are attributable to smoking.

Attfield, et al. (2012) also reported Cox Proportional Hazard (CPH) analyses for the cohort. The initial CPH analysis conducted for the total cohort did not yield statistically significant results. It was only when the ever-underground workers (122 lung cancers in 8,307 workers) were analyzed separately from the surface-only workers (78 lung cancers in 4,008 workers) that a statistically significant effect was found in the ever-underground workers. The HR was not elevated in surface-only workers who had low REC exposure. The HR was elevated for ever-underground workers in a cumulative REC exposure-related manner with a statistically significant increase in the HR for the two highest quantities of exposure, 445 to < 946 $\mu g/m^3$ –years, HR = 2.17, CI = 1.21-3.88 and > 946 $\mu g/m^3$-year, HR = 2.21, CI = 1.19-4.09. It is noteworthy that the REC effect on lung cancer was strongly influenced by excluding the most heavily exposed workers, >1870 $\mu g/m^3$ –years. The basis for these findings was not discussed.

It is noteworthy that Attfield, et al. (2012) did briefly comment on analysis of a radon exposure effect. They noted that "among ever-underground workers, there was some evidence of a cumulative radon exposure effect (P=0.037)," although detailed results were not shown. They went on to note this effect was absent in seven of the mines, and in the eighth mine (Mine A, the limestone mine) the radon effect was driven by workers aged 40 years or older employed before 1947. The cumulative radon effects on lung cancer were large and statistically significant in some analyses. They noted that removing the early older workers from the analysis removed the radon effect both for the facility and the total DEMS cohort.

In my opinion, the most significant DEMS results are those that were reported for the nested lung cancer case-control study in which cigarette smoking histories were ascertained from next of kin interviews for 198 lung cancer cases and 562 incidence density–sampled control subjects. (Silverman, et al., 2012) The Cox Proportional Hazard analysis odds ratios for subjects with cumulative REC over 536 $\mu g/m^3$ –years was 2.38 (CI = 1.28-6.26), a statistically significant finding.

It is commendable that the original investigators (Silverman, et al., 2012) explored the role of cigarette smoking in some detail and reported all of the results even though some of the findings as related below could not be fully explained. As expected, these analyses showed the overwhelming influence of cigarette smoking on lung cancer in this cohort. Indeed, Silverman, et al. (2012) concluded that the lung cancer risk experienced by surface-only workers who had quite low exposures to diesel exhaust was mainly due to smoking. This finding seems to be at odds with the observation of Attfield et al. (2012) who found the highest SMR in the surface-only workers.

For both surface workers and ever-underground workers combined, not unexpectedly, the risk of lung cancer was statistically significantly associated with both (a) smoking status (never, former, current smokers), and (b) smoking intensities. For example, for former smoker of ≥ 2 packs per day versus never smokers; OR = 5.40, CI = 2.23-13.06; current smoker of ≥ 2 packs/day versus never smoker; OR = 12.41, CI = 5.57-27.66. These results were certainly not unexpected and show the clear value of smokers quitting. The original investigators' analyses yielded an anomalous finding, a substantially greater lung cancer risk for workers who only worked on the surface vs. those who ever-worked underground. For example, the OR for current smokers of one to less than two packs per day who only worked on the surface was 13.34 (CI = 4.50-39.53) compared with an OR of 4.51 (CI = 1.50-13.58) for those who ever-worked underground. This unexplained difference is of special interest because, as noted earlier, the ever-underground workers group included two sub-groups: (a) individuals who always worked underground (4,080 workers and 82 lung cancers), and (b) individuals who had worked both on the surface and at other times underground (4,229 workers and < 44 lung cancers). In short, the crude incidence of lung cancer for the two groups differed by a factor of about 2.

The nested case-control Cox Proportional Hazard (CPH) analysis yielded a statistically significant REC effect on the odds ratio for the quartile with > 536 $\mu g/m^3$ –years, having an OR – 2.38, CI = 1.28-6.26. The trend test across all four quartiles was statistically significant. It is clear there is a strong, statistically significant signal from this original analysis of DEMS that exposure to diesel exhaust at some concentrations and durations of exposure elevates the lung cancer risk. This was the driver for the 2012 IARC characterizing diesel exhaust exposure as a human carcinogen. Moving beyond hazard characterization, the question now is whether the analyses of DEMS data are sufficiently robust for use in quantitative risk assessment.

X. Replication and Extended Analyses of DEMS Data

As noted earlier, NIOSH and NCI have allowed other investigators, beyond the original investigators, to have access to the DEMS data under carefully prescribed and controlled conditions. This critique will focus on the analyses conducted by the independent analysts funded by a coalition of private organizations coordinated by the Engine Manufacturers Association (EMA). The results of that substantial body of work have been reported in three papers published in the peer-reviewed literature (Moolgavkar, et al., 2015; Crump, et al., 2015, 2016). Other analyses are still in progress.

One of the teams of independent analysts, Moolgavkar, et al. (2015), reported analyses of the DEMs cohort data set originally analyzed on and reported by Attfield, et al. (2012). The re-analysis team was provided three de-identified data files with demographic, occupational and death outcome data. By the end of mortality follow-up, December 31, 1997, a total of 2,185 deaths and 200 lung cancer deaths had been ascertained. All of the analyses conducted by the independent analysts initially used the same REC exposure estimates developed and used by the original investigators. The independent team replicated the findings of Attfield, et al. (2012) using Standardized Mortality Rates (SMR) analyses and Cox Proportional Hazard Regressions. This step was crucial in that it verified the re-analysis team was using the same basic data set as the original investigators. While this replication lends confidence to the conduct of the original analyses, the replication of the results should not be taken as a blank endorsement of either the original analytical approach or the interpretation of those findings by the original DEMS investigators.

At the next step, the independent investigators conducted extended analyses using parametric functions based on the concepts of multistage carcinogens to estimate lung cancer hazard functions focusing on the role of temporal factors and mine type. The multistage models used were similar to those used by Dawson and Alexeeff (2001) who estimated units risk for diesel engine exhaust-associated lung cancer in a cohort of railroad workers (Garshick, 1987) using the now classical multistage model of carcinogenesis of Armitage and Doll (1954). The quantitative lung cancer risk assessment results of the Dawson and Alexeeff work were used by the California Air Resources Board as a basis for its early and stringent diesel emission regulations using a report of the California Environmental Protection Agency (CEPA, 1998).

The extended analysis of the DEMS cohort data set by Moolgavkar, et al. (2015) using the biologically-based model revealed a statistically significant association between REC and lung cancer for the entire cohort with a substantial influence related to the workers employed in

the limestone mining operation. Further, the REC-lung cancer association was observed in ever-underground workers and not observed in surface-only workers. The analyses showed a strong influence of time-related factors, i.e., when exposures occurred, exposure intensity and age. It is important to know that Moolgavkar, et al. (2015) could not control for radon in their analyses because the data sets they were originally given did not contain accurate radon data. The Moolgavkar team is now in the process of repeating some of their analyses having recently been given access to the radon data.

The next set of replication and re-analyses were conducted by Crump, et al. (2015) using the nested case-control DEMS data originally evaluated by Silverman, et al. (2012). By the time these analyses were conducted NIOSH/NCI had barred the independent analysts from using the DEMS data set except under closely controlled conditions. Thus, the Crump team analyses utilized DEMS data assembled and made available at the National Center for Health Statistics (NCHS) Research Data Center (RDC) in Hyattsville, Maryland. The Crump, et al. (2015) paper focused on evaluating alternative REC metrics developed by Crump and Van Landingham (2012) to evaluate the influence of changes in the REC metrics on the REC-lung cancer association. All of the REC exposure metrics evaluated had been developed assuming CO in the mines was a suitable surrogate for REC, the same approach as used by the original DEMS team. Without adjusting for radon exposure, the results were similar to those of Silverman, et al. (2012) with eight of nine REC exposure metrics showing an association between REC exposure and lung cancer mortality with trend slopes differing by only a factor of two. When exposure to radon was adjusted, the evidence for a REC effect was greatly diminished but still present in analyses that utilized the three original DEMS REC exposure estimates. When the six alternative REC exposure metrics developed by Crump were used and radon was controlled no REC effect on lung cancer mortality was observed in miners who only worked underground. The NIOSH/NCI investigators reported analyses on ever-underground workers and never reported any analyses for always underground workers. The finding of Crump et al. (2015) are of special interest since always underground miners are the individuals whose estimated exposure to diesel exhaust was likely to be the most certain.

In a third set of analyses, Crump, et al. (2016) extended the evaluation of alternative REC exposure estimates using the case-control DEMS data. As noted earlier, all four REC estimates developed and used by the original NIOSH and NCI team relied upon using CO as a surrogate for REC. There are serious shortcomings both with the use of CO as a surrogate and the CO data themselves. Recall from Table 4 that 50% of the CO measurements used by the original investigators in developing REC estimates were below the limits of detection varying

from 30% below the limits of detection in the limestone mine to 61% in one of the trona mines. Because of the substantial portion of CO measurements below the limits of detection it was necessary to impute (statistically assign) CO concentrations when detectable concentration values were not available.

A key concern with the REC estimates developed by the original investigators was this strong dependence on the relationship between engine HP and CO emissions. Figure 3 is a graph of data from Yanowitz, et al. (2000) showing the highly uncertain relationship of emissions of CO to HP for individual engines. This illustrates the uncertainty involved in assuming there is a constant quantitative relationship between CO and HP as assumed in the REC estimates of the original NIOSH/NCI team.

An alternative approach to more directly estimate REC exposure is based on yearly diesel equipment usage expressed in HP and ventilation rates as CFM for each mine, based on historical records for each year assembled by the original DEMS team. The records were made available to the independent analysts in response to a Freedom of Information Act request filed with NCI by the EMA. Further, adjustments in total PM emission per brake HP were made for the interval between 1975 and 1995 when major reductions in PM emissions occurred with improvements in diesel technology (Figure 4), data included in the Health Assessment Document prepared by EPA (2002). Particulate matter emissions per brake HP-hour were assumed to be constant pre-1975 and post-1995. This approach built on the earlier work of Crump and Van Landingham (2012) and Crump, et al. (2015). Most importantly, this HP-CFM approach was consistent with an approach suggested in the HEI Special Report 19, Appendix F, largely authored by Professor David Foster, the only expert on diesel technology who was a member of the HEI Epidemiology Panel.

The REC estimates based on HP-CFM developed by Crump, et al. (2016) are shown in Figure 2 for ease of comparison with the REC estimates developed by the original DEMS investigators using CO as a surrogate for REC. As may be noted, the most substantial differences are for the limestone mine and salt mine, both of which made substantial use of high HP diesel-powered equipment to haul ore (See Table 4). Recall also that limestone mine A was naturally ventilated.

The results of using the REC exposure estimates based on HP-CFM compared to the original analyses for REC exposure response analysis to evaluate the association between REC and excess lung cancer risk are shown in Table 7. This is a complex table that may be challenging to follow. The table includes analyses on three sets of subjects; (a) all subjects at the top of the table; (b) all subjects ever underground in the middle section of the table; and (c)

all subjects who only worked underground in the lower section of the table. The ever underground grouping is consistent with the grouping of the original DEMS investigators. The only worked underground group was developed by the independent analysts using the original DEMS data.

The results of Silverman, et al. (2012) analysis are shown at the top for all subjects and ever underground workers and were taken directly from the Silverman, et al. paper. Results for the first set of analyses below the original findings were a replication analysis performed by Crump, et al. (2016). These analyses verify that as closely as possible the original analyses were duplicated and, thus, the data sets used and reported in Crump et al. (2016) must be very similar to those used by Silverman, et al. (2012). These analyses were done without control for radon because Silverman, et al. did not control for radon. The next set of analyses for each of the three groups use the HP-CFM based REC exposure estimates without and then shown below with control for radon.

Going from left to right in the table, the columns are; (a) analysis; (b) quartiles of cumulative REC; (c) number of cases; (d) number of controls; (e) the Odds Ratio (with Confidence Interval); (f) the P trend value; and (g) the slope expressed as cases per $\mu g/m^3$ – year. The smaller the value, the shallower the slope. All of the results in Table 7 are based on use of a 15-year lag.

It may be noted that the initial analyses performed using the REC estimates as Silverman, et al. (2012) without control for radon yielded results that were almost identical to those of Silverman, et al. (2012) verifying that the same basic DEMS data are being analyzed by the original investigators and the Crump team. When these analyses were repeated using the REC estimates based on HP-CFM, the findings were reduced in statistical significance and the slopes were shallower without control for radon. With control for radon, the statistical significance was further reduced and the slopes were even more shallow. When the analyses were conducted for all subjects who only worked underground (58 lung cancer cases and 97 controls), there was a further reduction in statistical significance.

In summary, none of the trend slopes calculated using the REC estimates based on HP-CFM were statistically significant ($p > 0.05$). Moreover, these trend slopes were smaller by roughly factors of five without control for radon exposure and factors of 12 smaller with control for radon exposure compared to those estimated in the original DEMS analyses reported by Silverman, et al. (2012). In my opinion, several factors influence the results. One factor relates to the generally higher estimates of REC concentrations based on HP-CFM compared to the original REC concentration estimates. The higher the REC concentration in the denominator of

the slope the shallower the slope since the number of lung cancer cases remains constant in the analyses. Most importantly, the analyses of Crump, et al. (2015, 2016) show an influence of radon. This is not surprising since radon is well recognized as a cause of lung cancer in humans (Moolgavkar, et al., 1993; IARC, 1998). In my opinion, if radon is not controlled for in the analyses even with low exposures to radon the estimates of the potency of REC will be exaggerated. It is scientifically inappropriate to focus on analyzing the risk factor of current concern, in this case, diesel exhaust, and ignore other well-known risk factors such as radon.

The results reported by Crump, et al. (2016) using the HP-CFM based REC exposure estimates and control for radon compared to the results of Silverman, et al. (2012) emphasize how sensitive the results of analysis of the DEMS data are to choice of the exposure metric and control for the low level radon exposures. In my opinion, the HP-CFM based REC estimate metric is superior to the REC estimates developed by the original investigators because of uncertainties associated with using CO as a surrogate for REC have been removed. Recalling the analogy to the three-legged stool discussed earlier, the exposure leg of the stool for any analysis of the DEMS data is highly uncertain.

The re-analyses of the DEMS cohort data conducted by Moolgavkar, et al. (2015) using the same REC estimates used by the original investigators and without control for radon are now being extended to include the HP-CFM based REC exposure metric and control for radon. This is being done by accessing the DEMS data at the NCHS-RDC in Hyattsville, MD. The results of those analyses should be available in the near future.

XI. HEI Epidemiology Panel Evaluation

The HEI in November 2015 published Special Report 19 – "Diesel Emissions and Lung Cancer: An Evaluation of Recent Epidemiological Evidence for Quantitative Risk Assessment," authored by the HEI Diesel Epidemiology Panel that consisted of nine scientists (Table 8). In the interest of completeness, the Peer Reviewers of Special Report 19 are also shown in the table.

The HEI Epidemiology Panel *primarily focused* on evaluating the findings of the Diesel Exhaust in Miners Study (DEMS) as reported in papers authored by scientists from NIOSH and NCI, the two federal agencies that funded and conducted DEMS. The HEI Panel Report concludes "that the DEMS and the Truckers Study provided results and data that provide a useful basis for quantitative risk assessments of exposures in particular to older diesel engine

exhaust."[9] The report goes on to note -- "The uncertainties within each study should be considered in any attempts to derive an exposure-response relationship" for diesel exhaust particulate matter.[10]

In my opinion, the HEI Panel gave ***secondary consideration*** to analyses conducted by the independent scientists funded by a coalition of private sector entities organized by the Engine Manufacturers Association (EMA). The independent scientists encountered substantial difficulty in gaining access to the basic DEMS data sets assembled by the U.S. government scientists which delayed the conduct of their analyses. Ultimately, access to the DEMS data sets was given to the independent scientists to conduct analyses under carefully defined conditions, ostensibly to protect the identity and privacy of individuals enrolled in DEMS. The various delays in allowing access to the DEMS data resulted in the results of the independent analyses becoming available late in the HEI Panel's evaluation process. Indeed, some of the results of the extended analyses the independent analysts conducted were not available until after the HEI gave a preliminary report at the May 2015 HEI Annual Conference. At this HEI conference, one of the HEI Epidemiology Panelists noted that he intentionally gave secondary attention to the independent analyses because they were funded by industry.

By failing to consider ***all*** of the analyses of the DEMS data set in a more even-handed manner, the HEI Panel missed an opportunity to advocate for more open access and extended analyses of important epidemiological data sets, such as DEMS, assembled by either government or private sector funded scientists. This should be "the way of the future" and encouraged, i.e., open access to data, replication of results and extended analyses by multiple investigators. The HEI Panel ignored this opportunity and provides no guidance in its report as to how the interests of the original investigators (and subjects in the epidemiological studies) can be protected yet the broader interests of Society also better served by access to data and conduct of alternative analyses.[11]

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[9] HEI Report at 1.

[10] *Id.* at 7.

[11] The topic of more open access to data has received a great deal of attention during the last decade. This has included concern for access to epidemiological data such as that undergirding the setting of National Ambient Air Quality Standards for the criteria pollutants and especially the standards for $PM_{2.5}$. HEI is quite familiar with this controversy having sponsored the re-analysis of two data sets, one using data from the American Cancer Society (ACS) and the other data from the Harvard Six Cities study. HEI arranged to obtain restricted access to these data and sponsored re-analysis of the data. Ironically, Professor Daniel Krewski, who chaired the HEI Epidemiology Panel, had a lead role in conducting the earlier re-analyses of the ACS and Harvard data. The National Research Council (NRC, 2016) has recently published a

In the opinion of this reviewer, the construct of the HEI Report is biased toward support of the conclusions reported by the original DEMS investigators. The HEI Report does identify uncertainties in the DEMS original analyses, frequently noting these will pose "challenges" in the conduct of future quantitative risk assessments using DEMS.[12] However, in identifying issues that create uncertainties, the HEI Panel and their Report carefully avoids providing a roadmap or plan for conducting future quantitative risk assessments. This approach is understandable. However, the Panel had considerable latitude it did not use to note how key uncertainties would impact on the conduct of any quantitative risk assessments.

Some of the key issues relating to use of the DEMS data set and interpretation of the results are discussed below.

- *Panel Members' Experience in Mines:* Neither the HEI Panel members, individually or collectively, nor HEI staff, visited any of the DEMS mines despite being specifically invited to visit one of the trona mines. Nor was any evidence provided of Panel members having prior knowledge of underground nonmetal mining operations of the kind used in the DEMS mines. Knowledge of how the mines are operated and, specifically, how diesel-powered equipment is used in mining operations such as in the mining operations included in DEMS would have provided valuable context for the Panel's evaluation.
- *Exposure Assessment*: The DEMS report fails to clearly note that <u>all</u> of the Respirable Elemental Carbon (REC) metrics used in the original analyses and subsequent analyses of DEMS are based on uncertain retrospective extrapolations. Actual measured REC concentrations are not available pre-December 31, 1997, when the study concluded. Further, the report does not emphasize that with use of a 15-year lag in the analyses, the extrapolated REC estimates of greatest interest are the estimates for 1982 and earlier. In addition, the report does not make clear that CO measurements from the MIDAS data set were only available for 1976 and later. Despite these major short-comings, the overall tone of the HEI report is to laud the exposure assessment done by the original DEMS investigators and relegate key aspects of the Panel's valuation of the exposure assessment to Appendix F to the report.

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report summarizing a conference sponsored by the NRC on issues associated with more open access to data. The title of the NRC report – "Principles and Obstacles for Sharing Data for Environmental Health Research," in part indicates the difficulties of achieving wider "open access" of data.

[12] HEI Report at 7.

- *Work Location*: The original investigators conducted analyses on: (a) the total cohort; (b) surface only workers; and (c) ever underground workers. The latter is a mixed group of individuals who had worked sometimes on the surface and sometimes underground and those who always worked underground. The independent analysts subdivided the latter group and separately evaluated those who always worked underground from those who had mixed surface and underground work experience. The HEI Panel tended to dismiss this approach because the smaller size of this population of always underground workers reduced the statistical power of the analyses.
- *Lung Cancer Effect of Cigarette Smoking*: As expected, analyses of the DEMS nested lung cancer case-control data showed the overwhelming impact of cigarette smoking. Overall, for both surface-only and ever-underground workers combined, the risk of lung cancer was statistically significantly associated with (a) smoking status (never, former, current smokers) and (b) smoking intensity (former smoker of ≥ 2 packs per day vs. never smoker: OR = 5.40, 95% CI = 2.23 to 13.06; current smoker of ≥ 2 packs per day vs. never smoker: OR = 12.41, 95% CI = 5.57 to 27.66. The original investigators found that the lung cancer risks were substantially higher among workers who only worked on the surface in contrast to those who ever worked underground for both current and former smokers. For example, the OR for current smokers of one to less than two packs per day who worked only on the surface was 13.34 (95% CI = 4.50 to 39.53) compared with an OR of 4.51 (95% CI = 1.50 to 13.58) for those who worked ever underground. The HEI Panel did not explore this anomaly in any depth. This difference among surface-only and ever-underground workers is potentially very important because the original investigators grouped individuals together that had worked both on the surface and underground as an ever-underground group.

Retrospective Exposure Assessments

The HEI Report contains a series of useful Appendices. One of these is Appendix F, Technical Background and Further Evaluation of the DEMS Retrospective Exposure Model. This appendix, primarily authored by Professor David Foster of the University of Wisconsin, who was the Panel's only expert on diesel engines and their emissions, provides a thoughtful analysis of the DEMS retrospective exposure modeling activities. His analysis builds on previous criticisms of the exposure reassessment models used by the original investigators, criticisms that have largely gone unaddressed. Much attention is given in Appendix F to the issue of Horse Power (HP) – CO – REC relationships. Most importantly, Appendix F suggests a path forward that relies on use of engine horsepower and mine ventilation rates to estimate REC without the need to make any assumptions concerning CO as a surrogate for REC. That

is the approach that undergirds the analyses published in Crump, et al. (2016) and shown in Table 7.

Population Studied

The DEMS population of 12,315 individuals worked both on the surface and underground. About one-third worked exclusively on the surface, one-third exclusively underground and one-third worked, at different times, on the surface and underground. The original DEMS analyses combined the latter two subgroups to create an ever-underground cohort. Recognizing that the original DEMS investigators found anomalous results for the association between cigarette smoking and lung cancer related to work location (greater potency for surface workers smoking versus ever underground workers) the independent investigators deemed it important to analyze the always underground miners as a separate group. The HEI report does not address this critical issue in depth. Instead the HEI Panel and Report dismisses analyses using the always-underground miners as lacking statistical power.

Radon Exposure

Radon is a well-known cause of lung cancer especially in underground miners (Moolgavkar, et al., 1993; IARC, 1998; NRC, 1999). This was recognized initially in selecting the nonmetal mines for study in DEMS since it is generally acknowledged that nonmetal mines have low concentrations of radon. The HEI Panel explored the possible role of radon in the DEMS population in considerable depth. However, the Panel's evaluation of radon appears to have focused on attempting to support the view of the original DEMS investigators – that radon did not need to be included in the analyses evaluating the role of REC as a causative agent. The independent investigators' analyses showing a clear impact of radon exposure was down-played by the HEI Epidemiology Panel. This was especially disappointing since Attfield, et al., (2012) had called attention to this issue, especially related to the limestone mine workers in their paper. Recall that the Moolgavkar et al. (2015) paper also pointed at the influence of the limestone miners.

There is a fundamental difference of scientific opinion between the HEI Panel and the independent analysts with regard to control for radon in the analyses. The Panel raises concern that the radon effects are likely low and the radon exposure measurements are uncertain and, thus, are not worthy of inclusion in the analyses. In contrast, the independent analysts note the radon values that are available are actual measurements, not extrapolations, and it is appropriate to conduct analyses both with and without control for radon. The Crump et al. (2015 and 2016) analyses clearly show the influence of radon.

Mine to Mine Differences

The HEI Panel gave scant attention to the remarkable difference in the nature of the mining activities across the eight different operations mining four different types of ore in four different states. As already noted, neither the Panel collectively or any of the individual Panel members visited any of the DEMS mines. They were extended an invitation to visit one of the trona mines. The differences among the mines are very substantial, especially in how ore is mined and moved, the horsepower of the diesel-powered equipment used, the presence (or absence) of methane, and ventilation controls. By failing to address mine-to-mine differences, or at least call them to the attention of readers, the original investigators and the HEI Panel imply that all the mines are the same. This is certainly not the case. The most notable differences are between the single limestone mine (which was naturally ventilated and used very large horsepower equipment to haul ore from the face to the surface on a level plane) and the operations in other mines. As already noted, the limestone mine was naturally ventilated in contrast to the variable use of mechanical ventilation in the other mines. Concern for buildup of explosive gases in some of the other mines, such as the trona mines, prompts the use of higher ventilation rates in those mines. In mines other than the limestone mine, the horsepower of the diesel equipment used is relatively low because ore is primarily moved by electrical powered conveyors (except in the salt mine studied) and then hoisted to the surface. The salt mine used diesel powered units to haul ore from the face to central locations for processing and hoisting to the surface. In my opinion, the HEI Report should have more directly addressed these issues in critiquing the DEMS data set, even if nothing can be done in analyzing the DEMS data because of the relatively low number of lung cancer cases in individual mines, and thus, the lack of statistical power for evaluating individual mines and sub-populations.

It is especially noteworthy that the HEI Panel did not pursue further mine-to-mine differences considering that both the Attfield, et al. (2012) and Silverman, et al. (2012) papers opened the door to this subject. As already noted, Attfield, et al. called attention to differences between mines when they discussed the role of radon as a major risk factor in the limestone mine. Silverman, et al. (2012) examined the 102 lung cancer cases in the potash mining operations and 51 lung cancer cases in the trona mining operations and noted that the association between REC exposure and lung cancer was more consistent in the potash workers than in the trona workers. It is remarkable that Silverman, et al. (2012) did not call attention to the lack of statistical significance of the association between REC exposure and lung cancer in the trona workers although it is apparent in the tabular material in the paper. It is also of interest that Silverman, et al. (2012) did not address directly potential differences in smoking history

among the trona workers (in southwest Wyoming) versus potash workers (in New Mexico), recognizing that the southwest Wyoming population has many individuals of the Mormon faith, a which strongly discourages smoking. Indeed, it would have been of interest to learn if differences in smoking history were reflected in the next-of-kin interview data for the trona mines compared to other mines. Another issue relates to any work experience by DEMS participants in uranium mining with well-known exposure to high concentrations of radon and radon daughter products.

XII. Author's Conclusions

The HEI Report provides a blank endorsement of the use of the DEMS data set for quantitative risk assessment while noting the need to consider uncertainties in the data and their results. In this reviewer's opinion, the HEI Report does not adequately consider the implications of the results of the extended analyses conducted by the independent investigators. There is a stark contrast between the findings of Silverman, et al. (2012) and those of Crump, et al. (2016) based on analyses using the same DEMS data and different REC exposure metrics with and without control for radon. Silverman, et al. (2012) report a statistically significant association between exposure to REC and lung cancer for two groups: (a) all subjects; and (b) all subjects who ever worked underground. In contrast, Crump, et al. (2016) found reduced associations between REC and excess lung cancer with the HP-CFM based REC metric analyses conducted with and without control for radon. None of the trend slopes calculated using the new HP-CFM based REC estimates were statistically significant ($P > 0.05$). Moreover, these trend slopes were smaller by roughly factors of five without control for radon and factors of 12 with control for radon exposure compared to those of Silverman, et al. (2012). Also, the 95 percent confidence intervals for the newly derived trend slopes had only minimal overlap with those for the slopes in the original DEMS analyses.

It is the opinion of this reviewer that any quantitative risk assessment conducted using the DEMS data should consider the full range of potency for diesel exhaust particulate matter identified in the original and extended analyses. This should be the case whether developed to retrospectively to ascribe harm from diesel exhaust exposure to the worker population studied (or other populations with similar exposure) or prospectively to predict or estimate risk for other populations exposed to diesel exhaust.

Further, it should be noted that diesel engine technology, including the fuels used, has constantly changed over the past half century, resulting in continuous reductions in diesel exhaust particulate emissions, and more recently reduced NO_2, and the associated reduced

exposure of underground workers. Diesel engines currently marketed with modern control technology have virtually no particulate emissions and very low NO_x emissions (Khalek, et al, 2011, 2015).

XIII. Path Forward

The saga of the health effects of exposure to diesel exhaust continues and is likely to continue for some time. In the near future it will be important to anticipate a number of activities as enumerated below:

1. As noted above, another set of analyses of the DEMS cohort data are in progress under the direction of Dr. Suresh Moolgavkar. This work involves analysis of the DEMS cohort data originally reported on by Attfield, et al. (2012) and includes the use of the HP-CFM based REC metric with and without control for radon using the Cox Proportional Hazard model that was also used by Attfield, et al. These results should be available in the near future. It would be advantageous if these analyses could also be extended using biologically-based models as reported in Moolgavkar, et al. (2015). Unfortunately, it is uncertain if the biologically-based models can be used under the constraints imposed by NIOSH and NCI for use of DEMS data at the secure NCHS-RDC IN Hyattsville, MD. It will also be useful to encourage other investigators to seek to gain access to the DEMS data for extended analyses. This includes interested parties from Europe.

2. It is important to continue to make the results of the independent analyses of DEMS known to as many individuals and organizations as possible. Indeed, the access to data, replicative analyses and extended analyses using the DEMS data should be championed as a case study in how large data sets from government-funded studies should be made available as a matter of routine, especially when the results of analysis of the data will influence major public policy decisions. This is a topic that has been of considerable interest to some members of Congress.

3. The activities of NIOSH, EPA and other agencies that may conduct quantitative risk assessments for diesel exhaust from traditional diesel engines (pre-1990) need to be carefully monitored. At some juncture, such efforts are likely to shift from scoping or research activities to activities that clearly have potential regulatory impact. It is my impression that at some point these activities become part of the regulatory agenda and must be publicly disclosed. This should include holding public meetings in which the plans and protocols for conducting quantitative risk assessments should be disclosed and the opportunity provided for public comment.

4. The results of the HEI Epidemiology Panel evaluation and the findings of the independent analysts should be conveyed to interested workers, especially to workers in the mining operations that participated in DEMS, as the NIOSH/NCI investigators' findings have already been conveyed to those workers. The results of analysis of the DEMS data by the original investigators and the independent analysts reveal again that the major cause of lung cancer in workers is cigarette smoking. This emphasizes the importance of smoking cessation programs for workers and their families.

5. The DEMS data set includes a valuable compilation of data on diesel equipment usage and ventilation in the eight DEMS mines through 1997. It is important that these records be updated for the mining operations included in DEMS and similar records developed for other mines. It will be especially important to establish and maintain records on diesel fuel usage underground (both quantity and quality) to complement the records on diesel equipment. The quantity of diesel fuel used underground provides a simple index of exhaust emissions. These data, along with ventilation data, provide a useful index of potential exposures. It will also be important to clearly document the emission characteristics of both old engines and new engines as operations transition to increased use of new "low emission" diesel technology. Efforts to maximize the efficient use of ventilation to minimize worker exposures should continue.

6. Both worker and area monitoring activities should be reviewed to ensure they are in compliance with applicable regulations and, moreover, meet "best practice" standards for the industry. Current and future worker monitoring activities should focus on Respirable Particulate Matter (less than $PM_{2.5}$ microns) and REC. However, it is important to know that some individuals have trumpeted the potential harm of nanoparticles (particles less than 0.1 micron) and the potential greater importance of particle number versus particulate mass concentrations as indicators of potential harm. These are topics of active debate relative to environmental ambient air exposures and there is already evidence of these concerns being transferred to the occupational arena.

7. It will be important to continue to cooperate with investigators from NIOSH, MSHA and other organizations interested in using private facilities for research. However, it will be important to request the opportunity for prior review and approval of research protocols before research is initiated in private facilities.

XIV. The Author, Roger O. McClellan

Roger O. McClellan is an internationally recognized expert on the health effects of exposure to diesel exhaust. He was responsible for developing and leading the extensive

Lovelace Research Institute's multi-faceted research program on diesel exhaust beginning in the 1980s and served in an advisory capacity to other research programs on diesel exhaust health hazards around the world. He served on the National Research Council's (NRC) Board on Environmental Studies and Toxicology that provided guidance for the first NRC report on the health impacts of diesel technology. He was a founding member (1981-1992) of the Health Effects Institute Research Committee that had a major focus on designing and overseeing studies on diesel exhaust from engines in use in the 1980s. Later, he would serve on the external oversight committee for HEI's research in the early 2000s to study new technology diesel exhaust. He served as chair of the U.S. EPA's Clean Air Scientific Committee (1987-1992) and served on the Committee that reviewed the EPA's 2002 Health Assessment for Diesel Exhaust. He chaired the Animal Evidence Panel for IARC's 1988 evaluation of the carcinogenic hazard of exposure to diesel exhaust. He served as a member of the Department of Labor Mine Safety and Health Administration's review (1985-1987) of the use of diesel equipment in underground mines. He attended, as an observer, the 2012 IARC review of diesel engine exhaust.

McClellan received a Doctor of Veterinary Medicine degree from Washington State University in 1960. His early research was concerned with the effects of internally-deposited radionuclides. He was the leader of the Lovelace Inhalation Toxicology Research Institute from 1966-1988 conducting studies to evaluate the health risks of a range of airborne agents, including emissions from nuclear facilities and accidents to vehicles to coal-fired power plants. From 1988-1999, he was the President of the Chemical Industry Institute of Toxicology directing research that improved the scientific basis for assessing health risks of chemicals. Since 1999, he has served as an independent advisor to public and private organizations. McClellan has served on over 100 major advisory committees to all of the major U.S. federal agencies concerned with environmental and occupational health issues as well as international agencies. He has testified multiple times to Committees of both the U.S. Senate and House of Representatives on human health risk assessment issues. He occasionally testifies as an Expert Witness in legal proceedings.

He is a Diplomate of the American Board of Veterinary Toxicology and American Board of Toxicology. He is a Fellow of the Academy of Toxicological Sciences, American Association for Aerosol Research, International Assembly for Aerosol Research, Society for Risk Analysis, Health Physics Society and American Association for Advancement of Science. He was elected to membership in the National Academy of Medicine in 1990. He has received numerous honors for his contributions to improving environmental and occupational health through the

conduct of research at all levels of biological organization from cells to human populations and the application of the results to inform policy decisions impacting use of multiple technologies.

XV. Declaration of Interest

Roger O. McClellan prepared this critique as an independent contractor to the law firm of Crowell and Moring LLP, which in turn, was compensated by the Industrial Minerals Association – North America. The critique was prepared independently and the conclusions drawn and opinions expressed are exclusively those of the author.

XVI. References

Armitage P, Doll R. 1954. The age distribution of cancer and a multi-stage theory of carcinogenesis. Brit. J. of Cancer 8(1: 1-12.

Attfield MD, Schleiff PL Lubin JH Blair A, Stewart PA, Vermeulen R, Coble JB and Silverman DT. 2012. The Diesel Exhaust in Miners Study: A Cohort Mortality Study with Emphasis on Lung Cancer, J Natl Cancer Inst 104: 1-15.

Benbrahim-Talla L, Baan, R, Grosse, Y, Lanby-Secretan B, El Ghissassi F, Brouvard V, Cuha N, Loomis D, Straif K. 2012. Carcinogenicity of diese-engine and gasoline-engine exhausts and some nitroarenes. Lancet Oncology 13(7)663-664.

California Environmental Protection Agency. 1998. Office of Environmental Health Hazard Assessment. Health Risk Assessment for Diesel Exhaust, February 1998. Sacramento, CA:California Environmental Protection Agency.

Coble JB, Stewart PA, Vermeulen R., Yereb D, Stanevieh R, Blair A, et al., 2010. The Diesel Exhaust in Miners Study: II. Exposure monitoring surveys and development of exposure groups. Ann Occup Hyg 54:747-761.

Crump K, Van Landingham C, 2012. Evaluation of an exposure assessment used in epidemiological studies of diesel exhaust and lung cancer in underground mines. Crit Rev Toxicol 42:599-612.

Crump K. 2014. Meta-Analysis of Lung Cancer Risk from Exposure to Diesel Exhaust: Study Limitations. Environ Health Perspect 122(9). *http://dx.doi.org/10.1289/ehp.1408482.*

Crump KS, Van Landingham C, Moolgavkar SH, McClellan R. 2015. Reanalysis of the DEMS nested case-control study of lung cancer and diesel exhaust: suitability for quantitative risk analysis. Risk Anal 35(4):676-700. dol: 10.1111/risa. 12371.

Crump KS, Van Landingham C, McClellan R. 2016 (in press). Influence of alternative exposure estimates in DEMS miners study; diesel exhaust and lung cancer. Risk Anal.

Davis ME, Smith TJ, Laden F, Hart JE, Ryan LM, Garshick E. 2006. Modeling particle exposure in U.S. Trucking terminals. Environ Sci Technol 40:4226-4232.

Davis ME, Smith TJ, Laden F, Hart JE, Blicharz AP, Reasar P, et al. 2007. Driver exposure to combustion particles in the U.S. Trucking industry. J Occup Environ Hyg 4:848-854.

Davis ME, Laden F, Hart JE, Garshick E, Blicharz A, Smith TJ. 2009. Predicting changes in PM exposure over time at U.S. Trucking terminals using structural equation modeling techniques. J Occup Environ Hyg 6:396-403.

Davis ME, Hart JE, Laden F, Garshick E, Smith TJ. 2011. A retrospective assessment of occupational exposure to elemental carbon in the U.S. trucking industry. Environ Health Perspect 119:997-1002.

Dawson S, Alexeeff GV. 2001. Multi-stage model estimates of lung cancer risk from exposure to diesel exhaust, based on a U.S. railroad worker cohort. Risk Analysis 21:1-18.

DOL/MSHA (Department of Labor, Mine Safety and Health Administration). 2005. 70 FR 32868: Diesel particulate matter exposure of underground metal and nonmetal miners. Federal Register volume 70, issue 107.

EPA (Environmental Protection Agency). 2002. Health Assessment Document for Diesel Engine Exhaust. U.S. Environmental Protection Agency, EPA/600/8-90/057F.

Gamble JF, Nicolich MJ, Boffetta P. 2012. Lung cancer and diesel exhaust: An updated critical review of the occupational epidemiology literature. Crit Rev Toxicol 42:549-598.

Garshick E, Schenker MB, Munoz A, Segal M, Smith TJ, Woskie SR, et al. 1987. A case-control study of lung cancer and diesel exhaust exposure in railroad workers. Am Rev Resp Dis 135:1242-1248.

Garshick E, Schenker MB, Munoz A, Segal M, Smith TJ, Woskie SR, et al. 1988. A retrospective cohort study of lung cancer and diesel exhaust exposure in railroad workers. Am Rev Resp Dis 137:820-825.

Garshick E, Laden F, Hart JE, Rosner B, Davis ME, Eisen EA, et al. 2008. Lung cancer and vehicle exhaust in trucking industry workers. Environ Health Perspect 116:1327-1332.

Garshick E, Laden F, Hart JE, Davis ME, Eisen EA, Smith TJ. 2012a. Lung cancer and elemental carbon exposure in trucking industry workers. Environ Health Perspect 120:1301-1306.

Garshick E, Laden F, Hart JE, Davis ME, Eisen EA, Smith TJ. 2012b. Cox Model Setup: Garshick et al. Respond. Environ Health Perspect 120:A382-A383. *http://dx.doi.org/10.1289/ehp.1205573R* [Online 1 October 2012].

HEI Diesel Working Group. 1995. Diesel Exhaust: Critical Analysis of Emissions, Exposure, and Health Effects. Cambridge, MA:Health Effects Institute.

HEI Diesel Epidemiology Expert Panel. 1999. Diesel Emissions and Lung Cancer: Epidemiology and Quantitative Risk Assessment. Special Report. Cambridge, MA:Health Effects Institute.

HEI Diesel Epidemiology Working Group. 2002. Research Directions to Improve Estimates of Human Exposure and Risk from Diesel Exhaust. Cambridge, MA:Health Effects Institute.

Health Effects Institute. 2003. Research on diesel exhaust and other particles. Program Summary. Cambridge, MA: Health Effects Institute.

Health Effects Institute. 2007. Mobile-Source Air Toxics: A Critical Review of the Literature on Exposure and Health Effects. Special Report 16. Boston, MA:Health Effects Institute.

HEI Diesel Epidemiology Panel. 2015. Diesel Emissions and Lung Cancer: An Evaluation of Recent Epidemiological Evidence for Quantitative Risk Assessment. Special Report 19, Health Effects Institute, Boston, MA.

Hesterberg TW, Bunn WB, McClellan RO, Hart GA, Lapin CA. 2005. Carcinogenicity studies of diesel engine exhausts in laboratory animals: a review of past studies and a discussion of future research needs. Crit Rev Toxicol 35:379-411.

Hesterberg TW, Bunn WB 3rd, Chase GR, Valberg PA, Slavin TJ, Lapin CA, et al. 2006. A critical assessment of studies on the carcinogenic potential of diesel exhaust. Crit Rev Toxicol 36:727-776.

Hesterberg TW, Long CM, Bunn WB, Lapin CA, McClellan RO, Valberg PA. 2012. Health effects research and regulation of diesel exhaust: An historical overview focused on lung cancer risk. Inhal Toxicol 24 Suppl 1:1-45.

International Agency for Research on Cancer. 1989. Diesel and Gasoline Engine Exhausts and Some Nitroarenes. Vol. 46. Monographs on the Evaluation of Carcinogenic Risks to Humans. World Health Organization, International Agency for Research on Cancer, Lyon, France.

International Agency for Research on Cancer. 1998. Manmade mineral fibres and radon. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 43. World Health Organization (WHO), Lyon, France.

International Agency for Research on Cancer. 2012. Scientific Publication No. 161, Air Pollution and Cancer. Edited by Straif, K, Cohen, A, and Samet, J., IARC, Lyon, France.

International Agency for Research on Cancer. 2013. Diesel and Gasoline Engine Exhausts and Some Nitroarenes. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 105. Lyon, France:IARC. Available: http://monographs.iarc.fr/ENG/Monographs/vol105/monol05.pdf.

International Agency for Research on Cancer. 2015. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 109. Outdoor Air Pollution, IARC, Lyon, France.

Khalek IA, Bougher TL, Merritt PM, Zielinska B. 2011. Regulated and unregulated emissions from highway heavy-duty diesel engines complying with U.S. Environmental Protection Agency 2007 emissions standards. J Air Waste Manag Assoc 61:427-442.

Khalek IA, Blanks MG, Merritt PM, Zielinska B. 2015. Regulated and unregulated emissions from modern 2010 emissions-compliant heavy-duty on-highway diesel engines. J Air Waste Manag Assoc 65(8):987-1001.

Laden F, Hart JE, Smith TJ, Davis ME, Garshick E, 2007. Cause-specific mortality in the unionized U.S. Trucking industry. Environ Health Perspect 115:1192-1196.

Lee KP, Trochimowicz HJ, Reinhardt CF. 1985. Pulmonary response of rats exposed to titanium dioxide (TiO_2) by inhalation for two years. Toxicol. Appl. Pharmacology 79:179-182.

Loomis D, Grosse Y, Lauby-Secretan B. 2013. The carcinogenicity of outdoor air pollution. The Lancet 14(13):1262-1263.

Mauderly JL, Jones RK, Griffeth WC, Henderson RF, and McClellan RO. 1987. Diesel Exhaust as a pulmonary carcinogen in rats exposed chronically by inhalation. Fundament. Appl. Toxicol. 9:208-221.

Mauderly JL, Banas DA, Griffeth WC, Hahn FF, Henderson RF and McClellan RO. 1996. Diesel exhaust is not a pulmonary carcinogen in CD-1 mice exposed under conditions carcinogenic to rats. Fundament. Appl. Toxicol. 30:233-242.

McClellan RO. 1999. Human Health Risk Assessment: A Historical Overview and Alternative Paths Forward. Inhal Tox 11:477-518.

McClellan RO, Hesterberg TW, Wall JC. 2012. Evaluation of carcinogenic hazard of diesel engine exhaust needs to consider revolutionary changes in diesel technology. Regul Toxicol Pharmacol 63:225-258.

Moolgavkar SH, Luebeck EG, Krewski D, Zielinski JM. 1993. Radon, cigarette smoke, and lung cancer: A re-analysis of the Colorado plateau uranium miners' data. Epidemiology 4:204-217.

Moolgavkar SH, Chang ET, Luebeck G, Lau EC, Watson HN, Crump KS, et al. 2015. Diesel engine exhaust and lung cancer mortality — time-related factors in exposure and risk. Risk Analysis: doi: 0:1111/risa.12315 [Online 13 February 2015]. Available: *http://dx.doi.org/10.1111/risa.12315*.

Morfeld P, Spallek M. 2015. Diesel engine exhaust and lung cancer risk-evaluation of the meta-analysis by Vermeulen et al, 2014. J Occup Medicine and Toxicology 1:31.

National Cancer Institute-National Institute for Occupational Safety and Health. 1997. A cohort mortality study with a nested case-control study of lung cancer and diesel exhaust among nonmetal miners (NCI-NIOSH Interagency Project Protocol, 16 September 1997). [Source: Debra Silverman, Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, NCI Shady Grove, Room 6E142, Rockville, MD 20892;(240)26-7174; silverman@exchage.nih.gov]

National Research Council, Health Effects Panel of the Diesel Impacts Study Committee. 1981. Health Effects of Exposure to Diesel Exhaust: Impacts of Diesel-Powered Light-Duty Vehicles. Washington, DC:National Academies Press.

National Research Council. 1983. Risk assessment in the federal government: Managing the process. Washington, DC:National Academies Press.

National Research Council. 1993. Issues in Risk Assessment. Washington, DC:National Academies Press. Available: *www.nap.edu/catalog/2078/issues-in-risk-assessment.*

National Research Council. 1994. Science and Judgement in Risk Assessment. Committee on Risk Assessment of Hazardous Air Pollutants. Washington, DC:National Academies Press.

National Research Council. 1996. Understanding Risk: Informing Decisions in a Democratic Society. Committee on Risk Characterization. Washington, DC:National Academies Press.

National Research Council. 1999. Health Risks of Exposure to Radon: BEIR VI. Committee on Health Risks of Exposure to Radon, Board on Radiation Effects Research, Commission on Life Sciences, National Research Council. Washington, DC:National Academies Press. Available: *www.nap.edu/openbook.php?isbn= 0309056454.*

National Research Council. 2009. Science and decisions: Advancing Risk Assessment. Committee on Improving Risk Analysis Approaches Used by the U.S. EPA. Washington, DC:National Academies Press.

National Research Council. 2016. Principles and Obstacles for Sharing Data for Environmental Health Research: Workshop Summary, Rapporteus, Pool R and Rusch E., 114 pp, National Academies Press.

Neophytou AM, Picciotto S, Costello S, Eisen EA. 2016. Occupational diesel exposure, duration of employment, and lung cancer. Epidemiology 27(1):21-28.

Nikula KJ, Snipes MB, Barr EB, Griffith WC, Henderson RF, Mauderly JL. 1995. Comparative pulmonary toxicities and carcinogenicity of chronically inhaled diesel exhaust and carbon black in F344 rats. Fundam. Appl. Toxicol. 25:80-94.

Silverman DT, Samanic CM, Lubin JH, Blair AE, Stewart PA, Vermeulen R, et al. 2012. The Diesel Exhaust in Miners Study: A Nested Case-Control Study of Lung Cancer and Diesel Exhaust, J Natl Cancer Inst 104: 855-868.

Smith TJ, Davis E, Reaser P, Natkin J, Hoyt JE, Laden F et al. 2006. Overview of particulate exposures in the US trucking Industry. J Environ Monitoring 8:711-720.

Stewart PA, Coble JB, Vermeulen R, Schleiff P, Blair A, Lubin J et al. 2010. The diesel exhaust in miners study: I. Overview of the exposure assessment process. Ann Occup Hyg 54:728-746.

Stewart PA, Vermeulen R, Coble JB, Blair A, Schleiff P, Lubin JH, et al. 2012, The diesel exhaust evaluation of the exposure assessment methods. Ann Occup Hyg 56:389-400.

Vermeulen R, Coble JB, Lubin JH, Portengen L, Blair A, Attfield MD. 2010a. The diesel exhaust in miners study: IV. Estimating historical exposures to diesel exhaust in underground non-metal mining facilities. Ann Occup Hyg 54:774-788.

Vermeulen, R, Coble, JB, Yereb, D, Lubin, JH, Blair, A, Portengen, L et al. 2010b. The diesel exhaust in miners study: III. Interrelations between respirable elemental carbon and gaseous and particulate components of diesel exhaust derived from area sampling in underground non-metal mining facilities. Ann Occup Hyg 54:762-773.

Vermeulen R, Silverman DT, Garshick E, Vlaanderen J, Portengen L, Steenland K. 2014a. Exposure-response estimates for diesel engine exhaust and lung cancer mortality based on data from three occupational cohorts. Environ. Health Perspectives 122:172-177 (doi:10.1289/ehp 1306880).

Vermeulen R, Portengen L, Silverman DT, Garshick E, Steenland K. 2014b. Metaanalysis of lung cancer risk from exposure todiesel exhaust: Vermeulen Response. Environ. Health Perspectives 122:230-231 (doi:10.1289/ehp 1408428R).

Wolff RK, Henderson RF, Snipes MB, Griffith WC, Mauderly JL, Cuddihy RG, McClellan RO. (1987). Alterations in particle accumulation and clearance in lungs of rats chronically exposed to diesel exhaust. Fund Appl Toxicol 9:154-166.

Yanowitz J, McCormick RL, Graboski MS, 2000. In-use emissions from heavy-duty diesel vehicles. Environ Sci Technol 34:729-740.

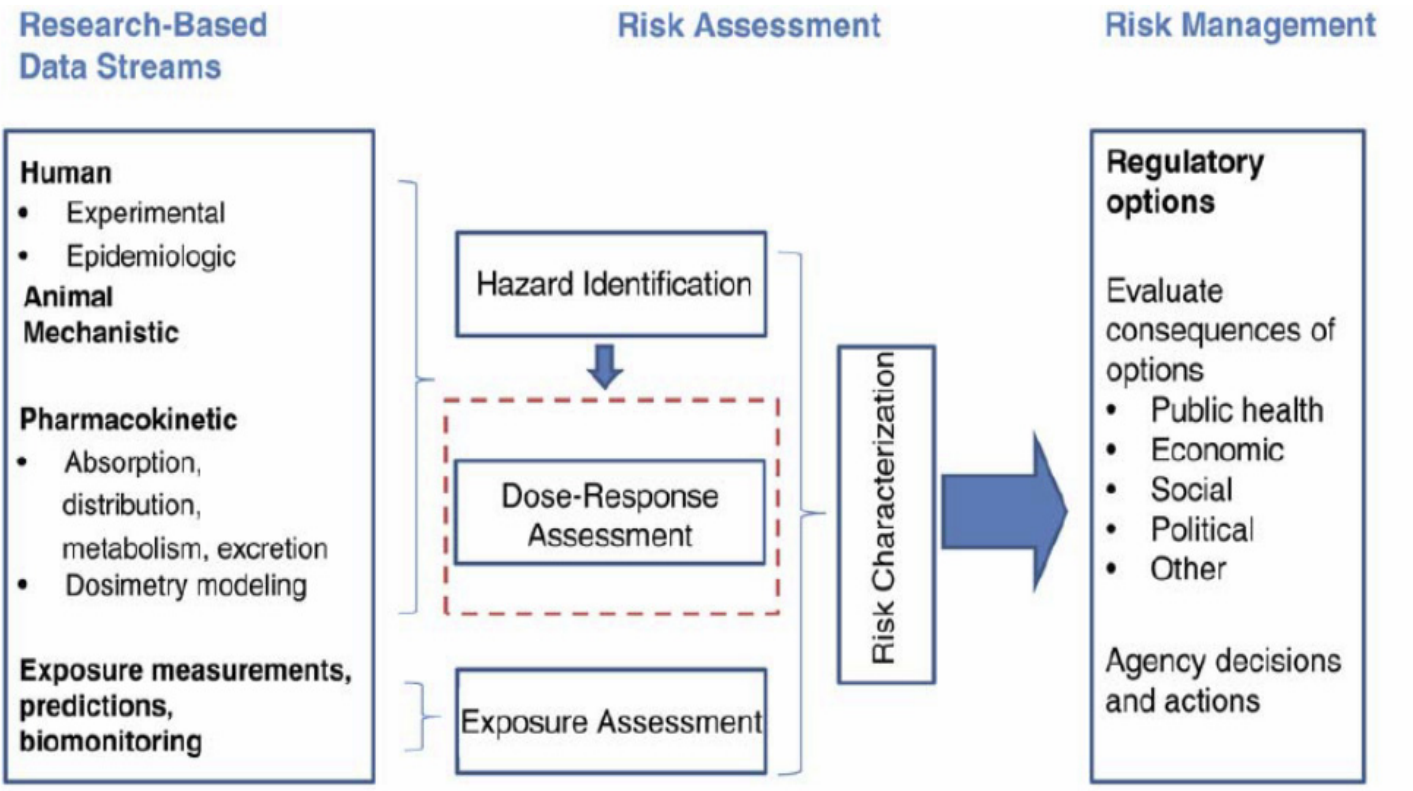

Figure 1: Risk Assessment Paradigm that emerged in the 1970s (National Research Council, 2014; from HEI, 2015).

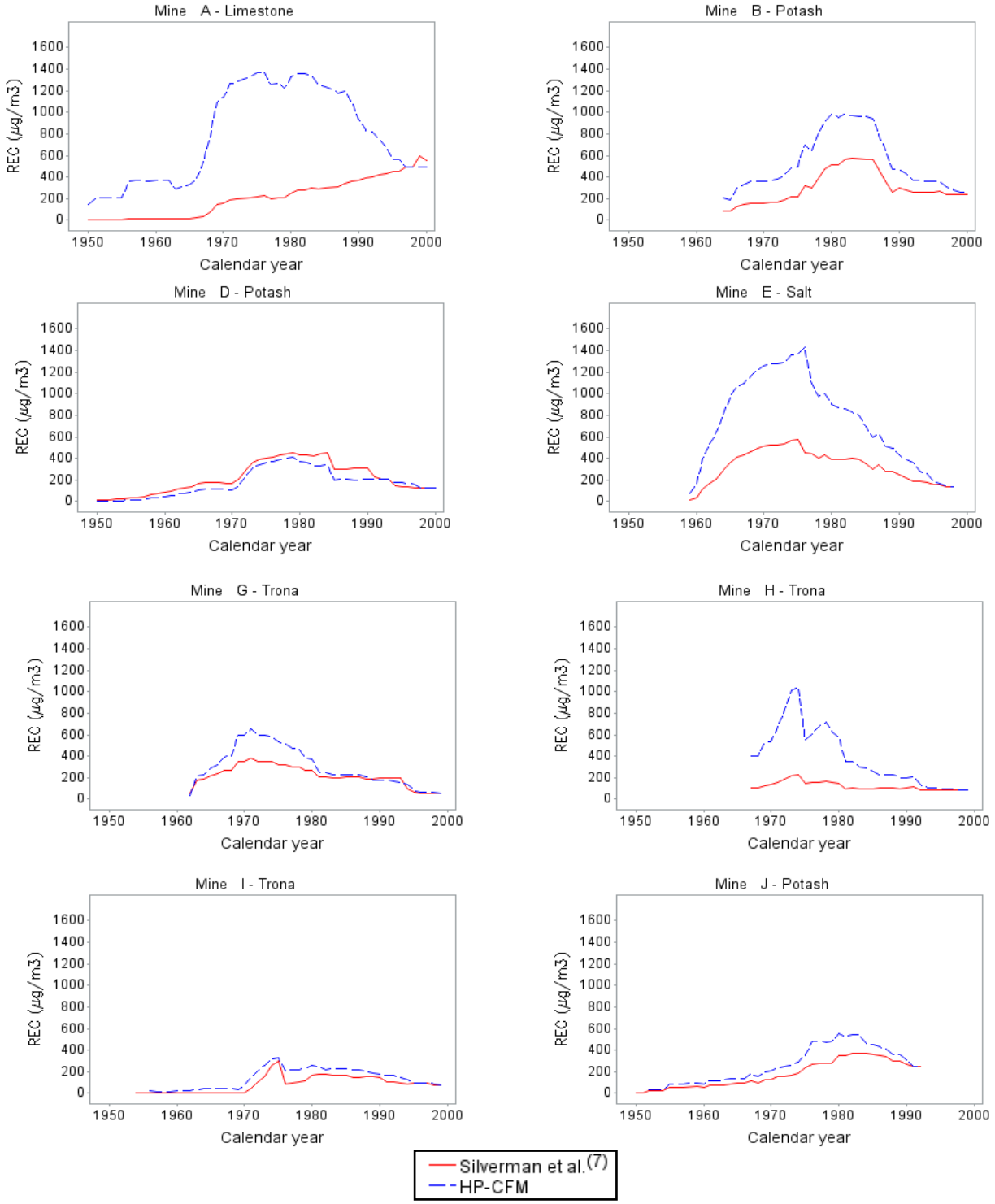

Figure 2: Alternative Respirable Elemental Carbon Metrics Using CO (red), the Original Investigators versus HP-CFM (blue) Developed by Crump et al (2016)

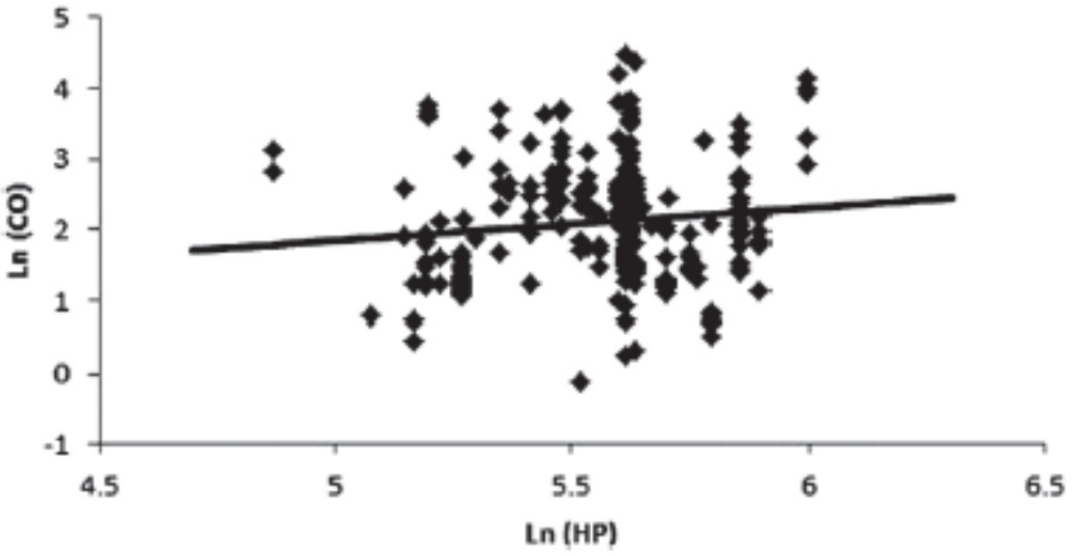

Figure 3: Poor Correlation Between HP and CO (Taken from Yanowitz et al, 2000 and reported in Crump and Van Landingham, 2012)

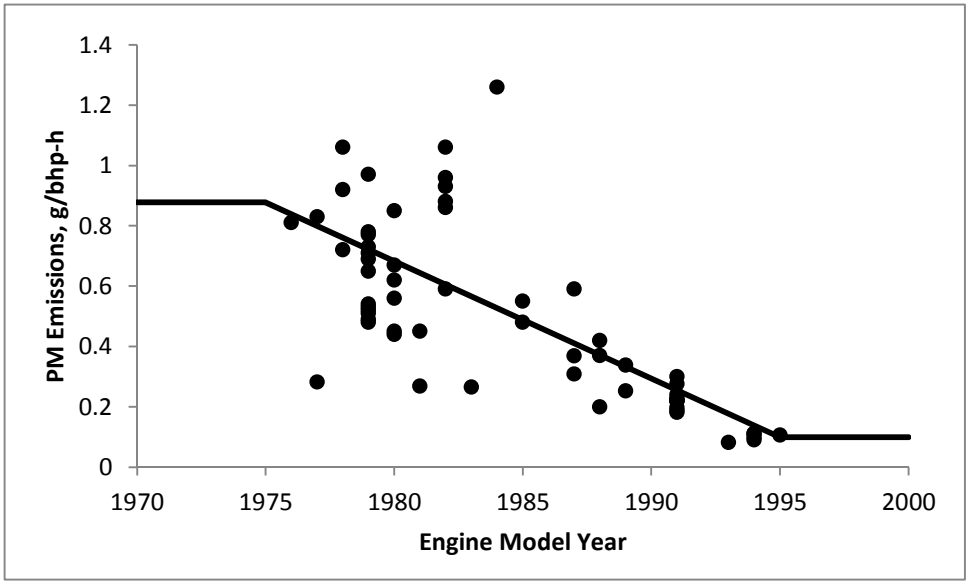

Figure 4: Reduced PM Emissions with Improved Diesel Technology (Reproduced from US EPA, 2002)

Table 1: Past Reviews of the human carcinogenic Hazard of Exposure to Diesel Exhaust (Taken from HEI Epidemiology Panel Report, 2015).

Organizational Reviews	Animal Data	Human Data	Classification	Quantitative Risk Assessment Conducted?
National Research Council (1981)	Negative	Not convincingly demonstrated	—	—
NIOSH (1988)	"Confirmatory"	"Limited"	"Potential occupational carcinogen"	None
IARC (1989)	"Sufficient" (rats)	"Limited"	"Probably carcinogenic to humans (Group 2A)"	None[a]
World Health Organization (1996)	Supportive (rats)	Suggest "probably carcinogenic"	—	Yes, based on rat data; epidemiologic data considered inadequate
Office of Environmental Health Hazard Assessment, California EPA (1998)	"Demonstrated" carcinogenicity (rats)	"Reasonable and likely"	"Toxic air contaminant"	Yes, based on epidemiologic data in railroad workers [cancer unit risk factor of 3×10^{-4} $(\mu g/m^3)^{-1}$]
U.S. EPA (2002)	"Adequate" (rats)	"Limited"	"Likely human carcinogen"	No; epidemiologic dose–response data inadequate
National Toxicology Program (2011)	"Supporting evidence"	"Limited evidence"	"Reasonably anticipated to be a human carcinogen"	None
IARC (2012, 2014)	"Sufficient evidence"	"Sufficient evidence"	"Carcinogenic to humans (Group 1)"	None[a]

[a] Note: IARC does not conduct quantitative risk assessments at this time for any chemicals.

Table 2: Summary of U.S. Truckers Study (from HEI, 2015).

Truckers Cohort	Exposure Assessment	Outcome Assessment	Analysis	Selected Results
Original Cohort (Laden et al 2007): 58,326 unionized trucking industry workers (93% male) who worked 1 day or more in 1985 **Garshick 2008, 2012a Cohort:** 31,135 male workers ≥ 40 years of age in 1985 with at least one year of work **Cohort description:** Ethnicity: 85% Caucasian, 9% Black, 6% Other/unknown Mean age in 1985: 49.1 years Mean total work: 21.6 years End of follow up: year 2000 Person-years of follow up: ≈106,000 for each quartile of exposure. **8 Job Groups:** *Drivers:* Long-haul, Pick-up & delivery / dockworker (combination), Hostler *Nondrivers:* dockworker, mechanic, clerks, other	**None** **Metric:** Submicron ($PM_{1.0}$) Environmental carbon (SEC) in μg/m³ **Exposure model:** *Current Exposures:* From 2001–2006, over 4000 personal and area measurements were taken for cross-shift (8–12 hr) SEC at 36 large terminals randomly chosen to be representative of all terminals. Personal SEC exposures were calculated using Structural Equation Modeling as a function of job category, terminal characteristics, and background EC *Historical Exposures:* Ambient SEC levels were modeled based on the ratio of SEC: Coefficient of haze data available from 1971–2000. Comparison of 1988–1989 data to 2001–2006 data was used to calculate job-specific multipliers for 1971–1989 and extrapolated linearly for 1990–2000 *Personal Exposure:* Modeled current exposures were combined with the historical models, including job-specific multipliers, to extrapolate SEC exposures.	**All cause, and cause-specific mortality** **Primary outcome:** Lung cancer, as indicated anywhere on death certificate **Total male deaths:** 4306 (779 lung cancer) **Ascertainment:** National Death Index (NDI-Plus) matched with Social Security Administration files, date of birth, and first, last, and middle names	**Standardized mortality ratios** Expected numbers of all cause and cause-specific deaths calculated from person-years in each race, 10-year age- and calendar period-specific stratum, and national reference rates. SMRs = ratio observed/expected deaths. **Internal cohort analysis:** Proportional hazard regression models, separate baseline hazards based on decade of hire, age in 1-year increments, exposure measured as cumulative SEC and average EC, lags of 0, 5, and 10 years as continuous, and in quartiles. **Adjustments:** age, lung cancer secular trends, calendar year, race, census region of residence, total years of employment (as a time-dependent covariate). There was no control for smoking. **Mechanic Workers:** Separate analyses also performed excluding workers present for ≥ 1 year as a mechanic (n = 1811) due to inconsistency in exposure modeling for mechanics.	**Standardized mortality ratios:** Ischemic heart disease (1133 cases) SMR = 1.41, 95% CI = 1.33–1.49) Lung cancer (769 cases) SMR = 1.04, 95% CI = 0.97–1.12 **Cohort excluding mechanics, adjusted for duration of work (Garshick et al. 2012a)** **Cumulative SEC (μg/m³-months)** / **HR (95% CI)** No lag < 530 — 1 530 to < 1061 — 1.25 (0.99–1.60) 1061 to < 2076 — 1.30 (0.99–1.72) ≥ 2076 — 1.24 (0.89–1.71) 5-yr lag < 371 — 1 371 to < 860 — 1.31 (1.01–1.71) 860 to < 1803 — 1.38 (1.02–1.87) ≥ 1803 — 1.48 (1.05–2.10) 10-yr lag < 167 — 1 167 to < 596 — 1.17 (0.88–1.57) 596 to < 1436 — 1.26 (0.90–1.78) ≥ 1436 — 1.41 (0.95–2.11)

Table 3: Summary of Diesel Exhaust in Miners Study (DEMS) (from HEI, 2015)

DEMS Cohort	Exposure Assessment	Outcome Assessment	Analysis	Selected Results
8 Nonmetal Mines 1 – limestone (Missouri) 3 – potash (New Mexico) 1 – salt (Ohio) 3 – trona (Wyoming) Year of dieselization in the mines: 1947–1967 Mean year of first exposure to DE: 1971 Mean underground tenure: 8.0 years **Cohort Population** 12,315 workers Sex: 96% male Ethnicity: 88% white, 2% black, 10% Hispanic Mean age at start of exposure: 29 years End of follow up: year 1997 278,041 person-years of follow up 2200 deaths at end of follow up 200 lung cancer deaths	**Metric**: Respirable elemental carbon (REC) in µg/m³ **Historical REC exposure reconstruction:** Models based on REC measurements, horsepower (HP), CO, ventilation (see details in report text). Individual-level annual and cumulative REC exposure assigned based on estimated historical REC levels and job history in the mines. **Confounding exposures measured:** Silica, asbestos, nonDE PAHs, radon, respirable dust. Mines selected for low levels of these contaminants.	**Primary:** Lung cancer defined as malignant neoplasm of the bronchus and lung, excluding tracheal cancer, as underlying cause of death. **Other**: all-cause mortality, other malignant neoplasms, and chronic diseases. **Ascertainment:** National Death Index (NDI-Plus) matched with Social Security Administration files.	**Cohort 'external' analysis:** Standardized mortality ratio analysis, externally standardized to state-, age-, gender-, and ethnic group-specific death rates for each mine. **Cohort 'internal' analysis:** Cox proportional hazards (CPH) models, quantiles of average and cumulative REC, unlagged and lagged 15 years. By work location (ever-underground, surface-only). Adjustments: race, birth year, sex, state Sensitivity analyses: exposure metric, tenure exclusion, continuous models, work location.	SMRs (95% CI): Lung Cancer (LC) Complete cohort: 1.26 (1.09–1.44) Ever-underground: 1.21 (1.01–1.45) Surface-only: 1.33 (1.06–1.66) Cohort CPH analysis: Hazard Ratios (95% CI) Cumulative REC (µg/m³-years), 15-yr lag Complete cohort (200 LC deaths) 0 to < 2.5 1.00 (referent) 2.5 to < 56 0.55 (0.35–0.85) 56 to < 583 1.03 (0.60–1.77) ≥ 583 1.39 (0.78–2.48) Ever-underground workers (122 LC deaths) 0 to < 108 1.00 (referent) 108 to < 445 1.50 (0.86–2.62) 445 to < 946 2.17 (1.21–3.88) ≥ 946 2.21 (1.19–4.09) Surface-only workers (78 LC deaths) 0 to < 0.70 1.00 (referent) 0.70 to < 4.6 1.28 (0.64–2.58) 4.6 to < 14 0.73 (0.35–1.53) ≥ 14 1.00 (0.44–2.28)
Nested Case–control: 198 lung cancer cases, 562 incidence density matched controls; matched on mine, sex, race/ethnicity, and birth year (Note that they had 666 controls for analysis purposes as some subjects served as controls for more than one case subject.)	**Nested Case–control: In addition to REC and confounding exposures above, individual questionnaire data collected on:** Smoking, medical history, occupational history, other personal risk factors		**Nested Case–control:** Conditional logistic regression: with quantiles of average and cumulative REC, unlagged and lagged 15 years, duration of exposure. Two-sided Wald test for linear trend. Various continuous models fit. Control for confounding: Smoking status and intensity, location (as a joint variable), history of high risk jobs. Sensitivity analyses: exposure metric, tenure exclusion, work location, continuous models, smoking metrics.	**Nested case–control CPH analysis: Odds Ratios (95% CI)** Cumulative REC (µg/m³-years), 15-yr lag 0 to < 3 1.00 (referent) 3 to < 72 0.74 (0.40–1.38) 72 to < 536 1.54 (0.74–3.20) ≥ 536 2.38 (1.28–6.26) P_{trend} = 0.001

Table 4: Characteristics of the Mines in the Diesel Exhaust in Miners Study (DEMS) (from Crump et al., 2016)

Mine	State	Ore	Ventilation	Year of First Diesel Use	Primary Mode of Operation	All Years				1982 Activity	
						CO		Radon		CFM	Diesel
						# samples	% > LOD	# samples	% > LOD	f^3/min (in thousands)	(Adj HP)
A	Missouri	Limestone	Natural	1947	Cv/H	248	70	37	84	--	6,862
B	New Mexico	Potash	Mechanical	1964	Cv/Con, Ct	447	62	18	44	250	892
D	New Mexico	Potash	Mechanical	1950	Cv/H, Cv/Con, Ct	323	54	61	39	360	2,326
J	New Mexico	Potash	Mechanical	1952	Cv/H, Cv/Con, Ct	178	52	13	38	240	1,421
E	Ohio	Salt	Mechanical	1959	Cv/H	207	66	39	70	233	2,804
G	Wyoming	Trona	Mechanical	1962	Cv/Con, Ct	276	50	17	24	450	638
H	Wyoming	Trona	Mechanical	1967	Cv/Con, LW, Ct	2361	39	40	15	950	1,110
I	Wyoming	Trona	Mechanical	1956	Cv/Con, Ct, LW	2000	54	54	20	1,630	1,493
Total						6040	50	279	42		

The above data were compiled from the Stewart et al.[(1)] and the substantial DEMS data files. Primary Mode of Operation: Cv/H – conventional with truck haulage, Cv/Con – conventional with conveyor belts, Ct – Continuous with conveyor belts, and LW – long wall with conveyor belts. Specific data for ventilation rates and HP are shown for 1982 for illustrative purposes, as 1982 was the last year of effective exposure for workers, assuming a 15 year-lag, as follow-up ended in 1997.

Table 5: Table 2 of Stewart et al. (2010) Summarizing the Data Available for Constructing Estimates of REC Exposures at the Eight Mining Facilities

Table 2. Number of area and personal DE-related measurements by agent for the eight mining facilities

Agent	Survey[a]										All surveys		Total
	MIDAS 1976–2001		DEMS 1998–2001		MESA/BoM 1976–1977		Feasibility study 1994		Other 1954–1996				
	Area[b]	Personal[b]	Area	Personal	Area	Personal	Area	Personal	Area	Personal	Area	Personal	
CO	9746	46	208	0	1099	0	25	0	46	0	11 124	46	11 170
CO_2	8234	15	390	0	961	0	17	0	49	0	9651	15	9666
NO	45	0	381	995	24	0	42	69	9	0	501	1064	1565
NO_2	4288	38	387	1031	252	646	42	69	76	11	5045	1795	6840
TD	1	782	215	0	161	667	32	0	69	703	478	2152	2630
RD	0	324	209	2	99	0	31	0	158	178	497	504	1001
SD	0	0	121	0	0	0	69	0	20	0	210	0	210
TEC	0	0	224	0	0	0	0	0	0	0	224	0	224
REC	0	0	216	1156	0	0	0	69	12	4	228	1229	1457
SEC	0	0	209	0	0	0	0	0	0	0	209	0	209
TOC	0	0	224	0	0	0	0	0	0	0	224	0	224
ROC	0	0	221	1151	0	0	0	0	0	0	221	1151	1372
SOC	0	0	207	0	0	0	0	0	0	0	207	0	207
DPM/SCD	0	0	212	0	0	0	0	0	180	102	392	102	494
Total	22 314	1205	3424	4335	2596	1313	258	207	619	998	29 211	8058	37 269

DPM, diesel particulate matter; RD, respirable dust; ROC, respirable organic carbon; SCD, submicron combustible dust; SD, submicron dust; SEC, Submicron elemental carbon; SOC, submicron organic carbon; TD, total dust; TEC, total elemental carbon; TOC, total organic carbon.

[a]Surveys: the MSHA MIDAS (1976–2001); the DEMS (1998–2001) (Coble *et al.*, 2010; Vermeulen *et al.*, 2010*b*); the MESA/BoM (1976–1977) (Sutton *et al.*, 1979); the feasibility study for the DEMS in Facility B (1994) (Stanevich *et al.*, 1997); compliance visits by the State of New Mexico, MSHA hard copy reports, and the mining facilities (1954–1996).

[b]Area measurements; personal measurements. The number includes both full-shift and short-term measurements.

Table 6: Workers Studied in Diesel Exhaust in Miners Study (DEMS) (from Moolgavkar et al., 2014)

			Ever-Underground Workers					
	Surface-Only Workers		Underground-Only Workers		Surface and Underground Workers		Complete Cohort	
Mine Type	**Miners**	**Deaths**	**Miners**	**Deaths**	**Miners**	**Deaths**	**Miners**	**Deaths**
Limestone	730	15	123	12	823	10	1676	37
Potash	1293	38	1951	46	1327	18	4571	102
Salt	50	<5	208	9	289	<5	547	<19
Trona	1935	23	1798	15	1788	11	5521	49
Entire cohort	4008	<81	4080	82	4227	<44	12315	<207

Table 7: Comparison of Conditional Original Logistic Regression Resulted (Silverman et al, 2012) with Results of Similar Analyses except based on New REC Estimates Defined Using HP and CFM (from Crump et al., 2016)

Analysis	Quartiles of cumulative REC, lagged 15 years ($\mu g/m^3$-y)	Cases	Controls	OR (95% CI)	p_{trend}	Slope $(\mu g/m^3\text{-y})^{-1}$ 95% CI
All Subjects						
Silverman et al.[7]	0 to < 3	49	158	1.0 (referent)	0.001	0.00073*
	3 to < 72	50	228	0.74 (0.40 to 1.38)		(0.00028,0.0012)*
	72 to < 536	49	157	1.54 (0.74 to 3.20)		
	≥ 536	50	123	2.83 (1.28 to 6.26)		
REC estimates from Silverman et al.[7] and "without radon" controls[12]	0 to < 3	49	158	1.0 (referent)	0.0006	0.00082
	3 to < 72	50	228	0.79 (0.41 to 1.52)		(0.00035,0.0013)
	72 to < 536	49	157	1.62 (0.75 to 3.49)		
	≥ 536	50	123	3.24 (1.40 to 7.55)		
HP-CFM REC estimates and "without radon" controls	0 to < 6.6	49	172	1.0 (referent)	0.06	0.00016
	6.6 to < 129	50	191	1.05 (0.58 to 1.93)		(-0.000012,0.0003)
	129 to < 891	49	168	1.60 (0.79 to 3.24)		
	≥ 891	50	135	2.37 (1.02 to 5.50)		
HP-CFM REC estimates and "with radon" controls	0 to < 6.6	49	172	1.0 (referent)	0.63	0.00005
	6.6 to < 129	50	191	1.02 (0.55 to 1.90)		(-0.00016,0.00026)
	129 to < 891	49	168	1.20 (0.56 to 2.56)		
	≥ 891	50	135	1.37 (0.5 to 3.77)		
All Subjects Who Ever Worked Underground						
Silverman et al.[7]	0 to < 81	29	92	1.0 (referent)	0.004	0.00065*
	81 to < 325	29	52	2.46 (1.01 to 6.01)		(0.00020,0.0011)*
	325 to < 878	29	69	2.41 (1.00 to 5.82)		
	≥ 878	29	51	5.10 (1.88 to 13.87)		
REC estimates from Silverman et al.[7] and "without radon" controls[12]	0 to < 97	31	158	1.0 (referent)	0.01	0.00073
	97 to < 384	31	90	1.90 (0.78 to 4.63)		(0.00022,0.0012)
	384 to < 903	31	80	2.73 (1.08 to 6.88)		
	≥ 903	31	84	5.04 (1.77 to 14.30)		
HP-CFM REC estimates and "without radon" controls	0 to < 130	31	144	1.0 (referent)	0.16	0.00014
	130 to < 531	31	99	2.03 (0.83 to 4.96)		(-0.000062,0.0003)
	531 to < 2149	31	99	3.45 (1.27 to 9.41)		
	≥ 2149	31	70	3.84 (1.07 to 13.74)		
HP-CFM REC estimates and "with radon" controls	0 to < 130	31	144	1.0 (referent)	0.69	0.00005
	130 to < 531	31	99	1.83 (0.73 to 4.61)		(-0.00020,0.00030)
	531 to < 2149	31	99	2.47 (0.79 to 7.73)		
	≥ 2149	31	70	2.5 (0.49 to 12.79)		
All Subjects Who Only Worked Underground						
HP-CFM REC estimates and "without radon" controls	0 to < 106	14	26	1.0 (referent)	0.27	0.00024
	106 to < 410	15	28	1.89 (0.4 to 9.07)		(-0.000179,0.0007)
	410 to < 1486	14	17	3.15 (0.47 to 21.05)		
	≥ 1486	15	26	4.73 (0.58 to 38.84)		
HP-CFM REC estimates and "with radon" controls	0 to < 106	14	26	1.0 (referent)	0.36	0.00027
	106 to < 410	15	28	1.91 (0.38 to 9.75)		(-0.000316,0.0009)
	410 to < 1486	14	17	5.61 (0.61 to 51.33)		
	≥ 1486	15	26	9.39 (0.47 to 187.84)		

* Calculated by us after reproducing Silverman et al. results.

Table 8: Contributors

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