Additional Comments on Mine Safety and Health Administration Exposure of Underground Miners to Diesel Exhaust Request for Information
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By

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I. <u>Summary</u>

The Mine Safety and Health Administration (MSHA) Exposure of Underground Miners to Diesel Exhaust Request for Information is the initial step in potential revision of the Agency's Diesel Rule regulating exposure of underground miners to diesel exhaust in coal and metal non-metal mines aimed at assuring that regulations are sufficient to preserve miner's health. A key component of the Diesel Rule-making activity is to understand the health hazards/risks of past, current and projected future exposures of underground miners to diesel exhaust. In this paper, I emphasize the distinction between hazard and risk noting that past MSHA regulations, as well as those issued in the past by the U.S. Environmental Protection Agency (EPA), were based on concern for the lung cancer hazard of diesel exhaust exposures and were not based on quantitative risk estimates.

The International Agency for Research on Cancer (IARC), a part of the World Health Organization, as part of its monograph program has classified about 1000 agents or workplace conditions as to their human cancer hazard. The IARC monograph program does not routinely provide estimates of the cancer causing potency of agents or workplace circumstances that it classifies as to potential hazard, information that is essential for quantitative risk estimation. An IARC Panel meeting in 1987, with a report published in 1988, classified diesel exhaust exposure as a "probable human carcinogen." At a meeting in 2012, an IARC Panel upgraded the cancer hazard classification of diesel exhaust exposure to a "human carcinogen" with a report published in 2014. This upgrade by IARC was driven primarily by findings published in 2012 from the Diesel Exhaust in Miners Study (DEMS) initiated in the early 1990s by the National Institute of Occupational Safety and Health (NIOSH) and the National Cancer Institute (NCI). The DEMS included workers from 8 mines (1 limestone mine in Missouri; 1 salt mine in Ohio; 3 potash mines in New Mexico; and 3 trona (soda ash) mines in Wyoming. It included both (1) a cohort study of 12,315 workers (with 200 lung cancer cases) with about one-third of the workers in each of three categories; (a) surface workers, (b) always underground miners, or (c) worked both on the surface and underground and (2) a nested study of lung cancer cases and controls. It is noteworthy that DEMS involved mines dieselized as early as 1947. Vital data for workers was collected from 1947 through December 31, 1997. The exposure of workers to Respirable Elemental Carbon (a marker of diesel exhaust) was estimated from measurements of carbon monoxide. The results that were most positive for an excess of lung cancer hazard were obtained when lagged by 15 years for exposure to occurrence of an excess of lung cancer. The results of analysis of the DEMS data are most directly applicable to diesel exhaust exposures in Non-Metal mines from traditional diesel-powered equipment operating in 1982 and earlier.

Similar studies have not been conducted on coal miners so it is tempting to assume the results from analysis of the DEMS data are applicable to coal miners. However, this is a substantial extrapolation which I believe would be unwarranted.

Improvements in diesel technology (improved engine design, use of ultra-low sulfur fuel, introduction of exhaust after-treatment devices, and electronic sensing and control) occurred rapidly in the 1980s and accelerated further with new diesel emission regulations issued by EPA and MSHA in the 1990s and early 2000s. These improvements in diesel technology have markedly reduced diesel exhaust emissions; initially of diesel exhaust particulate matter and, more recently, of emissions of oxides of nitrogen to virtually zero levels. These technological improvements have been reflected in reduced exposure of underground miners as the new technology, reduced emission-diesel equipment has replaced older traditional diesel engines with that had high emissions of both particulate matter and oxides of nitrogen.

In these comments I emphasize that the IARC classification in 2012 of diesel exhaust exposure as a human carcinogen is applicable to diesel-powered equipment typical of the 1980s and earlier and is _not_ directly applicable to current and recently manufactured diesel-powered equipment. Moreover, the upgrading of the hazard classification of diesel exhaust exposure does not necessarily mean that the estimates of the cancer hazard potency of diesel exhaust from engines of circa 1980s and earlier have changed when based on the published new epidemiological findings as compared to potency estimation developed based on earlier published epidemiological data. A change in hazard classification does not necessarily translate into a change in the potency of the diesel exhaust from old technology and increased risk.

In these comments I note that recently published results of extended analyses of the DEMS data by independent analysts using alternative analytical approaches, alternative REC exposure estimates and adjustments control for radon exposures yielded reduced estimates of the lung cancer hazard of exposure to exhaust from the older diesel engines. Indeed, the estimates of excess lung cancer hazards based on alternative estimates of REC exposure, with control for radon, were not statistically significant. Some observers have suggested that if these additional results using the DEMS data set had been available to the participants in the IARC cancer hazard classification review, the new findings might have tempered the IARC Panel's enthusiasm for upgrading the cancer hazard classification for diesel exhaust exposure.

The Health Effects Institute (HEI), a non-profit entity principally supported by the U.S. Environmental Protection Agency, other government agencies and engine manufacturers, convened a panel to evaluate the most recent studies of diesel exhaust exposed workers with regard to their utility for conducting quantitative risk assessment (QRA). The HEI Panel Report concluded the recent studies were "well-designed and carefully conducted embodying the attributes of epidemiological studies that are considered important for quantitative risk assessment." It is important to recognize the HEI Panel did not attempt to conduct a QRA or give guidance as to how a QRA for diesel exhaust exposure might be conducted. The HEI Panel did emphasize that any findings from analysis of the DEMS data were only applicable to older traditional diesel engines and not new technology diesel engines.

Since the IARC (IARC, 2014) hazard classification review was concluded in 2012, a detailed paper has been published in 2013 analyzing the association between diesel exhaust exposure and lung cancer mortality in underground miners in potash mines in the south Harz Mountains region of Germany. This study by scientists from the German Federal Institute for Occupational Safety and Health involved approximately 5,819 workers (with 68 lung cancer deaths). Diesel-powered equipment was introduced in these mines during 1969 replacing electrical-powered equipment. In 1991, exposure measurements of total carbon and elemental carbon in airborne fine dust were undertaken. In the first half of the 1990s, the potash mines were consecutively closed leading to peak layoffs in 1991. Therefore, the duration of exposure to diesel exhaust was restricted to 22 years for most of the miners. The vital status for the cohort members was followed from 1970 through 2001. The authors reported that "the study results give no evidence for an association between REC exposure and lung cancer risk. Only for very high cumulative dose, corresponding to at least 20 years of exposure in production area, some weak hints for a possible risk increase could be detected."

Very recently, in 2016, the lead scientist on the German Potash Miner study and a colleague, have prepared a comprehensive review of the relationship between occupational exposure to diesel exhaust and increased lung cancer risk. This review paper includes a detailed critique of the original and recent publications using the DEMS data. The review concludes that the original analyses of the DEMS data had several methodological flaws, "amongst them over-adjacent bias, selection bias and confounding bias." They concluded that the recently "published studies provide little evidence for a definitive causal link between diesel exhaust exposure and lung cancer risk." They further noted – "Based on two studies in mines, the DEMS and the German Potash Miners Study, QRA may be conducted. However, DEMS data should be reanalyzed in advance to avoid bias that affects the original published risk estimates."

The issues identified above are highly relevant to the current MSHA diesel rule making. This is the case since the nature of the exposure-response relationship for diesel particulate matter, whether characterized as Respirable Elemental Carbon, Total Carbon (TC) or some other metric, provides guidance for setting an occupational exposure limit (as used in the metal non-metal mine regulations) or as guidance for setting engine emission limits (as used in the coal mine regulations).

The recent German review used the data from the German Potash Workers study to propose use of a threshold exposure-response model to establish a cumulative exposure of 2.5 mg/m^3-years as sufficient to prevent a detectable increase in lung cancer. This value corresponds to an annual average concentration of 50 μg REC/m^3 assuming a working life of 45 years. The German investigators measurements in 1991 indicated that 63% of the TC was EC. Thus, 50 μg REC/m3 would correspond to an exposure limit of 80 μg TC/m3 compared to the limit of 160 μg TC/m3 that MSHA promulgated on May 20, 2008. In comparing these values, it is important to recognize that the German recommendation is an annual average while the MSHA regulation is an 8-hour average. An 8-hour limit will always be less than an annual average limit.

It is important to note there are no studies of the potential association between diesel exhaust exposure and excess of lung cancer in underground coal miners using diesel equipment that are similar in quality to the DEMS or German Potash Workers Studies. Thus, it has been assumed by some regulatory agencies, including MSHA, that it is reasonable to assume any exposure (concentration and duration)-lung cancer relationship for underground coal miners will be similar to that for the potash and other non-metal miners as assessed using the DEMS data. It is important to recognize that this is an assumption. Any use of information from epidemiological studies to inform policy decisions on an acceptable occupation exposure limit to diesel exhaust particulate matter in metal non-metal mines and derived limits on diesel engine emissions in underground coal mines should consider threshold exposure-response models as recommended by the German scientists.

The MSHA RFI includes useful data in Part E. MNM Miners Personal Exposure Limit (PEL) on reductions in measured TC concentrations from 2006 to 2015. These substantial improvements are consistent with a steady replacement of traditional diesel engines with high particulate emission with new low emission diesel engines in the MNM mines. If the rule-making proceeds, it will be important to critically evaluate the influence of new low emission diesel equipment on TC levels measured in MNM mines.

In the case of coal mines, diesel exhaust exposures in underground coal mines are controlled indirectly based on limits imposed on emissions of specific diesel-powered equipment and ventilation. This is the case since it is not feasible to measure TC or REC in underground coal mines. It will be useful to critically evaluate the extent to which replacement of old traditional diesel engines with new low emission diesel engines has resulted in lower estimated coal miner exposures consistent with the intent of the diesel rule makings in the late 1990s and 2000s.

Any potential revisions in the MSHA diesel rules for underground coal mine equipment and the workplace environment in MNM mines should be informed by rigorous analysis of all of the available data on exposure-health relationships (taking into account the time period when the exposures occurred and the emissions of the diesel engines then in use) and information on the continued improvements in diesel technology and the application of this low emission diesel equipment in mining operations.

II. Introduction

A. The Author

The comments I offered at the earlier public meeting and I now offer for the Docket are my professional views as an Advisor on Toxicology and Human Health Risk

Analysis matters with emphasis on issues concerning airborne materials and their potential health effects in workers and the general population. A copy of my professional biography is provided as Appendix A. My first experience with diesel exhaust was gained as a summer worker in 1954 in the wheat fields of Southeastern Washington when, as a "cat skinner," I operated diesel-powered equipment. That real world experience with diesel equipment no doubt contributed to my continuing interest in diesel technology as it has continually evolved. In the 1970s, I began investigating the size and chemical characteristics of diesel exhaust and how these parameters would influence the potential health effects of exposure to diesel exhaust, in particular, the occurrence of lung cancer using a range of laboratory and field methods. This multi-disciplinary research effort involved a range of approaches, including studies with cells treated with extracts of diesel exhaust particles and studies with laboratory rodents exposed for their lifespan to various dilutions of whole diesel exhaust. These experimental studies were intended to complement epidemiological information gained from studies of occupationally exposed human populations.

As an aside, the early scientific research I conducted on diesel exhaust starting in the 1970s was conducted at what was then called the Lovelace Inhalation Toxicology Research Institute in Albuquerque, New Mexico with funding from what is now the Department of Energy. Our multi-disciplinary team effort benefited greatly from collaboration with other scientists, including those at Bureau of the Mines laboratories in Bartlesville, OK and Morgantown, WV, the Department of Transportation Research Center in Cambridge, MA and U.S. Environmental Protection Agency laboratories in Cincinnati, OH and Research Triangle Park, NC. In the 1990s, I served as President and Chief Executive Officer of a non-profit research laboratory in Research Triangle Park, NC which was supported principally by the chemical industry. My research on diesel exhaust health effects during that time period was carried out as a part of my day-to-day scientific work related to important national policy issues.

Since 1999, I have been engaged as an Advisor on Toxicology and Risk Analysis issues by a number of private and public entities. I relate this background in the interest of completeness. It is my personal belief that scientists from all sectors of society (academic, government, labor and private industry) have much to contribute to developing and synthesizing the scientific and technological information required to inform the development of public policy and related regulations in many arenas, including the use of diesel technology.

B. Purpose of Comments

These comments are offered to extend and supplement the written and oral comments I offered at the Mine Safety and Health Administration (MSHA) Public Meeting on July 22, 2016 held in Arlington, VA related to the Department of Labor, Mine Safety and Health Administration (30 CFR Parts 57, 70, 72 and 75, RIN 1219-AB86, Docket No. MSHA-2014-0031) Exposure of Underground Miners to Diesel Exhaust: Request for Information. The Federal Register Notice of June 8, 2016 requested "information and data on approaches to control and monitor miner's exposure to diesel exhaust" as a basis for MSHA "reviewing the Agency's existing standards and policy guidance on controlling miner's exposure to diesel exhaust to evaluate the effectiveness of the protections now in place to preserve miner's health."

The copy of the Written Comments I offered at the July 22, 2016 public meeting are attached to the current written comments for the convenience of the reader (Appendix B). I have also attached a copy of my critique of the HEI Epidemiology Panel Report on the use of selected epidemiological studies for Quantitative Risk Analysis (Appendix C). In addition, attached is a transcript of the portion of the July 22, 2016 public meeting in Arlington, VA at which I offered comments (Appendix D). This transcript includes an extensive exchange with Sheila McConnell who presided over the Public Meeting. I greatly appreciated the informal nature of the public meeting and the opportunity it provided for extensive dialogue with Ms.

McConnell on the strengths and weaknesses of the Diesel Exhaust in Miners data set and the various analyses conducted using that data set.

The last quarter of the 20th Century was a period when substantial new information was acquired on all facets of diesel technology from the mechanisms by which diesel exhaust particles are formed during compression ignition to how inhalation of the diesel exhaust particles may cause health effects. This information acquired using traditional diesel technology (TDE) would provide the baseline for revolutionary changes in diesel technology (engines, fuels, exhaust after-treatment and electronic controls) resulting in today's diesel technology with near zero emissions of particular matter and oxides of nitrogen. These remarkable changes were reviewed in McClellan, Hesterberg and Wall (2012) and are illustrated schematically in Figure 1.

Regulations, particularly those issued by the U.S. Environmental Protection Agency, had a major role in driving the revolution in diesel technology at the turn of the century through the issuance of extremely stringent diesel engine emission limits for particulate matter and, with a later enforcement date, oxides of nitrogen. The EPA also issued stringent regulations for the sulfur content of fuel used in on-road diesels mandating the wide availability of ultra-low sulfur fuel, (less than 15 ppm sulfur). The regulatory actions of MSHA, as outlined in the Diesel Rule RFI, were very influential in fostering the development and use of low emissions diesel equipment in mining operations. I was personally involved in the scientific review of both the EPA regulations, as a member of the EPA's Clean Air Scientific Advisory Committee, and the DOL/MSHA Advisory Committee on Use of Diesel Equipment in Mining. It is noteworthy that the regulations of both EPA and MSHA were developed based on concern for the potential lung cancer hazard of exposure to diesel exhaust. Importantly, the EPA and MSHA regulations formulated and issued in the late 1990s were <u>not</u> based on quantitative lung cancer risk assessments, a point I will discuss next. Indeed, the EPA's Health Assessment for Diesel

Exhaust began in the early 1990s and went through multiple iterations before the Diesel Exhaust Health Effects Assessment was finalized (EPA, 2002). The multiple iterations and revisions of the report related to continuing debate over whether the epidemiological data, which was constantly changing as new publications emerged, were or were not adequate for quantitative risk assessment. The final decision of the EPA and the Advisory Committee on which I served was that the epidemiological data as published through 2000 were not adequate for quantitative risk assessments. However, the Agency and the Advisory Committee accepted the view that the data were adequate to characterize diesel exhaust exposure as a potential hazard and inform development and issuance of new regulations limiting emissions of diesel engines, thereby limiting diesel exhaust particulate matter exposures of the public and workers. To state the obvious, quantitative risk assessments are not always necessary to develop highly effective regulations to protect health.

C. Concepts of Hazard and Risk

Let me briefly expand on the concepts of hazard and risk, concepts that are closely related and frequently confused and are at the core of the MSHA rule making. Hazard is a qualitative concept. It is a description of the likelihood that under some exposure conditions (intensity and duration) an agent or workplace circumstance (such as exposure to diesel exhaust from particular engines of a given time period) may or may not cause cancer in humans. The evidence of carcinogenic hazard may come from (a) epidemiological observations on diesel exhaust-exposed populations (workers or other defined populations), (b) controlled exposure studies in laboratory animals, (c) mechanistic information from experimental studies with isolated cells or tissues or using laboratory animals or (d) a combination of results using the various methods (McClellan, 1999). Various agencies, such as IARC, typically report the results for different levels of evidence; Category 1- a human carcinogen, Category 2a- a probable human carcinogen, Category 2b- a possible human carcinogen, or rarely, Category 3- not likely to be a human carcinogen. As I recall, an IARC Panel has only on one occasion used this category to deem a chemical as not likely to be carcinogen to humans.

It is important to recognize that the IARC hazard characterizations do not address the potency of the agent for causing cancer with a given intensity and duration of exposure. Indeed, an agent classified as "a human carcinogen" based on abundant evidence might be less or more potent than an agent classified as a possible or probable human carcinogen based on less certain evidence. Conversely, the same could be the case. Evidence of a causal association does not automatically translate into quantitative evidence of potency for the agent causing cancer. It is important to recognize that the current MSHA rule making activity has been triggered by the IARC change in the hazard classification for diesel exhaust not by any evidence that underground miners, either those in coal or metal non-metal mines, using diesel equipment are at any greater risk than prior to the 2012 IARC pronouncement.

In contrast, risk is a quantitative concept, the probability that a population of a given age exposed to a hazardous agent under specified conditions (intensity and duration) of exposure will have an increased incidence of cancer over and above that occurring spontaneously or occurring from exposure to other agents or life style factors. It is important to recognize that cancer, a family of related diseases, occurs is a common disease. Cancer occurs frequently in populations with long lifespans as typical of economically advanced countries. In these countries about one in three individuals will have some kind of cancer diagnosed during their life and one in four individuals will die with a cancer. Thus, estimation of risk requires information on both the potency of the agent and the intensity and duration of exposure for a specified population in contrast to the occurrence of cancer in individuals without exposure to the agent or to lower levels and durations of exposure to the agent. It is important to recognize that IARC did not evaluate the cancer causing potency of diesel exhaust exposures.

At this juncture, let me emphasize that for diesel exhaust exposure the cancers of greatest concern are lung cancers. It is well recognized that in economically advanced countries the single most significant factor involved in causing lung cancer is cigarette smoking. This is important in both acquiring and interpreting studies on the role of other risk factors, such as diesel exhaust exposure, in causing lung cancer. It is absolutely crucial to have data on cigarette smoking (on the entire cohort or a sub-group, such as in a nested case-control study) if one is to interpret the role of other putative agents, such as diesel exhaust, in causing cancer. It is clear that the majority of lung cancers in the epidemiological studies of diesel exhaust exposure are related to cigarette smoking. It follows then, although it is not the topic of the diesel rule making that reductions in cigarette smoking in worker populations are of vital importance to reducing the occurrence of lung cancer.

To provide context for my comments on the MSHA RFI, I have included Figure 2. This schematic figure is intended to assist the reader in understanding the overall strategy being used to limit the potential for use of diesel equipment having a negative impact on worker's health. The overall objective shared by workers, mine operators and MSHA is to avoid any potential increase in health effects in workers related to the use of diesel equipment. This is illustrated by the box on the right side of the figure labeled increase in lung cancer. It is labeled in this way since it is well recognized that lung cancer may arise from multiple occupational, environmental and lifestyle risk factors, especially cigarette smoking, as discussed earlier. To limit the potential impact of exposures to diesel exhaust, it is necessary to limit engine emissions which, in turn, taking account of ventilation and other work practices, limits concentrations of diesel exhaust emissions in the air in the workplace.

The MSHA uses two different, but complementary, strategies to limit workplace exposures to diesel exhaust emissions. In the case of metal non-metal mines it establishes an 8-hour exposure limit, currently set at 160 µg Total Carbon (TC)/m^3, hour average. In coal mines, it is not practical to routinely measure TC because coal is carbon. Thus, MSHA uses an alternative approach setting limits on the exhaust emissions of diesel-powered equipment (the box on the left) and regulates certain workplace practices such as ventilation. This approach indirectly regulates work place exposures to minimize any harm to coal miners. Both approaches, (a) engine emission limits or (b) workplace exposure limits, have the same objective, limit the exposure of miners to concentrations of diesel exhaust that will not impact the health of workers. The settings of regulations on diesel-powered equipment and exposure limits for miners both use the same knowledge base on diesel technology, mining practices for coal and metal non-metal mines and the exposure-cancer response relationship for miners in the different mines.

D. Need for Periodic Review

I applaud the initiative of MSHA in initiating a review of the Agency's Diesel Rule as it applies to coal mines and metal non-metal mining operations. It is appropriate at this time to take stock of the progress made since the current diesel regulations for underground mines were put in place and, in the first instance, determine if the current regulations are adequate to protect the health of miners. Recall that the IARC classification of diesel exhaust as a human carcinogen does not, in and of itself, establish that current mines, in underground coal or metal non-metal miners are being exposed to diesel concentrations that cause an increased risk of lung cancer.

It is now 20 years since MSHA published on October 23, 1996 a final rule establishing revised requirements for the approval of diesel engines and related components used in underground diesel mines (61 FR 55412) and 15 years since MSHA published a final rule establishing new health standards for underground metal and non-metal mines that use equipment powered by diesel engines (30 CFR Part 57). As I have briefly noted above, over that time period there has been a substantial increase in knowledge in two related arenas; (a) the human health effects of exposure to diesel exhaust, and (b) improved diesel technologies. It is highly appropriate that MSHA assemble, synthesize and integrate all of the available information in both arenas as a basis for considering if the present regulations are adequate to "preserve miner's health."

As I have already emphasized, our collective knowledge of the potential health effects of exposure to traditional diesel exhaust from diesel engines, circa 2000 and earlier, is greatly improved since the time of the earlier rule-making. However, it is important to recognize that improved knowledge of the health effects of diesel exhaust exposure does not automatically translate to recent or current diesel exhaust exposures of miners being deemed more or less hazardous than previously thought.

It is also important to note that diesel exhaust emissions of the earlier diesel engines are very different than the emissions of new technology diesel engines. Two papers by Khalek et al (2011, 2015) provide excellent documentation of how the exhaust emissions of heavy duty diesel engines compliant with 2007 and 2010 EPA regulations differ, quantitatively and qualitative, from emissions of traditional diesel engines marketed and used earlier. The Khalek et al (2011, 2015) papers provide information acquired on diesel engines of the kind typically in routine on-road use. It will be important as the MSHA rule making activity goes forward to assemble and review the specific improvements in diesel-powered equipment and work practices used in mining operations over the last quarter century. Such a review is beyond the scope of my comments.

It is important to <u>not</u> assume that the data base on the older, traditional diesel engines is applicable to the emissions of the new technology diesel engines. Thus, any descriptors of the hazard potential or risk potential of using diesel technology <u>must</u> specify the time period of the diesel technology studied or under consideration as a basis for estimating hazard or risks for any specific past, current or future situations. Statements such as "diesel exhaust causes lung cancer" are meaningless since the statement has no technological context.

E. IARC Cancer Hazard Classification of Diesel Exhaust

The MSHA Request for Information (RFI) is grounded in the International Agency for Research on Cancer (IARC), June 2012, classification of "diesel exhaust as a human carcinogen" (Benbrahim-Tallia et al, 2012; IARC, 2014). This represented an upgrading of the earlier cancer hazard classification of "diesel exhaust is a probable human carcinogen" given by an IARC Panel I served on in 1987 (IARC, 1988). I also attended the 2012 IARC hazard classification review, however, as an observer my participation was limited. The reclassification of diesel exhaust in 2012 was largely driven by the initially published findings from the Diesel Exhaust in Miners Study (DEMS) conducted jointly by scientists from the National Institute for Occupational Safety and Health (NIOSH) and the National Cancer Institute (NCI).

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

The DEMS investigation involved 12,315 workers (4,008 always surface workers, 4,080 always underground miners, and 4,227 individuals who had worked both on the surface and as underground miners) in 8 mines (3 potash mines in New Mexico, 3 trona mines in Wyoming, 1 salt mine in Ohio and 1 limestone mine in Missouri) (Tables 1 and 2). It is important to note that DEMS did not include any underground coal mines, thus, any use of the results of analyses of the DEMS data for estimating the cancer hazards/risks to coal miners using diesel-powered equipment represents an extrapolation from the mining practices and ores of DEMS to the coal mining situation. The population of workers studied in DEMS dates from the first dieselization of these mines (as early as 1947 for the limestone mine to later dates for other mines) through December 31, 1997 when the collection of vital data on the DEMS workers was discontinued. Thus, all of the exposures evaluated in DEMS are to diesel exhaust emissions from engines before the revolutionary changes in technology and emissions discussed earlier.

Measurements of Respirable elemental carbon (REC), the markers of diesel exhaust exposure used in DEMS, were not available prior to December 31, 1997. Thus, all of the REC exposure estimates used in the DEMS epidemiological analyses involve complex extrapolations based primarily on measurements of CO as a surrogate for REC. The complex retrospective exposure assessments are documented in five peer-reviewed papers (Stewart et al., 2010; Coble et al., 2010; Vermeulen et al., 2012a and 2012b; and Stewart et al., 2012). These papers are not referenced in the MSHA RFI and need to be entered in the Docket since the retrospective exposure assessments are crucial to evaluating the strengths and weaknesses of the epidemiological analyses. In addition, a number of papers that call attention to short-comings in the original exposure assessments should be entered in the Docket (Gamble et al, 2012; Boffetta, 2012a; Crump and Van Landingham, 2012; McClellan, 2012; Gamble et al. 2012; Crump et al, 2015; Moolgavkar et al, 2015; Health Effects Institute, 2015).

The results of the original epidemiological analyses of the DEMS data are reported in two peer-reviewed papers. The initial results of the cohort study were reported by Attfield et al (2012) and the initial results of the nested case-control study (approximately 200 lung cancer cases) were reported by Silverman et al (2012). Both of these papers are referenced in the MSHA RFI. The MSHA RFI also references a Report by a Health Effects Institute (HEI) Epidemiology Panel that evaluated the use of the results of the DEMS investigation and a related study, the Trucking Industry Particle Study, for quantitative risk assessment. The HEI Panel concluded the studies were "well designed and carefully conducted, embodying the attributes of epidemiological studies that are considered important for quantitative risk assessment" (HEI, 2015). It is important to note the HEI Panel did not conduct a QRA for diesel exhaust. Indeed, the HEI Report is quite guarded in giving guidance as to how to conduct a QRA for diesel exhaust. I have independently evaluated the HEI Report and noted its strengths and weaknesses, including biases of some of the Panel Members (McClellan, 2016).

It is generally recognized that the DEMS investigation is one of the largest studies of miners exposed to diesel exhaust from traditional diesel technology engines conducted using contemporary exposure assessment and epidemiological methods. In view of the attention given to the results of the original analyses of the DEMS data and the comprehensive nature of the DEMS data, it is highly appropriate for other investigators to use the same data and attempt to replicate and then extend the analyses of the original investigators. This is especially the case in view of the potential role of the results of analyses of the DEMS data for informing important national policy and regulations such as those now being developed by MSHA. Indeed, sharing of data sets with replication and extension of analyses is how science should work! This is especially the case since the DEMS data set was acquired by U.S. government scientists and analyses of it are being used to inform important federal policies and regulations.

Even before the original papers based on the DEMS data were published, the Truck and Engine Manufacturers Association (EMA) initiated efforts to gain access to the original DEMS data for analyses by independent investigators. After substantial delays and negotiations the original data set on diesel equipment used and ventilation conditions in 7 of the 8 mines was released to the EMA. One of the mines was closed and, thus, data were no longer available. Part of the delay in making the DEMS exposure data available to interested parties, such as the EMA, related to some of the DEMS data having been retained by individual scientists working on the DEMS project. In one case, the investigator who had temporarily worked for NCI had returned to his home institution in the Netherlands and took key DEMS data with him. In another case, the NCI employee had retired and had retained possession of the DEMS data. Ultimately, the NCI assembled a data set that under-girded the DEMS retrospective exposure assessments and released it to the EMA.

Proactively, NIOSH also made available limited files of the epidemiological data used for the DEMS cohort study and NCI also made available limited epidemiological data used for the DEMS embedded case-control study. In both cases, the Agencies set up specific procedures for acquiring and using the DEMS data that included some substantial restrictions, including a not clearly defined prohibition on linking the several data sets. Concern for linking the various data sets was stated to be related to concern for maintaining the "confidentiality" of information on individual participants in DEMS as well as adherence to agreements between the federal government and states and territories in assembling and using vital statistics in individuals. Difficulties in conducting analyses under the restrictions originally imposed by NIOSH and NCI led to NIOSH proposing an alternate approach in which independent investigators, with approval from NIOSH/NCI, were allowed to conduct analyses using the DEMS data at a National Center for Health Statistics Research Center under certain carefully prescribed conditions. A primary condition imposed on analysts was prior review and approval of the data analysis plan and subsequently approval of any analytical results before release to the analysts.

To date, four analyses using the DEMS data have been conducted and published by a team of independent investigators funded by an industry/trade association coalition organized by the EMA. One retrospective exposure assessment has been published by Crump and Van Landingham (2012). An extended analysis of the cohort data set using the original REC exposure estimates and alternative analytical methods has been published by Moolgavkar et al (2015). An extended analysis of the case-control data using both the original REC exposure estimates and new REC estimates has been published by Crump et al (2015). More recently, Crump, Van Landingham and McClellan (2016) have published an extended analysis of the DEMS case control data using both original and new REC exposure estimates and control for radon exposures. In each case, the independent analysts were able to first perform analyses that yielded results closely approximating those of the original investigators. This was important in that it indicated the various analysts were using the same DEMS data.

The new REC exposure estimates used by Crump et al (2016) are of special interest since they are based solely on the Horse Power (HP) of diesel engines used in the mines on a year-by-year basis, estimated REC emissions per HP, and reported ventilation in air, cubic feet per minute (CFM). This approach using HP and CFM was originally suggested in Appendix F to the HEI Report authored primarily by David Foster of the University of Wisconsin-Madison. An attractive feature of this approach to retrospectively constructing exposure estimates is that it does not use CO as a surrogate for REC, thus, avoiding major assumptions inherent in using CO, a gas, as a surrogate for the REC particles. This has been a major criticism of the retrospective exposure estimates developed and used by the NIOSH/NCI investigators.

The publication of results with and without control/no control for radon are especially important because radon is a well-known respiratory tract carcinogen. The radon exposure estimates, although limited, are based on actual measurements in the mines included in DEMS. Quantifiable levels of radon varied among the mines with the limestone mine having the highest percentage of radon assessments that could be quantified.

Most of the papers discussed above were not referenced in the MSHA RFI. Thus, it is presumed the papers were not available to MSHA staff at the time the MSHA RFI was prepared. The Docket No. 2014-0031, which includes 2014 for the year, implies the MSHA RFI was originally prepared and submitted to senior officials for approval for dissemination in calendar year 2014 even though it was not published in the Federal Register until June 8, 2016.

In addition to the extended analyses of the DEMS data sets by Moolgavkar et al (2015) and Crump et al (2015, 2016), a recent review by Möhner and Wendt (2016) critically evaluates the original analyses of the DEMS data by Attfield et al (2012) and Silverman et al (2012). The Möhner and Wendt (2016) critique highlights several methodological flaws in the original DEMS analyses, including over adjustment bias, selection bias, and confounding bias. They conclude, based on their review, "that the currently published studies provide little evidence for a causal link between DE exposure and lung cancer risk." Further, they conclude "Based on two studies in miners, the DEMS and the German Potash Miners Study, Quantitative Risk Assessment may be conducted. However, the DEMS data should be reanalyzed in advance to avoid bias that affects the original published risk estimates."

F. Detailed Comparison of the Original Analyses of DEMS Versus More Recent Independent Analyses.

This section of my comments focuses on relating the results of the independent analyses of the DEMS data set and, when appropriate, a comparison of these new findings with the results reported by the original DEMS investigators (Attfield et al, 2012 and Silverman et al, 2012). It is important at the outset to recognize that DEMS was a very large and complex body of research that extended over about two decades from its conception in the early 1990s to publication of the seminal papers noted above. The DEMS was conducted with substantial funding from two U.S. federal agencies; the National Institute of Occupational Safety and Health (NIOSH) and the National Cancer Institute (NCI) ad collaboration by scientists with the two agencies. It also involved extensive cooperative effort from the owners and operators of the 8 mines in DEMS and their employees who agreed to participate in the DEMS.

Key characteristics of the mines included in DEMS are shown in Table 1. It can be immediately noted that the eight mines are quite diverse. The year of first diesel use in the different mines extended over two decades from 1947 to 1967. Four different ores were mined. The primary mode of operation in the various mines differed markedly, especially in how ore was moved with diesel truck haulage used in the limestone and salt mines versus primarily electrically-powered conveyors in some other mines. Ventilation differed from primary use of natural ventilation in the limestone mine to varying degrees of mechanical ventilation in other mines with differences, in part, related to concern for build-up of hydrocarbon gas. In the mechanically ventilated mines, total ventilation differed by more than a factor of six from 250 to

1630 CFM during 1982. The kind of diesel equipment used and total HP used differed by an order of magnitude from 638 to 6862 HP during 1982. The year 1982 has been used for illustrative purposes since that links to the 15-year lag (1997 minus 15 years) shown by the original DEMS investigators to give the most positive results. The concentration of Carbon Monoxide, used by the original DEMS investigators as a surrogate for Respirable Elemental Carbon, varied widely across the mines with one trona mine having 39% of the samples over the limit of detection compared to 70% over the limits of detection in the limestone mine. The percentage of samples with radon concentrations over the limits of detection ranged from 15% in one trona mine to 84% in the limestone mine. This diversity led Möhner and Wendt (2016) to note that – "The DEMS is strictly speaking, a pooled study of 8 cohorts that differ considerably by year of dieselization, by range of exposure, by size of the work force, and possibly other factors like history of former employment in other mines." At a minimum, DEMS is a pooled study of four cohorts mining different types of ore (limestone, salt, potash and trona) using diesel equipment and ventilation controls in very different ways in four states differing in cultural and work place practices.

As noted, the few measurements of REC available pre-1998 were not sufficient for use in the epidemiological analyses as estimates of exposure of workers to REC. As a result the original DEMS team elected to collect data on REC and CO in 1998 to 2001 and use a job-exposure matrix along with pre-1998 measurements of CO to retrospectively estimate REC exposures for individual workers pre-1998 back to the beginning of dieselization in each mine. This procedure is documented in five papers (Stewart et al., 2010; Coble et al., 2010; Vermeulen et al., 2012a and 2012b; and Stewart et al., 2012). This approach is dependent on the assumption of a stable quantitative relationship between HP and CO. This assumption is open to question as illustrated in Figure 3.

Crump, Van Landingham and McClellan (2016) used an alternative approach to retrospectively estimate REC in the 8 mines. This approach was suggested in Appendix F in the HEI Panel Report, an appendix authored primarily by Robert Foster, a highly regarded expert on combustion engines and their emissions, University of Wisconsin-Madison (HEI, 2015). A cornerstone of that approach is use of data compiled by the U.S. Environmental Protection Agency on the relationship between diesel engine particulate matter (PM) emissions in grams per brake horsepower-hours (g/bhp-h) as a function of model year as shown in Figure 4 (EPA, 2002; Crump et al 2016). The REC estimates using the HP-CFM approach are shown in Figure 5. For comparison, the original estimates used by Silverman et al (2012) and Attfield et al (2012) are also shown in Figure 5. The differences in estimated REC exposure are most substantial for the limestone and salt mines that made major use of heavy-duty diesel-powered equipment to haul ore. It is my professional judgment that the HP-CFM REC exposure estimates are superior to those of the original DEMS team because the HP-CFM calculations do not rely on any assumptions relating to CO as a surrogate for REC. Recall the scatter plot relationship shown in Figure 3.

The cohorts of workers studied in the 8 mines are summarized in Table 2. The original analyses by the DEMS team focused on grouping workers as surface-only or ever-underground workers. Other investigators have sometimes further sub-divided the ever-underground workers into two sub-groups; (a) underground only and (b) mixed surface and underground work.

G. Results of Original DEMS Analyses

The primary findings reported in the cohort paper by Attfield et al (2012) was that in comparison to the general population, miners had an increased risk of lung cancer (overall SMR for lung cancer of 1.26). However, despite the ever-underground workers having REC exposures intensities that were nearly 2 orders of magnitude greater than the surface-only workers, the lung cancer risk for ever-underground workers (SRM 1.21) was somewhat lower than for surface only workers (SMR 1.33). A careful reading of the Attfield et al (2012) paper reveals that the primary (a-priori defined) internal cohort analysis did not show an association between cumulative REC exposure or REC intensity and lung cancer mortality. A positive exposure-lung cancer response relationship was only seen when the (time-dependent) binary variable "work location" was included in the model. Subsequently, the investigators incorporated this variable in both their cohort and case-control analyses.

Silverman et al (2012) in the original DEMS case-control analyses reported a statistically significant positive association between lung cancer and increasing cumulative REC exposure as well as average REC intensity. The case-control analyses showed, as expected, a substantial effect of cigarette smoking intensity and duration on lung cancer. The OR comparing the highest and lowest quartiles of cumulative REC was 2.83 (95% Confidence Interval of 1.28-6.26), adjusted for work location cross-classified by smoking status and intensity. The DEMS investigators concluded that their analyses of the DEMS data provided evidence that exposure to diesel exhaust increases the risk of mortality from lung cancer.

The results published in Attfield et al (2012) and Silverman et al (2012) were the primary drivers for IARC upgrading the cancer hazard classification for diesel exhaust exposure.

These original results by the DEMS team have led to a number of commentaries and Letter to Editors raising concerns about various aspects of the methodologies used by the original investigators (Boffetta, 2012b; Hesterberg et al, 2012; McClellan, 2012; Möhner et al, 2012, Morfeld, 2012; Tse and Yu, 2012; and Pallpies et al, 2013). These opinions were not available at the IARC Panel meeting because of the short interval between publication of the original DEMS analyses and the IARC Panel meeting.

Later, the HEI published a critique of the DEMS work focusing on the original reports. In turn, I have offered a critique of the HEI Report (McClellan, 2016).

H. Extended Analyses by Independent Analysts Using the DEMS Data

As described earlier, the DEMS data have been analyzed by other independent investigators. They first attempted to replicate the results of the original DEMS investigators and, then, used alternative methods including alternative exposure estimates and control for radon, a well-known lung carcinogen. Teams led by Moolgavkar and Crump made use of the actual DEMS data. The German government scientists, Möhner and Wendt (2016), did not have access to the DEMS data and, thus, as an alternative approach used data and results published in the open literature by the original DEMS team.

Using a DEMS data set provided by NIOSH, Moolgavkar et al (2015) first replicated the results of Attfield et al (2012) on the DEMS cohort. They then proceeded with alternative analyses using parametric functions based on concepts of multi-stage carcinogenesis. They found that the REC-associated risk of lung cancer mortality was driven by increased risk in only one of the four mine types, the limestone mine, demonstrating statistically significant heterogeneity by mine types and no significant exposure-lung cancer response relationship after removal of the limestone mine workers from the analysis. These findings were based on use of the original DEMS REC exposure estimates. They concluded that temporal factors, such as duration of exposure, play an important role in determining the risk of lung cancer mortality following exposure to REC and the relative lung cancer risk declines after exposure to REC stops. They found evidence of effect modification by attained age. Moolgavkar et al. (2015) urged caution in using the DEMS data for quantitative risk analysis without further evaluation.

Crump et al (2015) conducted extended analyses of the DEMS case-control data at the NCHS Research Data Center in Hyattsville, MD. They used the original REC exposure estimates and substantially replicated the findings of the original DEMS investigators using the case-control data. They then proceeded to use additional estimates of diesel exhaust exposure and adjust for radon exposure. When exposure to radon was adjusted, the evidence for a diesel exhaust exposure effect was greatly diminished but was still present in some analyses that used the original REC exposure estimates. An effect on lung cancer risk was not observed when six alternative REC exposure estimates were evaluated and radon was adjusted. They found no consistent evidence of a diesel exhaust exposure effect on lung cancer in workers who only worked underground. This was a surprising finding since these individuals were not consistently exposed to diesel exhaust. Crump et al. (2015) also urged caution and further research before the DEMS data are used for quantitative risk assessment.

In a recent extended analysis of the DEMS case control data, Crump, Van Landingham and McClellan (2016) conducted analyses at the NCHS-RDC in Hyattsville, MD using the HP-CFM based REC exposure estimates and adjustment for radon. These are the REC exposure estimates labeled as HP-CFM in Figure 5 and compared to the REC exposure estimates originally used in the analyses reported by Silverman et al (2012) and also Attfield et al (2012).

The results of these analyses are shown in Table 3. The methodological approach used a conditional logistic regression of the nested case-control data very similar to the one applied in the original analyses reported by Silverman et al (2012). None of the trend slopes calculated using the new HP-CFM based REC exposure estimates were statistically significant ($p \geq 0.05$). Moreover, these trend slopes were smaller by roughly factors of five without control for radon exposure and factors of 12 with control for radon exposure compared to those estimated in the original DEMS analyses. Crump et al. (2016) urged caution in using estimates of lung cancer potency for diesel exhaust exposure to circa 1960-1980 diesel technology because of uncertainty in the estimates of exposure for the DEMS workers.

Möhner and Wendt (2016) have recently critically reviewed the literature on the relationship between occupational exposure to diesel exhaust emissions and lung cancer risk focusing on the studies evaluated by IARC in 2012, including the papers by Attfield et al (2012) and Silverman et al (2012) and subsequent analyses of the DEMS data by other analysts. The efforts of Möhner and Wendt (2016) related to the DEMS data were particularly heroic because they did not have direct access to the DEMS data. Thus, their evaluation was based on analyses they could perform using the results originally published by the DEMS team. Even without direct access to the DEMS data, they identified a number of critical issues that must be addressed in using the DEMS data for quantitative risk assessment. These include over-adjustment bias, selection bias, and confounding bias. They strongly recommend consideration of a 5-year lag rather than the 15-year lag used in the original analyses and for comparison purposes, by subsequent independent analysts. Möhner and Wendt (2016) concluded – "At present, the DEMS does not add evidence to an exposure-response relationship between DE and lung cancer. A reanalysis of the original data is recommended."

Möhner, Kersten and Gellisen (2013) have published a study on the association between diesel exhaust exposure and lung cancer mortality in a cohort of German Potash miners. This study involved 5,819 workers in potash mines that were dieselized in 1969 with TC measurements and some EC measurements made in 1991. Diesel exhaust exposures were assumed to remain constant in the mines as the original equipment was routinely repaired and not replaced. The vital status of workers was ascertained until 2001. Data on smoking status was available on 79.8% of the workers. A total of 68 lung cancer cases were observed and matched to 340 controls. This study is similar in size to the Silverman et al (2012) nested case-control study of DEMS workers. Seven of the lung cancer cases were determined to have occurred in mines that had previous work experience in uranium mines and, thus, had been previously exposed to radon and daughter products, well known lung carcinogens. As expected, smoking was identified as the primary risk factor for lung cancer. Their analyses did not show any notable association between cumulative REC exposure and lung cancer risk. Introducing cumulative REC exposure as a continuous variable into the conditional logistic regression model yielded an odds ratio of 1.04 (95 Confidence Interval of 0.70-153). Möhner and his colleagues interpreted the results as providing no evidence of an association between REC exposure and lung cancer risk. They did note that only for a very high cumulative exposure, corresponding to at least 20 years of exposure in the production area, some weak hints for a possible risk increase could be detected. The authors do not recommend the use of the German Potash Miners Study (GPMS) for quantitative risk assessment.

Möhner and Wendt (2016) have raised the possibility of a combined analysis of DEMS data acquired in U.S. non-metal mines and the GPMS data acquired in the potash mines in the former East Germany. The two studies have remarkably similar REC exposures and the number of lung cancer cases in always-underground miners in the two studies is remarkably similar. A challenge in conducting such a combined analysis would relate to adjustment for smoking in the two populations that had very different cultural and work environments.

In their review, Möhner and Wendt (2016) indicate that an upper bound for cumulative exposure of 2.5 mg/m^3-years seems to be sufficient to prevent a detectable increase of lung cancer risk. This value corresponds to an annual value of 50 μg REC/m^3 assuming a working life of 45 years. This would correspond to about 80 μg TC/m^3 based on the observed ratio of EC to TC measurements made in 1991 in the German mines.

The multiple analyses using the DEMS data have yielded very different results. The results may be sufficient for use in classifying diesel exhaust as a human carcinogen as was done by IARC in 2012 and published in 2014 (IARC, 2014). However, the wide range of results from positive associations between REC exposure and elevated lung cancer risk to no statistically significant REC exposure lung cancer risk using alternative REC exposure estimates and control for radon suggest that a high degree of caution should be exercised in using the positive DEMS results to inform policy judgments made in reviewing the MSHA diesel rule regulations for underground miners using modern diesel engines fueled with ultra-low sulfur fuels and having contemporary exhaust after-treatment devices.

Finally, it is important to note that none of the results discussed ae based on observations in underground coal miners. The author is not aware of any studies on underground coal miners similar to DEMS nor any reports of population studies of underground coal mines using diesel equipment and reporting an excess of lung cancer. Thus, the findings from DEMS, as diverse as they are, should be extrapolated with great caution to coal miners.

References

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-Tallia 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.

Boffetta PA. 2012a. The Diesel Exhaust in Miners Study: A Nested Case-Control Study of Lung Cancer and Diesel Exhaust and a Cohort Mortality Study with Emphasis on Lung Cancer. JNCI 104: 1842-1843.

Boffetta P. 2012b. The Diesel Exhaust in Miners Study: A Nested Case-Control Study of Lung Cancer and Diesel Exhaust and a Cohort Mortality Study With Emphasis on Lung Cancer. Journal of the National Cancer Institute, 104: 1842-1843.

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 KS, Van Landingham C, McClellan R. 2016. Influence of alternative exposure estimates in DEMS miners study; diesel exhaust and lung cancer. Risk Anal. 36 (9): 1803-1812.

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 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.

EPA. 2002. Health :Assessment Document for Diesel Engine Exhaust. EPA/6900/8-90/057F. Washington, DC. National Center for Environmental Assessment, 2000.

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.

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, Long CM, Valberg PA. 2012. The Diesel Exhaust in Miners Study: A Nested Case-Control Study of Lung Cancer and Diesel Exhaust and a Cohort Mortality Study With Emphasis on Lung Cancer. Journal of the National Cancer Institute, 104: 1841.

IARC (International Agency for Research on Cancer) 2014. Diesel and Gasoline Engine Exhausts and Some Nitroarenes, IARC Monographs Vol. 105, pp 1-609, International Agency for Research, Lyon, France.

IARC (International Agency for Research on Cancer). 1988. Man-made Mineral Fibers and Radon. IARC Monographs on the Evaluation of Carcinogenic Risk to Humans. Vol. 43, International Agency for Research on Cancer, Lyon, France.

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.

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.

McClellan RO. 2016. Providing Context for Ambient Particulate Matter and Estimates of Attributable Mortality. Risk Analysis 36 (9): 1755-1765.

McClellan, RO. 2015. 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).

McClellan RO. 2012. The Diesel Exhaust in Miners Study: A Nested Case-Control Study of Lung Cancer and Diesel Exhaust, a Cohort Mortality Study with Emphasis on Lung :Cancer, and the Problem with Diesel. JNCI 104: 1842-1845.

McClellan, RO, Hesterberg TW, Wall JC. 2012. Evaluation of Carcinogenic Hazard of Diesel Engine Exhaust Needs to Consider Revolutionary Changes in Diesel Technology. Reg. Toxicol. Pharmacol. 63: 225-258.

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

Möhner M, Wendt A. 2016. A Critical Review of the Relationship Between Occupational Exposure to Diesel Emissions and Lung Cancer Risk. Crit. Rev. in Toxicol. (in press).

Möhner M, Kersten N, Gellissen J. (2013). Diesel Motor Exhaust and Lung Cancer Morality: Reanalysis of a Cohort Study in Potash Mines. Eur J Epidemiol 28: 155-168.

Möhner M, Kersten N, Gellissen J. (2012).Re: The Diesel Exhaust in Miners Study: A Nested Case-Control Study of Lung Cancer and Diesel Exhaust and a Cohort Mortality Study with Emphasis on Lung Cancer. Journal of the National Cancer Institute, 104: 1846-47.

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 35 (4): 663-675.

Morfeld P. (2012). Diesel Exhaust in Miners Study: How to Understand the Findings? Journal of Occupational Medicine and Toxicology 7: 10.

Pallpies D, Taeger D, Bochmann F, Morfeld P. 2013. Comment: Carcinogenicity of Diesel-Engine Exhaust (DE). Arch Toxicol. 87: 547-549.

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.

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.

Tse LA, Yu IS. 2012b). The Diesel Exhaust in Miners Study: A Nested Case-Control Study of Lung Cancer and Diesel Exhaust. Journal of the National Cancer Institute, 104: 1843-43.

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.

Evolutionary Followed by Revolutionary Changes in Diesel Technology

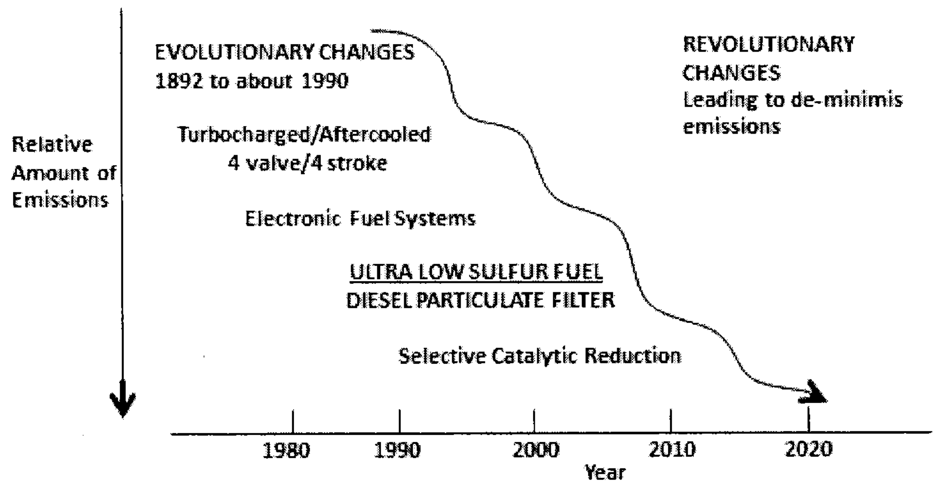

Figure 1. Remarkable changes in diesel technology have led to substantial reductions in diesel engine exhaust emissions. The emissions of contemporary engines ae totally different than the emissions typical of the pre-2000 era, the time period when most of the exposures occurred that have been the basis of epidemiological studies

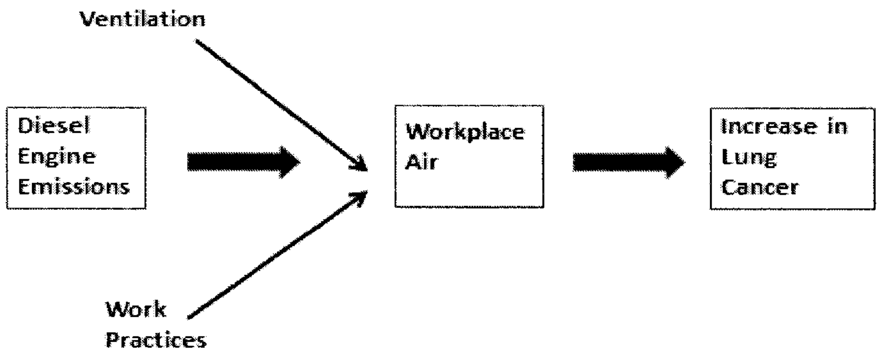

Figure 2. Critical Linkages in Evaluating and Controlling Potential Health Effects of Diesel Engine Exhaust Emissions. MSHA regulations for underground coal mines focus on regulation of diesel equipment exhaust emissions. MSHA regulations for metal non-metal mines focuses on regulation of workplace exposures. Both strategies are intended to limit any increase in lung cancer in underground miners.

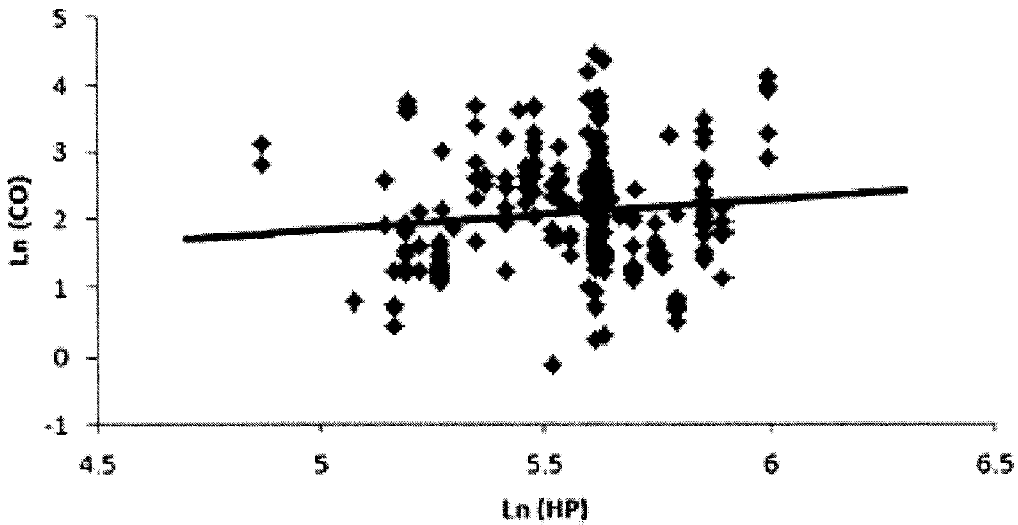

Figure 3. Poor Correlation between HP and CO raises questions about estimating REC values from CO measurements.

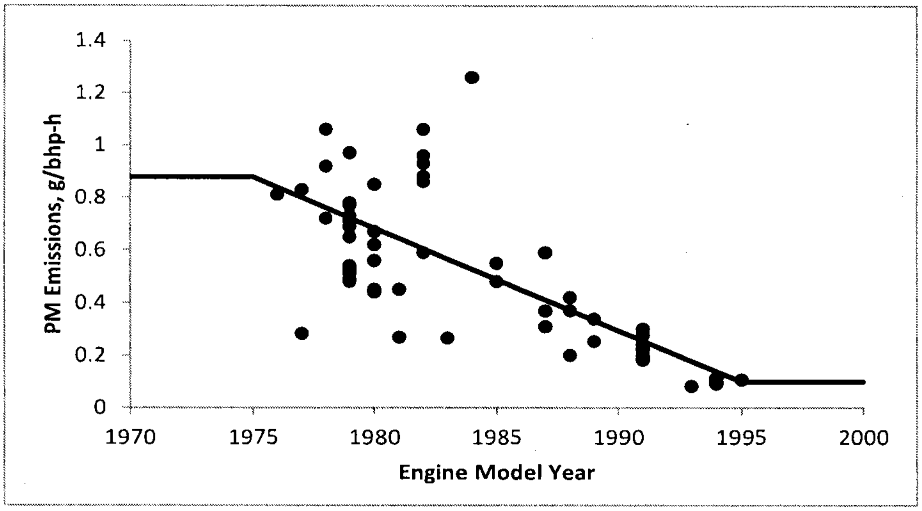

Figure 4. Reduced PM Emissions with improved Diesel Technology needs to be accounted for in retrospectively estimated REC exposures.

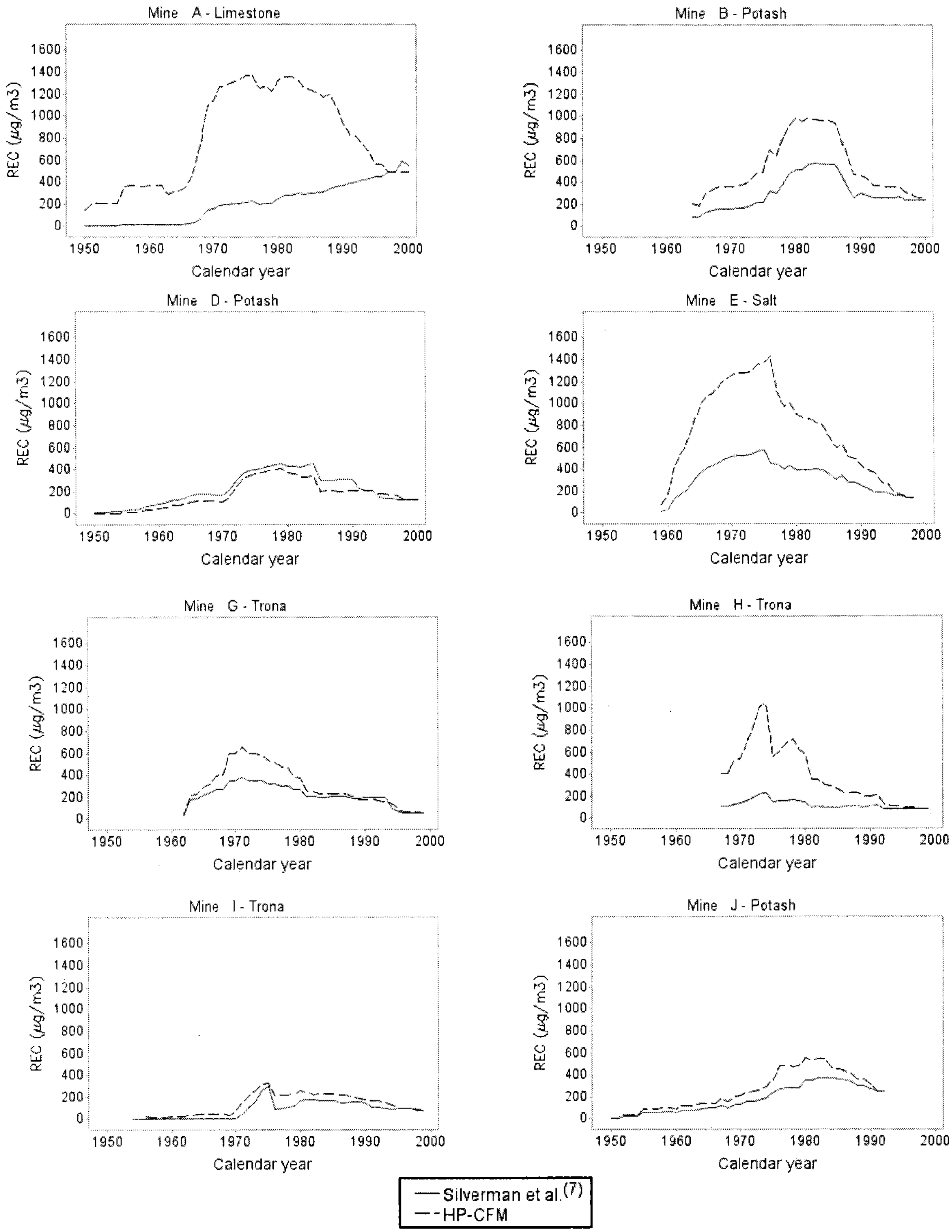

Figure 5: Alternative Respirable Elemental Carbon Metrics Using CO (red), the Original Investigators versus HP-CFM (blue) Developed by Crump et al. (2016).

Table 1: Characteristics of the Mines in the Diesel Exhaust in Miners Study (DEMS)

Mine	State	Ore	Ventilation	Year of First Diesel Use	Primary Mode of Operation	All Years CO # samples	All Years CO % > LOD	All Years Radon # samples	All Years Radon % > LOD	1982 Activity CFM f^3/min (in thousands)	1982 Activity Diesel (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 2. Number of miners and lung cancer deaths by worker location and mine type in the DEMS cohort.

			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	200

Table 3: Comparison of Conditional Original Logistic Regression Results (Silverman (7)) With Results of Similar Analyses Except Based on New REC Estimates Defined Using HP and CFM

Analysis	Quartiles of cumulative REC, lagged 15 years $(\mu g/m^3\text{-}y)$	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	0 to < 3	49	158	1.0 (referent)	0.0006	0.00082
Silverman et al.(7)	3 to < 72	50	228	0.79 (0.41 to 1.52)		(0.00035,0.0013)
and "without	72 to < 536	49	157	1.62 (0.75 to 3.49)		
radon" controls(12)	≥ 536	50	123	3.24 (1.40 to 7.55)		
HP-CFM REC	0 to < 6.6	49	172	1.0 (referent)	0.06	0.00016
estimates and	6.6 to < 129	50	191	1.05 (0.58 to 1.93)		(-0.000012,0.0003)
"without radon"	129 to < 891	49	168	1.60 (0.79 to 3.24)		
controls	≥ 891	50	135	2.37 (1.02 to 5.50)		
HP-CFM REC	0 to < 6.6	49	172	1.0 (referent)	0.63	0.00005
estimates and	6.6 to < 129	50	191	1.02 (0.55 to 1.90)		(-0.00016,0.00026)
"with radon"	129 to < 891	49	168	1.20 (0.56 to 2.56)		
controls	≥ 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	0 to < 97	31	158	1.0 (referent)	0.01	0.00073
Silverman et al.(7)	97 to < 384	31	90	1.90 (0.78 to 4.63)		(0.00022,0.0012)
and "without	384 to < 903	31	80	2.73 (1.08 to 6.88)		
radon" controls(12)	≥ 903	31	84	5.04 (1.77 to 14.30)		
HP-CFM REC	0 to < 130	31	144	1.0 (referent)	0.16	0.00014
estimates and	130 to < 531	31	99	2.03 (0.83 to 4.96)		(-0.000062,0.0003)
"without radon"	531 to < 2149	31	99	3.45 (1.27 to 9.41)		
controls	≥ 2149	31	70	3.84 (1.07 to 13.74)		
HP-CFM REC	0 to < 130	31	144	1.0 (referent)	0.69	0.00005
estimates and	130 to < 531	31	99	1.83 (0.73 to 4.61)		(-0.00020,0.00030)
"with radon"	531 to < 2149	31	99	2.47 (0.79 to 7.73)		
controls	≥ 2149	31	70	2.5 (0.49 to 12.79)		
All Subjects Who Only Worked Underground						
HP-CFM REC	0 to < 106	14	26	1.0 (referent)	0.27	0.00024
estimates and	106 to < 410	15	28	1.89 (0.4 to 9.07)		(-0.000179,0.0007)
"without radon"	410 to < 1486	14	17	3.15 (0.47 to 21.05)		
controls	≥ 1486	15	26	4.73 (0.58 to 38.84)		
HP-CFM REC	0 to < 106	14	26	1.0 (referent)	0.36	0.00027
estimates and	106 to < 410	15	28	1.91 (0.38 to 9.75)		(-0.000316,0.0009)
"with radon"	410 to < 1486	14	17	5.61 (0.61 to 51.33)		
controls	≥ 1486	15	26	9.39 (0.47 to 187.84)		

* Calculated by us after reproducing Silverman et al.(7) results.

APPENDIX A

BIOGRAPHY

ROGER O. McCLELLAN, DVM, MMS, DSc (Honorary),
Dipl-ABT and ABVT;
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ROGER O. McCLELLAN serves as an advisor to public and private organizations on issues of air quality in the ambient environment and work place using his expertise in inhalation toxicology, comparative medicine, aerosol science and human health risk analysis. He received his Doctor of Veterinary Medicine degree with Highest Honors from Washington State University in 1960 and a Master of Management Science degree from the University of New Mexico in 1980. He is a Diplomate of the American Board of Toxicology and the American Board of Veterinary Toxicology and a Fellow of the Academy of Toxicological Sciences.

He served as Chief Executive Officer and President of the Chemical Industry Institute of Toxicology (CIIT) in Research Triangle Park, NC from September 1988 through July 1999. During his tenure, the organization achieved international recognition for the development of scientific information under-girding important environmental and occupational health decisions and regulations. Prior to his appointment as President of CIIT, Dr. McClellan was Director of the Inhalation Toxicology Research Institute, and President and Chief Executive Officer of the Lovelace Biomedical and Environmental Research Institute, Albuquerque, New Mexico. The Institute continues operation today as a core element of the Lovelace Respiratory Research Institute. During his 22 years with the Lovelace organization, he provided leadership for development of one of the world's leading research programs concerned with the health effects of airborne radioactive and chemical materials. Prior to joining the Lovelace organization, he was a scientist with the Division of Biology and Medicine, U.S. Atomic Energy Commission, Washington, DC (1965-1966), and Hanford Laboratories, General Electric Company, Richland, WA (1959-1964). In these assignments, he was involved in conducting and managing research directed toward understanding the human health risks of internally deposited radionuclides.

Dr. McClellan is an internationally recognized authority in the fields of inhalation toxicology, aerosol science, comparative medicine, and human health risk analysis. He has authored or co-authored over 350 scientific papers and reports and edited 10 books. In addition, he frequently speaks on risk assessment and air pollution issues in the United States and abroad. He is active in the affairs of a number of professional organizations, including past service as President of the Society of Toxicology and the American Association for Aerosol Research. He serves in an editorial role for a number of journals, including service since 1987 as Editor of Critical Reviews in Toxicology. He serves or has served on the Adjunct Faculty of 8 universities.

Dr. McClellan has served in an advisory role to numerous public and private organizations. He has served on senior advisory committees for all the major federal agencies concerned with human health. This included service as past Chairman of the Clean Air Scientific Advisory Committee, Environmental Health Committee, Research Strategies Advisory Committee, and Member of the Executive Committee, Science Advisory Board, U. S. Environmental Protection Agency; Member for 30 years, National Council on Radiation Protection and Measurements; Member, Advisory Council for Center for Risk Management, Resources for the Future; a former Member, Health Research Committee, Health Effects Institute; and service on National Academy of Sciences/National Research Council Committee on Toxicology (served as Chairman for 7 years), Risk Assessment for Hazardous Air Pollutants, Health Risks of Exposure to Radon, Research Priorities for Airborne Particulate Matter, as well as the Committee on Environmental Justice of the Institute of Medicine. He has served on the Board of Scientific Councilors for the Center for Environmental Health Research of the Centers for Disease Control and Prevention and the Agency for Toxic Substances and Disease Registry and on the National Institutes of Health Scientific Advisory Committee on Alternative Toxicological Methods. He served on the National Aeronautics and Space Administration Lunar Airborne Dust Toxicity Advisory Group.

Dr. McClellan's contributions have been recognized by receipt of a number of honors, including election in 1990 to membership in the National Academy of Medicine. He is a Fellow of the Society for Risk Analysis, the American Association for Aerosol Research, the Health Physics Society, the International Aerosol Research Assembly, and the American Association for the Advancement of Science. In 1997, he received the Thomas T. Mercer Prize for research on inhalable materials from the International Society for Aerosols in Medicine and the American Association for Aerosol Research. In 1998, he received the International Achievement Award of the International Society of Regulatory Toxicology and Pharmacology for outstanding contributions to improving the science used for decision making on chemical safety and the International Aerosol Fellow Award of the International Aerosol Research Assembly for outstanding contributions to aerosol science and technology. In 2002, he was inducted into the University of New Mexico Anderson School of Management Hall of Fame for contributions to the effective management of multi-disciplinary research organizations. He received the Society of Toxicology Merit Award in 2003 for a distinguished career in toxicology and the Society's Founders Award in 2009 for contributions to science-based safety/risk decision-making. In 2012, he received a career achievement award from the International Dose-Response Society and the American Association for Aerosol Research and in 2014 from the Academy of Toxicological Sciences. In 2016, he received the American Veterinary Medical Association Meritorious Service Award for public service. In 2005, The Ohio State University awarded him an Honorary Doctor of Science degree for his contributions to comparative medicine and the science under-girding improved air quality. In 2006, he received the New Mexico Distinguished Public Service Award. In 2008, Washington State University presented Dr. McClellan the Regents Distinguished Alumnus Award, the highest recognition the University can bestow on an Alumnus.

Dr. McClellan has a long-standing interest in environmental and occupational health issues, especially those involving risk assessment and air quality and in the management of multidisciplinary research organizations. He is a strong advocate of science-based decision- making and the need to integrate data from epidemiological, controlled clinical, laboratory animal and cell studies to assess human health risks of exposure to toxic materials and to inform policy makers in developing standards and guidance to protect public health. He is internationally recognized for his knowledge of the health issues associated with a range of energy technologies, including nuclear power, coal combustion, oil/gas extraction and internal combustion engines, including the transition from traditional to clean diesel technology.