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RE: Public Comments on Nominations, National Toxicology Program Report on Carcinogens, Diesel Exhaust Particulates

Dear Dr. Lunn:

I am writing on my own behalf, as a scientist knowledgeable of the health effects of diesel exhaust particulates, in response to the "Request for Public Comments on Nominations," Federal Register/Vol. 77, No. 12/, Thursday, January 19, 2012/Notices, pp 2728-2729. I have attached my biography and a Declaration of Interest Statement at the end of this letter.

Specifically, in this letter I offer comments on "Diesel Exhaust Particulates" which is identified under the heading – Some Substances Nominated to the RoC. I was pleased to see the footnote to the list of agents – "Nominations to the RoC may seek to list a new substance in the report, reclassify the listing status of a substance already listed, or remove a listed substance." My comments address the need for actions related to "Diesel Exhaust Particulates," which I will hereafter refer to as DEP, and more broadly, the emissions from diesel compression ignition engines (and associated exhaust treatment system) and using diesel fuel.

This letter provides a basis for two recommendations:

(1) *NP should update the Background Document for Diesel Exhaust Particulates (NTP, 1998) and use it for a re-evaluation of the listing for "diesel exhaust particulates (DE)." That updated listing should explicitly identify the characteristics of DEP and note that the listing only applies to Traditional Diesel Exhaust that contains DEP (elemental carbon particles with associated hydrocarbons). The listing should explicitly note it does not apply to diesel engines using oxidation catalysts and wall flow diesel exhaust particulate filters and using ultra-low sulfur fuel (<15 ppm) or any other technology that results in emissions that are virtually free of DEP.*

(2) *NTP should at the conclusion of the Advanced Collaborative Emissions Study (ACES) now in progress, evaluate New Technology Diesel Exhaust (NTDE) as to its carcinogenic hazard potential recognizing that NTDE emissions contain remarkably lower concentration of key constituents than TDE emissions and most importantly, contains very low concentrations of material sampled as particulate material and that the particle mass is very different in composition than DEP.*

The comments I offer are based on my professional interest, as an aerosol scientist, inhalation toxicologist and human health risk analyst, in the health effects of airborne materials. I have more than 35 years of experience conducting and evaluating research on the potential health hazards of diesel engines and fuels. Under my leadership, the Lovelace Inhalation Toxicology Research Institute, now a part of the Lovelace Respiratory Research Institute, with support from the U. S. Department of Energy, initiated in the late 1970s one of the earliest, broad-based research programs on the potential health effects of emissions from diesel engines and fuels. The results of that research program, and follow-on efforts, have been reported in the peer-reviewed literature. Early results from that research program were considered by the International Agency for Research on Cancer (IARC) Working Group (WG) that prepared IARC Monograph 46 on Diesel and Gasoline Engine Exhausts and Some Nitroarenes (IARC, 1989). I served on that WG as Chair of the sub-group on animal evidence. The IARC Monograph (IARC, 1989) classified whole diesel exhaust in IARC's Group 2A, a probable human carcinogen.

Later, when the NTP considered listing DEP in the RoC, I offered comments (McClellan, 1998) to the NTP on the proposed listing. In my 1998 Comments, I noted the strengths and weaknesses in the epidemiological and animal evidence for identifying a causative association between exposure to diesel exhaust particulates and the occurrence of human lung cancer. I concluded – "the epidemiological data support a conclusion of limited evidence of carcinogenicity for diesel exhaust particulates." I also concluded then "Taken in aggregate, the laboratory animal data, when interpreted for human relevance, supports a conclusion of limited evidence of carcinogenicity for diesel exhaust particulates." I concluded – "Considering all of the data, it is my professional judgment that "diesel exhaust particulates" should be listed as "reasonably anticipated to be a human carcinogenic" using the NTP criteria." At the conclusion of the review, the NTP listed DEP as "reasonably anticipated to be a human carcinogen" in the 9th RoC released in 2000 (RoC, 2000). The listing has been repeated in each subsequent RoC including the most recent report (RoC, 2011).

It is important to recognize that the IARC carcinogenic hazard classification was for "whole diesel exhaust" and the NTP carcinogen hazard classification was more specific, "diesel exhaust particulates." In my opinion, this distinction is very important and reflected a wise decision on the part of the NTP in 2000.

Over the past 35 years substantial research has been conducted on the potential carcinogenic hazards of diesel engine emissions and, specifically, DEP emissions from diesel engines and fuels. This research has included epidemiological, animal and *in vitro* studies. That extensive literature has been reviewed in multiple papers. In particular, I call your attention to the papers by Mauderly (2000), Hesterberg et al. (2005, 2006, 2011) and Gamble (2010). In addition, I call your attention to two papers recently submitted for publication (Hesterberg et al. 2012 and McClellan et al. 2012). These two papers contain numerous references that will be useful to the NTP in reviewing the potential health effects of various emissions form diesel engines. When these papers are published I will provide copies to the NTP.

I do not intend to use this letter to exhaustively review the substantial body of information on the potential health effects of emissions from diesel engines and fuels. Alternatively, I will briefly make several points:

(1) It is increasingly recognized that it is essential to consider as an integrated diesel system; (a) diesel engines, (b) exhaust after-treatment systems, and (c) diesel fuel. Emissions are profoundly influenced by each of these elements of the system. Unfortunately, many studies in the biomedical literature provide only vague reference to the source of the emissions studied and reported on. Such reports are of limited value for evaluating the carcinogenic hazards of diesel exhaust and relating it to specific technology and emission characteristics. Based on today's scientific knowledge, it is not appropriate to treat all diesel exhaust emissions as being the same and having equal hazard potential.

(2) Most of the health effects literature on diesel engines and fuels published pre-2005 involved emissions from engines whose designs were still evolving and were conducted prior to major improvements in diesel fuel quality. They typically used high sulfur content fuel (usually 500 ppm or more) and the engines did not have exhaust after-treatment systems. Those emissions did contain appreciable concentrations of DEP as shown in Figure 1. The diesel exhaust particulates in the figure are described in the RoC Background document for Diesel Exhaust Particulates as "aggregates of carbon particles coated with organic and inorganic substances." This is the agent listed in the 9th and subsequent RoCs as "reasonably anticipated to be a human carcinogen."

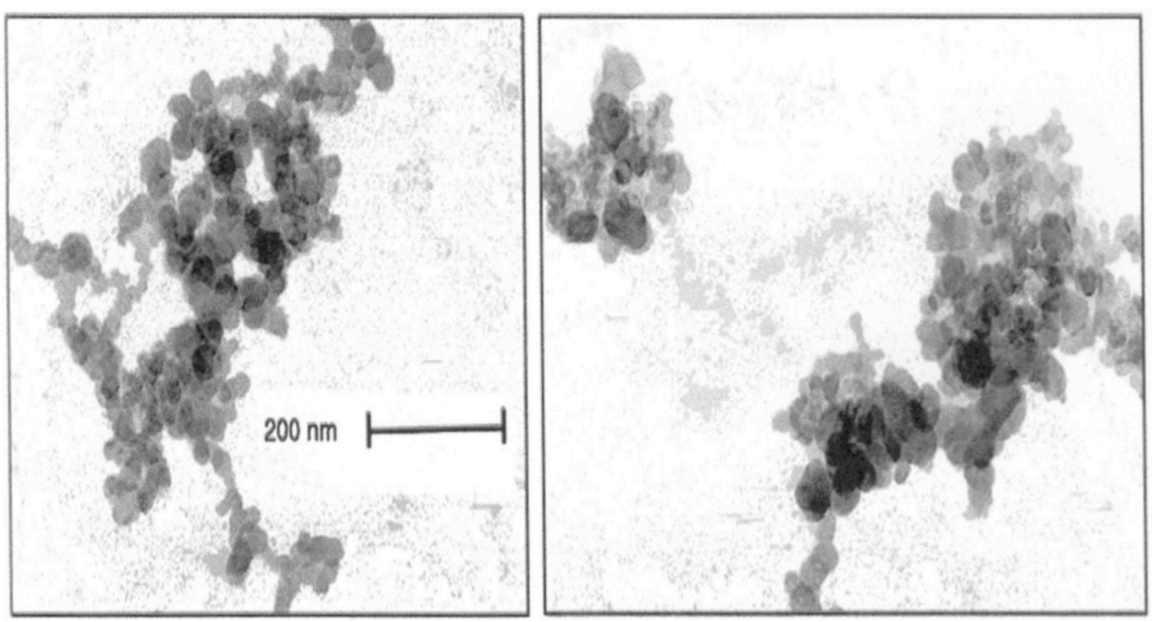

Figure 1: Scanning electron micrograph of traditional diesel exhaust particulate matter (from Tschoeke et al. 2010). Primary particles with diameters of less than 10 nanometers that rapidly aggregate to a size distribution that is log-normal and with median diameter of approximately 80-100 nanometers. The elemental carbon particles adsorb and absorb hydrocarbons, sulfates and trace metals.

(3) Numerous epidemiological studies have been conducted, typically using some indicator of DEP as an exposure variable. A serious shortcoming in all those studies as evaluated for the 2000 RoC listing and continuing to the present, is their lack of quantitative data on DEP exposure for any significant time period for which attempts have been made to test for an association between DEP exposure and increased cancer hazard. As a result, it is my professional opinion that the current epidemiological evidence remains as it did at the time of the earlier NTP (2000) evaluation and the earlier IARC (1989) review – "limited evidence for the carcinogenicity in humans of diesel engine exhaust". The words "Diesel Exhaust Particulates" could be substituted for "diesel engine exhaust" in the IARC review and the conclusions would be the same.

In my professional judgment, the present epidemiological literature on the cancer hazard potential of DEP in Traditional Diesel Exhaust is still characterized as limited evidence of human carcinogenicity.

(4) The situation with regard to interpretation of the animal evidence for diesel exhaust and, specifically, DEP to cause cancer in laboratory animals changed remarkably in the late 1980s and 1990s. The early evidence, including key studies such as those of Mauderly et al. (1987, 1995) conclusively showed that long-term (up to 30 month exposures in contrast to the typical NTP cancer bioassay of 24 months) to high concentrations of DEP (normalized to continuous exposures of over 100,000 $\mu g\text{-}hr/m^3$) resulted in an excess of lung cancer in rats, but not in mice or Syrian hamsters. Companion papers by Wolff et al. (1987, 1989) demonstrated impaired clearance and an overloading of the lungs with particulate matter at the high concentrations compared to low concentrations. Later, studies with pure Carbon Black (devoid of associated hydrocarbons) and Titanium Dioxide gave remarkably similar results – excess lung cancer with chronic, high concentration exposures. It is now well known that the "overload" mechanism of lung cancer induction is a species-specific effort for relatively insoluble particles (Wolff et al. 1987, 1989; Mauderly 2000; Heinrich et al. 1995; Oberdorster 2002; McClellan 1996; Mauderly and McCunney 1996; Hesterberg et al. 2005). Thus, the findings in the rat cancer bioassays with DEP are not relevant to evaluating human cancer hazards of DEP. It is my professional opinion that today it would be appropriate to view the rat cancer bioassay results as providing – "insufficient evidence of carcinogenicity" for evaluating human cancer hazard, a conclusion that represents a reduced weight of evidence relative to my judgment in 1998.

(5) Based on the points made above, it is my professional opinion that DEP from engines using high sulfur fuel and operating without exhaust after-treatment systems should continue to be classified as "reasonably anticipated to be a human carcinogen" as in the 9th RoC (RoC, 2000). I view this as a highly precautionary cancer hazard classification in view of the substantial uncertainties associated with the epidemiological evidence (especially, the continuing difficulties in characterizing exposure of workers to DEP) and the lack of human relevance of the results of the rat cancer bioassays.

(6) Extensive research on diesel engines, fuels and exhaust treatment in the late 1990s and early 2000s, in response to very stringent particulate matter emission standards, has led to revolutionary advances in diesel technology. These advances were introduced in engines marketed in the USA beginning in 2007. The key inter-related advances were (a) use of ultra-low sulfur fuel (<15 ppm), and (b) use of oxidation catalysts in company with wall flow diesel exhaust particulate filters. Hesterberg et al. (2005) coined the term, "New Technology Diesel Exhaust" (NTDE) to describe the exhaust from these integrated systems. The characteristics of NTDE are extraordinarily low concentrations of regulated and unregulated chemicals and essentially zero content of the DEP that was viewed as the putative hazardous material in traditional diesel exhaust particulates as evaluated in the 9th RoC (2000). Recall Figure 1. The extraordinarily low concentrations of mass identified as particles in NTDE contains only trace amounts of elemental carbon that predominated in DEP and, instead, contains trace concentrations of sulfates, nitrates, and other chemicals. The characteristics of NTDE compared to TDE have been reported by Khalek et al. (2011) and Liu and co-workers (2007, 2008a, 2008b, 2009a, 2009b, 2010) and reviewed by Hesterberg et al. (2011, 2012) and McClellan et al. (2012).

To illustrate the profound change, consider first engine out emissions from a traditional diesel engine using high sulfur fuel as studied by Mauderly and associates in the 1980s. That exhaust contained about 70,000 μg of DEP/m^3. Exposure to that exhaust at a 10 to 1 dilution (about 7,000 $\mu g/m^3$, 7 hr/day/5day/week) produced lung cancer in rats (Mauderly et al. 1987) and did not produce lung cancer in mice (Mauderly et al. 1995). A Advanced Collaborative Emissions Studies (ACES) in rats now being conducted at the Lovelace Respiratory Research Institute (Mauderly, 2010; Mauderly and McDonald, 2012) with Health Effects Institute sponsorship. In that study, the engine out emissions after passing through the exhaust after-treatment system contains about 400 $\mu g/m^3$ of particle mass.

Preliminary findings from the ACES rat study were presented orally to the California Air Resources Board on February 28, 2012 (McDonald, 2012). He reported exposure of rats for 12 months (16 hr/day, 5 days/week) to the lowest dilution, 40 to 1, yielded a particulate matter concentration at the chamber inlet of 9 $\mu g/m^3$ and a NO_2 concentration of 4.2 ppm (other key constituents were NO-5.8 ppm, NO_x-9.9 ppm, CO-6.8 ppm, Total Hydrocarbons-0.5 ppm and SO_2-23.9 ppm). He reported that the exposure produced "minimal inflammatory tissue remodeling and respiratory function changes in rats." The mild histopathological changes were expected based on an earlier study by Mauderly et al. (1989) of the effects of exposure to NO_2 alone (9.5 ppm NO_2, 7 hr/day, 5 days/week). NO_2 is a well-known oxidant gas. The Mauderly et al. exposures were to 17,290 ppm-hr over 12 months and the McDonald ACES exposures were to 17,472 ppm-hours of NO_2 over 12 months. The results of the Mauderly et al. (1989) study of NO_2 were used to select the "Maximum Tolerated Dose" of NO_2 and, thus, determined the maximum concentrations of the other exhaust constituents at the lowest dilutions for the ACES rat study.

McDonald et al. (2012) indicated the ACES study in rats is to be continued until the rats reach 30 months of age in November and December of 2012. The results of the ACES study will be valuable in assessing any potential health hazards of NTDE. However, in anticipating the results of that study it is important to recognize that it is essentially a study of high concentrations of NO_2 and traces of other chemicals and without DEP. It is NOT a study of Diesel Exhaust Particulates as shown in Figure 1, the diesel exhaust particulates that were the subject of the previous RoC cancer hazard classification (RoC, 2000).

(7) In any future review by NTP of DEP, it will be important to separately evaluate (a) DEP from traditional diesel engines using high sulfur content fuel (>500 ppm) and operating without oxidation catalysts and wall flow diesel particulate traps versus (b) exhaust from the New Technology Diesel engines using ultra-low sulfur fuel (<15 ppm) and using oxidation catalyst, wall flow diesel exhaust particulate traps in the exhaust stream.

It will be important for any future RoC listing of Diesel Exhaust Particulates to explicitly define what diesel technology (engine, fuel and exhaust after-treatment) that the cancer hazard listing applies to and, which it does not apply, so as to recognize the revolution in technology that has occurred and its associated public health benefits. It is no longer scientifically valid to develop broad cancer hazard classifications for diesel exhaust, or even, diesel exhaust particulates that treats all diesel exhaust as though it were the same.

(8) It is important to recognize important differences between the carcinogenic hazard classification schemes used by IARC and that used by the NTP in developing listings for the RoC. The IARC scheme includes five groups; 1 – a human carcinogen, 2A – a probable human carcinogen, 2B – a possible human carcinogen, 3 – not classifiable as to human carcinogenicity, and 4 – not likely to pose a carcinogenic hazard to humans. It is remarkable that only one chemical, caprolactam, has been placed in Group 4. I suspect this reflects the inherent precautionary attitude of scientific review groups. I call attention to Group 3 – not classifiable as to human carcinogenicity. That is the classification I and my colleagues have recommended IARC use for NTDE when it conducts its review of diesel exhaust in June 2012 (McClellan et al. 2012).

In contrast, the NTP scheme only has provision for the listing of agents as "Human Carcinogens" or "Reasonable Anticipated to be Human Carcinogens." For a previously listed agent, the potential exists for delisting. For new agents, a decision can be made to not list. This scheme is not very helpful in informing the public as to agents that do not pose a cancer hazard. This is not a particularly serious dilemma for specific chemicals. A specific chemical, such as benzene or caprolactam, will have the same physical and chemical properties over time – they never change. In contrast, evidence as to the biological and hazardous properties of a chemical may change as new scientific methods are brought to bear in studying the chemical. The situation is quite different for an agent, such as exhaust, produced by a changing technology. Indeed, as described above, diesel engines, fuels and after-treatment systems evolved over nearly a century and, then more recently, revolutionary changes occurred in response to stringent regulations and a desire on the part of the producers and marketers of diesel engines to provide Society with inherently safer products (McClellan et al. 2012).

The NTP/RoC classification scheme needs to be able to recognize these technological improvements and convey their reduced hazard potential to the public. Based on the physical and chemical characteristics of NTDE, it is anticipated that it will be demonstrated to not have carcinogenic hazard potential. Of course, that is what is being tested now in the ACES study.

(9) *Based on the current approach used by the NTP in preparing the RoC, I recommend that the current listing for "diesel exhaust particulates" be re-evaluated and modified so it is very clear as to the specific characteristics of the agent being listed and its sources and what characteristics and sources are excluded from the listing.*

(10) *It will be appropriate for the NTP to review NTDE and make a determination as to its being listed or not listed in the RoC after the current long-term ACES study of NTDE is completed and reported in the peer-reviewed literature. A listing/no-listing determination will have to be made exclusively based on an understanding of the physical and chemical properties of NTDE and the results of the animal bioassays. Because this is a new technology, epidemiological findings are not available now nor will they be in the near future. Indeed, in view of the ultra-clean nature of NTDE and its lack of any unique physical and chemical characteristics it is quite possible that it will never be feasible to conduct epidemiological studies of NTDE. It is important to also recognize that the differences in concentration of key constituents and the composition of the particulate material found in traditional diesel exhaust (TDE) and new technology diesel exhaust (NTDE) are so profound that it cannot be assumed that findings from TDE have scientific relevance to the evaluation of NTDE.*

I request that I be informed of further actions of the NTP on reviewing the listing for "diesel exhaust particulates." I look forward to participating in the public review of any materials the NTP develops. If I may be of assistance in any way, please feel free to contact me.

Sincerely,

[Redacted]

Roger O. McClellan

Attachments:
References
Biography
Declaration of Interest

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BIOGRAPHY

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ROGER O. McCLELLAN is currently an advisor to public and private organizations on issues concerned with human health risk analysis and inhalation toxicology focusing on issues of air quality in the ambient environment and work place.

He is President Emeritus of the Chemical Industry Institute of Toxicology, having served as Chief Executive Officer and President of the Institute from September 1988 through July 1999. The Institute has a mission of creating an improved knowledge base for understanding and assessing the adverse effects of exposure to chemicals. During his tenure, the organization achieved international recognition for the development of science undergirding important environmental and occupational health 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. He began his career with Lovelace in 1966. 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 toxic effects of airborne radioactive materials and chemicals. The Institute continues operation today as a core element of the Lovelace Respiratory Research Institute. 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). He received his Doctor of Veterinary Medicine degree from Washington State University in 1960 and a Master of Management Science degree from the University of New Mexico in 1980.

Dr. McClellan has served in an advisory role to numerous public and private organizations. He has served on numerous U.S. Environmental Protection Agency advisory committees including past Chairman of the Clean Air Scientific Advisory Committee (CASAC), *Ad Hoc* Committee to Review Criteria Document for Airborne Lead, Environmental Health Committee, Research Strategies Advisory Committee, CASAC Panels for all the Criteria Pollutants, and Member of the Executive Committee, Science Advisory Board, U. S. Environmental Protection Agency. In addition, he was a Member (1971-2001) and Distinguished Emeritus Member (2002-present), National Council on Radiation Protection and Measurements; Member, Advisory Council for Center for Risk Management, Resources for the Future; Member, Health Research Committee, Health Effects Institute; and service on numerous National Academy of Sciences/National Research Council Committees, including Committees on Toxicology (Past Chairman), 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.

Dr. McClellan serves or has served as Adjunct Professor at Duke University, University of North Carolina at Chapel Hill, North Carolina State University, University of New Mexico, University of California-Los Angeles, University of Arkansas, Colorado State University, and Washington State University. In addition, he frequently speaks on risk assessment and air pollution issues at other institutions and meetings 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 as Editor of CRC Critical Reviews in Toxicology. 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, the Society for Risk Analysis, the Health Physics Society, and the American Association for Aerosol Research.

Dr. McClellan's contributions have been recognized by receipt of a number of honors, including election in 1990 to membership in the Institute of Medicine of the National Academy of Sciences. He is a Fellow of the American Association for the Advancement of Science. In 1998, he received the International Aerosol Fellow Award from the International Aerosol Research Assembly for his contributions to aerosol science and technology. He received the Society of Toxicology 2005 Merit Award for a distinguished career in toxicology. In 2005, The Ohio State University awarded him an Honorary Doctor of Science degree for his contributions to the science under-girding improved air quality. He has a long-standing interest in environmental and occupational health issues, especially those involving risk assessment and air pollution, and in the management of multidisciplinary research organizations. He is a strong advocate of risk-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 the health of workers and the public.

Declaration of Interest Statement

Roger O. McClellan has had a long-standing interest in the potential health hazards of Diesel Engine Exhaust and the development of ultra-clean diesel technology. He has served on numerous advisory committees to the U.S. EPA and other government and private organizations on air quality issues. He was first alerted to issues concerning the potential health effects of diesel exhaust emissions from traditional diesel technology while serving on an EPA Advisory Committee in the 1970s. In the late 1970s, he was responsible for providing leadership for initiating the Lovelace organization's pioneering studies of diesel exhaust. From that time to the present time, he has served in an advisory role to the Health Effects Institute, the Engine Manufacturers Association and private firms concerned with diesel technology and its potential health impact. In addition, he has served in an Advisory Role to the U.S. Environmental Protection Agency on setting of air quality standards, including service as Chair of the U.S. Environmental Protection Agency Clean Air Scientific Advisory Committee (CASAC), service on CASAC Panels for the revision of National Ambient Air Quality Standards for all the criteria pollutants and served on the CASAC Sub-Committee that reviewed EPA's Health Assessment Document on Diesel Exhaust. He served as a member of the Working Group that prepared the IARC (1989) Monograph on Diesel and Gasoline Exhaust and Some Nitroarenes. He provided comments to the NTP on its 2000 listing of Diesel Exhaust Particulates.

The analyses, interpretations and recommendations in this letter are solely those of Roger O. McClellan. They do not necessarily reflect the views of any public or private sector clients.