UNITED STATES OF AMERICA
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Request for Public Comment on Nominations and Call for Additional Nominations to the Report on Carcinogens	))))	Federal Register Notice (77 FR 2728)

COMMENTS OF THE TRUCK AND ENGINE MANUFACTURERS ASSOCIATION

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1. Introduction

The Truck and Engine Manufacturers Association ("EMA") hereby submits its comments regarding the proposed nomination of "diesel exhaust particulates" for possible review and evaluation in a future edition of the Report on Carcinogens ("RoC"), which nomination was announced in the request for comments that the Division of the National Toxicology Program ("NTP") caused to be published in the Federal Register on January 19, 2012 (77 FR 2728).

EMA is the trade association that represents the world's leading manufacturers of internal combustion engines and heavy-duty motor vehicles, including diesel-fueled engines and vehicles. EMA members' products are utilized in on-highway, nonroad, farm and construction, locomotive, marine and stationary applications. EMA represents the interests of its member-companies in federal and state rulemaking procedures, and in connection with standard-setting measures and other actions relating to the control of emissions from diesel-fueled engines and vehicles. EMA also participates in and provides technical expert input for the various reviews and assessments that are conducted to assess the potential health effects of mobile source emissions, including the emission constituents of diesel engine exhaust. Accordingly, EMA has a direct and substantial interest in the pending nomination to include a formal evaluation of "diesel exhaust particulates" in a future edition of the RoC.

The assessment of any complex mixture of substances, such as "diesel exhaust particulates," as opposed to a single chemical, is an inherently challenging exercise, because unlike a single chemical, the nature and composition of a complex mixture can change over time as the processes that result in the production of the mixture are refined and improved. That is precisely the case with "diesel exhaust particulates." Over the past several decades, and in response to, among other things, increasingly stringent particulate matter ("PM") emission standards, the nature and sophistication of diesel engine technologies, aftertreatment systems and fuels have progressively evolved. The net result, as explained below, is that what "diesel exhaust particulates" may have been assumed to be before the advent of technology-forcing emission-control regulations (i.e., prior to the mid-1980s) is not what "diesel exhaust particulates" are today.

The NTP first listed "diesel exhaust particulate" (hereinafter "DEP") as "reasonably anticipated to be a human carcinogen" in 2000. That listing was based on "limited evidence of

carcinogenicity from studies in humans and supporting evidence from studies in experimental animals and mechanistic studies."

As detailed below, since 2000, there have been numerous advances in the understanding of the available epidemiologic and toxicological data pertaining to DEP, which advancements call into greater question whether DEP could be "reasonably anticipated" to be a human carcinogen, and, at a minimum, preclude any elevation of the risk characterization ascribed to DEP. In addition, there also have been numerous paradigm-shifting developments in diesel engine systems, technologies and fuels, and in emission-control regulations, that have impacted the nature and composition of DEP in fundamental ways. Consequently, any evaluation of DEP that NTP might undertake will also need to account for the dramatic changes that have occurred with respect to the nature and composition of diesel exhaust particulates over the past several decades.

2. Executive Summary

A. There is Insufficient Evidence to Alter the Hazard Classification for Diesel Exhaust Particulate

The currently available laboratory and epidemiological data does not provide a convincing argument for a causal relationship between exposure to DEP and an increased incidence of lung cancer. The data from laboratory studies of DEP, both *in vivo* and *in vitro*, have only limited relevance in assessing the carcinogenic potential of DEP in humans. Laboratory rats exposed to very high levels of DEP (>2200 $\mu g/m^3$) developed an excess of lung tumors; however, the tumor incidence was consistent with that observed in rats exposed to the same overload levels of other types of fine particles (*e.g.*, TiO_2, talc, and carbon black). Other species (mice and hamsters) exposed at similar, high DEP levels did not show an excess of lung tumors, nor did rats exposed at lower DEP levels. In rats, high exposures to a variety of different particulates (DEP as well as inert TiO_2, talc, and carbon black) resulted in lung overload, lung inflammation, cell proliferation, and eventually tumors. This mechanism is not specific to DEP and did not occur in the rats at DEP exposure concentrations below 2000 $\mu g/m^3$, a concentration level that is 100-fold greater than DEP levels to which railroad and trucking industry workers might be exposed. Thus, the effect of high levels of DEP in rats is now considered to be a nonspecific particle effect that resulted from a species-specific overload mechanism. Such a mechanism has little or no relevance to humans exposed either to low levels in occupational environments or to even lower ambient levels.

Furthermore, mutagenicity studies in which cultures of mammalian or bacterial cells were exposed to organic solvent extracts of DEP are of limited utility for understanding the potential carcinogenicity of whole DEP. Whole DEP itself has not been found to be mutagenic in most studies. The mutagens extractable from DEP dissolve either minimally or not at all in aqueous based fluids, such as body fluids or cell culture medium. Thus, the adsorbed mutagens are generally not considered to be bioavailable, which could explain why most studies have not shown DEP to be a direct-acting mutagen.

Epidemiologic studies of the transportation industry (primarily trucking and railroad workers) generally show a weak association with a low elevation in lung cancer incidence (RRs

generally below 1.5), but dose-response for DEP exposure is lacking, and the studies are limited by minimal or inadequate latency periods, a lack of quantitative concurrent exposure data, and inadequate or lack of controls for tobacco smoking. Furthermore, there were similar elevations in lung cancer incidence in truck drivers prior to dieselization. These findings suggest that lifestyle or an unidentified occupational agent other than DEP might be responsible for the low elevations in relative risk reported in the transportation studies. In contrast to the transportation industries studies, epidemiologic studies of underground miners, many of whom are exposed to perhaps the highest known human DPM exposures, are generally negative for lung cancer.

All of the foregoing scientific studies and findings demonstrate that there is no sufficient basis to amend or increase the current hazard assessment that NTP has ascribed to DEP. Accordingly, NTP should retain the current classification for DEP in any future Report on Carcinogens.

B. Any Reassessment of DEP Will Need to Account Separately for New-Technology Diesel Engines

NTP's reassessment of DEP also will need to account separately and distinctly for the emissions from current advanced technology diesel engines -- or, as some have termed it "new-technology diesel exhaust" ("NTDE"). In that regard, NTP's 2000 evaluation of DEP was premised on a number of key findings and assumptions regarding the nature and composition of DEP. More recent scientific data and observations have demonstrated that those foundational premises (while still insufficient to alter the listing for DEP) simply do not apply to NTDE.

NTDE does not contain high rates of PM. NTDE is not dominated by elemental carbon and a solid carbon core. NTDE does not contain significant amounts of TACs and HAPs. NTDE does not contain higher levels of smaller particles. NTDE does not contain significant amounts of semi-volatile organic compounds, and does not contain significant amounts of unregulated pollutants of concern. And, NTDE is not a unique carrier of genotoxic components. In addition, DEP levels have been reduced approximately 100-fold in NTDE, and similarly large reductions have also been achieved for numerous other emission species, including PAHs and nitro-PAHs. Thus, there is now a critical mass of data relating to the nature and composition of NTDE, and supporting the idea that any future DEP hazard assessment should evaluate NTDE separately.

There are currently few health effects data of relevance to the carcinogenic potential of chronic exposures to NTDE, although a chronic inhalation rat bioassay for NTDE (the "Advanced Collaborative Emissions Study") is currently in progress. There are no epidemiologic studies of direct relevance to NTDE and there may not be any for many years, not because populations have not been exposed to NTDE, but because historical exposures are entirely for TDE and current exposures continue to be a mixture of TDE and NTDE. Nonetheless, there is now available an abundance of emissions characterization data, as well as preliminary toxicological data, relating to NTDE. Those data demonstrate major reductions in numerous regulated and unregulated DE constituents in NTDE, chemical and physical changes to the particles in DEP, and the elimination of some previously postulated biological responses. Taken together, those data are clearly not sufficient to support a cancer risk classification for

NTDE, and they also provide scientific justification for the independent evaluation of NTDE hazards.

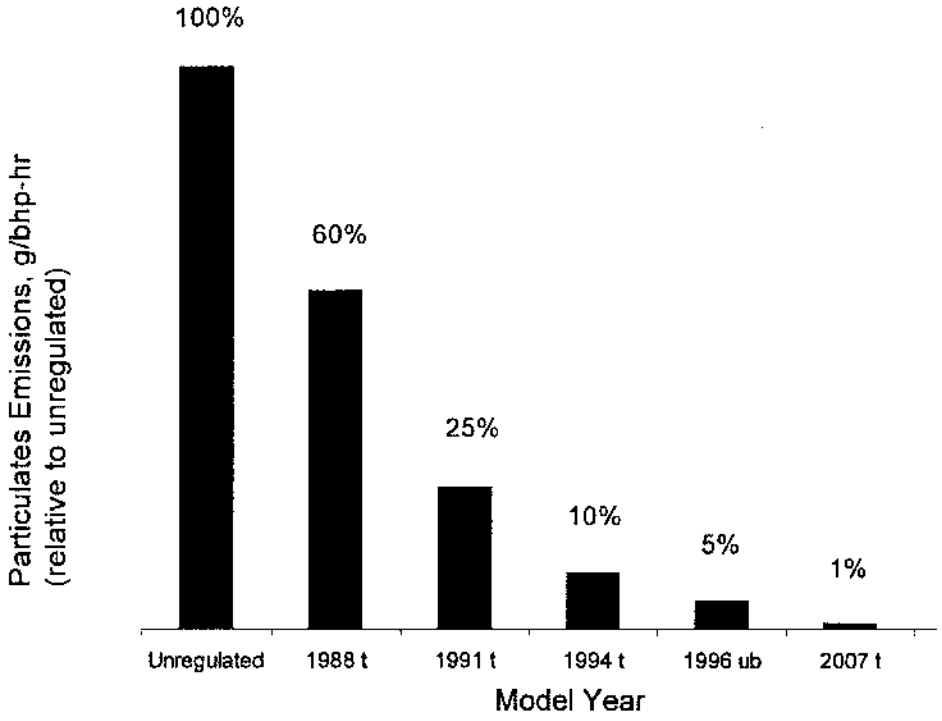
3. Regulatory Overview

For the past 20-plus years, particulate matter and oxides of nitrogen have been the two diesel engine emissions of greatest regulatory interest. Oxides of nitrogen ("NOx") warrant control because they can contribute to the formation of ambient levels of ozone and secondary particulates. Like most gaseous emissions, NOx consist of a readily identified compound, and a clearly described molecular structure. Thus, the measurement and quantification of NOx emissions have been relatively straight-forward.

Directly emitted particulate matter ("PM") emissions from diesel-fueled engines are a more complex substance due to their varied chemical composition and size distribution, which can range from a few nanometers (10^{-9} meters) to a few microns (10^{-6} meters) in diameter. The chemical composition of diesel PM usually, but not always, can depend on size, thus making it difficult to establish uniform test procedures and methods for determining PM measurements, control metrics, and potential health effects.

In light of this, and prior to 1988, regulators and regulations sought to limit PM emissions by requiring reductions in the visible smoke emissions from diesel-fueled engines. Lower visible smoke generally resulted in lower particle mass emissions, but particle mass measurement was (and is) considerably more complex than simply measuring visible smoke.

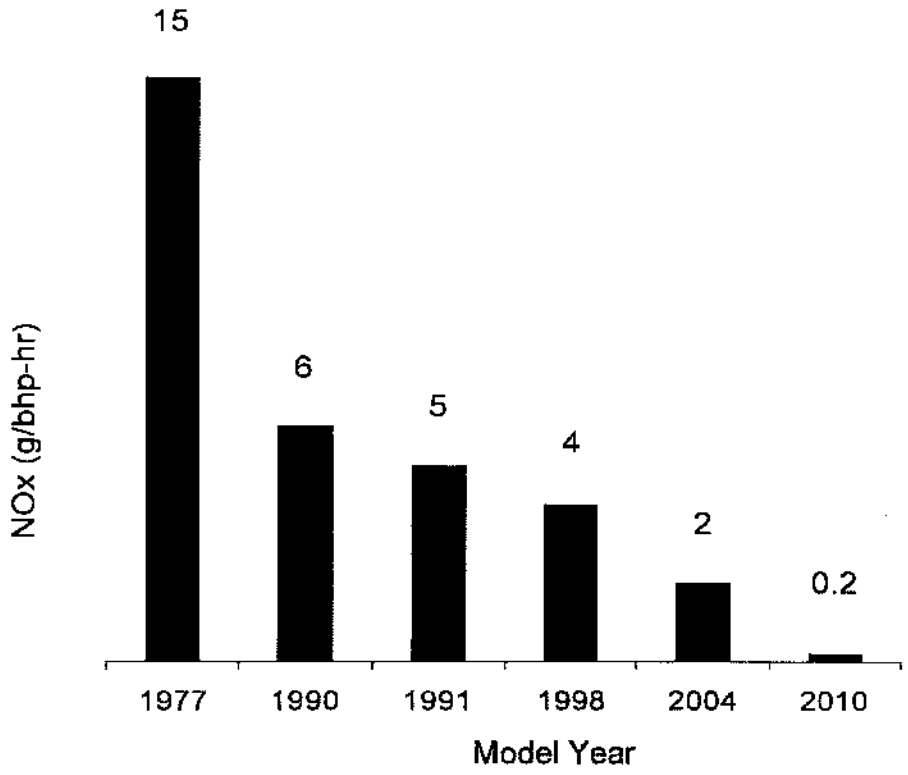
Beginning with the 1988 model year for heavy-duty on-highway ("HDOH") diesel-fueled engines and vehicles (and subsequently for diesel-fueled nonroad engines and vehicles), the U.S. EPA established an official method for PM mass measurement. Because there was no established PM measurement method before then, PM mass emissions from pre-1988 model year HDOH engines are frequently referred to as being "unregulated." Starting in 1988, a series of increasingly stringent PM mass emission regulations have come into effect, as depicted in the figure below. For comparison purposes, pre-1988 "unregulated" engines are ascribed a relative PM emission level of 100%. With reference to that "unregulated" baseline, 1988 model year HDOH engines were required to produce no more than 60% of the pre-1988 PM mass levels. Follow-on regulations have required diesel PM mass emissions of 25% in 1991; 10% in 1994; (5% for urban buses in 1996); and 1% in 2007. Each of those percent values is related to a reduced PM mass emission level starting with 1988, of 0.6, 0.25, 0.10, 0.05 and 0.01 g/bhp-hr, respectively. Similar reductions also have been achieved with respect to the PM emissions from stationary and nonroad diesel-fueled engines, including marine and locomotive engines, albeit over a slightly longer phase-in period (e.g., the nonroad "Tier 4" ultra-low PM emission limits for engines rated between 130 – 560kW began in 2011).



U.S. EPA standards for particulate emissions from heavy-duty diesel trucks (t) or urban buses (ub), calculated as grams per brake-horsepower hour (g/bhp-hr) and adjusted relative to pre-1988 "unregulated" engine emissions. (U.S. EPA Health Assessment Document for Diesel Engine Exhaust, May 2002, Table 1:4, p. 2-16.)

With the exception of the 2007 PM standard, which required the use of exhaust aftertreatment systems, PM mass reductions since 1988 have been achieved through enhanced fuel delivery control, increased injection pressure, injection rate-shaping, improved combustion chamber design, air-delivery improvements (including higher pressure turbocharging and charge-air cooling), and fuel quality improvements (mainly dramatic reductions in the sulfur and aromatic content of diesel fuel). Each of those engine enhancements has gone through several generations of improvements as diesel technologies have continued to advance.

NOx emission control regulations began in 1977 with a 15 g/bhp-hr limit for HDDH diesel-fueled engines. As depicted in the chart below, EPA and CARB have implemented increasingly stringent NOx standards of 6, 5, 4 and 2 g/bhp-hr for the respective model years 1990, 1991, 1998 and 2004. The most recent HDDH NOx emission limit -- 0.2 g/bhp-hr for the 2010 model year -- requires advanced exhaust aftertreatment systems. As with PM, similar reductions have been achieved with respect to the NOx emissions from stationary and nonroad diesel-fueled engines, including marine and locomotive engines, although over a slightly longer phase-in period.



U.S. EPA standards for NOx emissions from heavy-duty on-highway diesel engines, calculated as grams per brake horsepower-hour (g/bhp-hr). (U.S. EPA Health Assessment Document for Diesel Engine Exhaust, May 2002, Table 2:4, p. 2-16.)

Like the reductions achieved for PM emissions, NOx emission reductions have been achieved through fuel injection timing control, improved turbocharging, intake air temperature control, combustion chamber design, exhaust gas recirculation, and aftertreatment. Each of those technologies also has gone through several generations of improvement as diesel engine technologies and capabilities have advanced.

4. Regulatory Developments Since 2000

Significantly, since the time of NTP's evaluation of DEP in 2000, there have been a comprehensive series of ground-breaking emission control regulations that have led to dramatic advancements in diesel engine technologies. Included among the several technology-forcing regulations that have come into effect in the U.S. and Europe since 2000 are the following:

(i) diesel fuel sulfur levels for most applications have been reduced from 500 ppm to less than 15 ppm;

(ii) HDDOH diesel engine PM emission standards have been reduced by 90%, from 0.10 g/bhp-hr to 0.01 g/bhp-hr (see chart supra);

(iii) HDDOH diesel engine NOx emission standards have been reduced by more than 90%, from 4.0 g/bhp-hr to 0.20 g/bhp-hr (see chart supra);

(iv) nonroad (including marine and locomotive) diesel engine PM emission standards have been reduced by more than 90%, from 0.54 g/kW-hr to 0.02 (0.03) g/kW-hr;

(v) nonroad (including marine and locomotive) diesel engine NOx emission standards have been reduced by more than 90%, from approximately 9.2 g/kW-hr (or higher) to 0.40 g/kW-hr; and

(vi) for stationary diesel engines, new source performance standards have been established that are equivalent to the emission standards for new nonroad diesel engines.

All of these regulations, taken together, have resulted in fundamental changes and advancements in the design, performance, sophistication and efficiency of diesel engine systems and the fuels upon which they operate. This, in turn, has yielded fundamental changes and advancements in the control and composition of diesel engine exhaust, including DEP, since the time of NTP's publication of the Ninth Report on Carcinogens in 2000.

5. Diesel Technology Developments Since 2000

The comprehensive regulatory programs enacted to reduce diesel emissions to near-zero levels have resulted in a major paradigm shift in diesel engine emission control technologies. Diesel emission control strategies have moved from the earlier engine-based designs and specific hardware improvements to fully integrated designs and systems -- systems that encompass improved diesel fuels, diesel engine components, and catalyzed exhaust aftertreatment systems. This fully integrated approach has enabled order-of-magnitude (or greater) emission reductions and, in many cases, the virtual elimination of the emission compounds that were of potential concern.

Among the myriad technological advancements that have been developed over the past two decades through the integrated approach to reduce diesel emissions are the following:

(i) diesel engine control systems are now fully electronic and computerized, not mechanical, which allows for very precise, second-by-second management of the fuel injection and combustion processes;

(ii) fuel-injection pressures and fuel atomization have increased dramatically through the introduction of high-pressure fuel-injection systems and turbochargers, which promote more complete and clean combustion;

(iii) diesel exhaust cooling systems have advanced to control NOx emissions through sophisticated fuel-injection timing and rate-shaping, exhaust gas management, and enhanced charge-air cooling systems;

(iv) diesel oxidation catalysts have advanced to the point where they can allow for the virtual elimination of hydrocarbons and other organic emission species under a broad range of operating conditions;

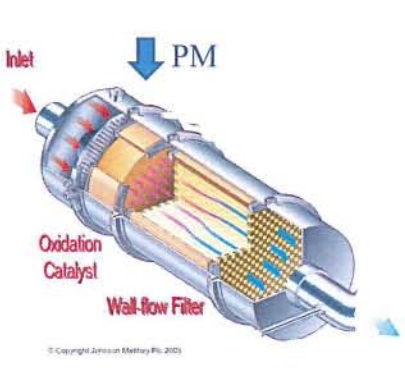
(v) filters or coalescers have been installed in crankcase ventilation systems to reduce significantly the particulate matter emissions from crankcase gases; and

(vi) the introduction of ultra-low sulfur diesel ("ULSD") fuels has allowed for the deployment of wall-flow diesel particulate filters ("DPFs"), which have fundamentally changed the composition of diesel particulates while reducing their emissions to near-zero levels.

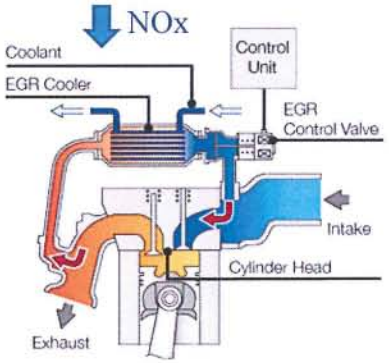
The foregoing new-technology diesel engine system components have resulted in what has been referred to as "new-technology diesel exhaust" (hereinafter, "NTDE"), which is quantitatively and qualitatively different from the "unregulated" traditional diesel exhaust (hereinafter, "TDE") (Hesterberg, *et al.*, 2011.) Schematic depictions of current new-technology diesel engine systems are set forth below. In light of the advent and deployment of these new-technology diesel engine systems, and as detailed in these comments, NTP's anticipated reevaluation of DEP will need to include a separate and distinct assessment of NTDE.

NTDE Exhaust Treatment Systems

—Particle Removal and NOx Elimination Using EGR —



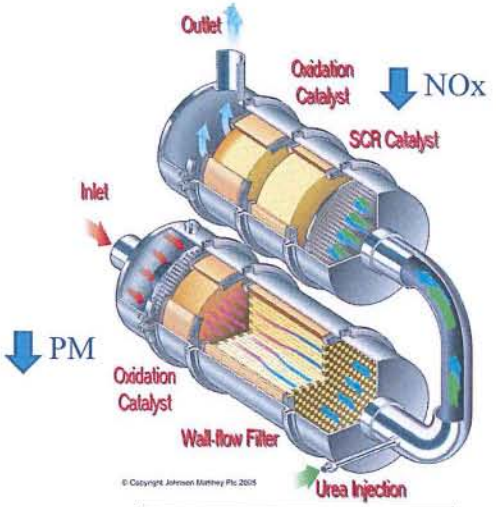
DOC+DPF



Exhaust Gas Recirculation (EGR)

NTDE Exhaust Treatment Systems

—Particle Removal and NOx Elimination Using SCR-Urea—



DOC+DPF+SCR

6. Assessment of the Possible Carcinogenicity of DEP[1]

Before addressing the issues and differences that will necessarily impact any assessment of NTDE, it is equally important to catalogue the growing uncertainties that pertain to, and preclude, any elevated finding regarding the carcinogenic potential of DEP. Over the years, a number of authors as well as some regulatory agencies have concluded that the weight of the evidence supports a role for DEP in the risk of lung cancer. (Wichmann, 2006; U.S. EPA, 2002; Lloyd and Cackette, 2001; IARC, 1989.) However, other assessments of the DEP epidemiologic database have concluded that the existing epidemiological studies are unable to predict potential human health effects from exposure to DEP, or to link DEP to increases in lung cancer. (Muscat and Wynder, 1995, Stöber and Abel, 1996; Cox, 1997; Morgan, *et al.*, 1997; Bunn, *et al.*, 2004.)

As noted above, NTP first listed DEP as "reasonably anticipated to be a human carcinogen" in 2000. The NTP listing was based on "limited evidence of carcinogenicity from studies in humans and supporting evidence from studies in experimental animals and mechanistic studies."

The finding of *limited evidence* from the human studies for the carcinogenicity of TDE rested primarily on the epidemiological studies of railroad workers, especially those reported by Garshick, *et al.* (1987, 1988), in part because those studies had *some* quantitative exposure data available from which attempts were made to estimate historical worker exposures. (Woskie, *et*

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[1] This portion of EMA's comments is based primarily on the peer-reviewed article authored by Hesterberg, *et al.*, "A Critical Assessment of Studies on the Carcinogenic Potential of Diesel Exhaust," *Crit. Rev. in Toxicology*, 36:727-776 (2006).

al., 1988a, 1988b.) Nonetheless, there were no direct data for the workers' TDE exposures. Rather, the historical exposures were either assumed based on job title or were estimated from more recent exposure assessments.

The finding of *supporting evidence* from the animal studies was based primarily on studies in which rats (but not mice or hamsters) developed tumors after lifetime inhalation of very high concentrations of DEP (greater than 2200 $\mu g/m^3$ of DEP). At the time of the NTP review, strong evidence had not yet been fully developed regarding the role of a rat-specific lung clearance "overload" mechanism in the association between high exposure rates to DEP and lung cancer in the rat, and, as a result, this now-established finding could not have been fully considered by NTP.

C. Laboratory Studies

(i) Animal Inhalation Bioassays

Compelling arguments have been made that the only relevant animal studies for the assessment of human risk from airborne respirable particulates such as DEP are those studies in which exposure was by inhalation. (CRARM, 1997; CASAC, 2000; ILSI, 2000; Mauderly, *et al.*, 2000; Hesterberg, *et al.*, 2005.)

Effects of inhalation of DEP in laboratory animals have been reviewed in detail. (*See* Hesterberg, *et al.*, 2005.) Of the various animal species chronically exposed to DEP by inhalation (rats, hamsters, mice, monkeys, and cats), only rats consistently developed lung tumors and only following inhalation exposure to very high levels of DEP (greater than 2000 $\mu g/m^3$ DEP) -- levels significantly higher than human occupational exposures (mean human exposures measured as elemental carbon (EC) typically range from 1.4 $\mu g/m^3$ for ambient exposures to exposure levels of 460 $\mu g/m^3$ in certain underground mines). Rats did not develop elevated tumor incidences after being exposed to lower DEP levels that were more comparable to occupational and environmental exposure levels in humans. Importantly, exposures of rats to high levels of other inert particles, including TiO_2, talc, and carbon black, also resulted in lung overload, inflammation, and eventually lung tumors.

Numerous analyses point to a lack of relevance of the data from lung-overloaded rats for risk calculations in humans exposed at environmental or ambient levels of TDE or DEP (*see, e.g.*, HEI, 1999; U.S. EPA, 2002; Greim, *et al.*, 2001; ILSI, 2000). At realistic human levels of exposure to TDE or DEP, no lung cancer hazard is anticipated based on the rat data. (ILSI, 2000.) Accordingly, the general consensus today is that the tumorigenic effects observed in the high-DEP-dose rat studies were primarily due to a rat-specific lung clearance overload mechanism that is not applicable to humans. (Heinrich, *et al.*, 1986; Lewis, *et al.*, 1986; Stöber, 1986; Heinrich, *et al.*, 1989, 1995; Mauderly, *et al.*, 1996; McClellan, *et al.*, 1996; Mauderly, *et al.*, 2000.)

Moreover, a review of responses to inhaled DEP at the cellular level in the rat lung suggests that the mechanistic series of steps related to tumorigenesis in rats is not likely to be relevant to humans. (Watson and Valberg, 1996.) Instead, the unique sensitivity of the rat to particle-induced tumorigenesis relates to a rat-specific exaggerated influx of leukocytes, which

produce oxygen free radicals that lead to oxidative damage. The free radicals stimulate epithelial cell proliferation and contribute to DNA damage. In the rat, DNA repair mechanisms are apparently unable to keep up with the chronic damage to the genome. Accordingly, "even though differences in dosimetry may contribute some to species differences in response, the available evidence indicates that species-specific (i.e., rat-specific) reactions dominate." *(Id.)*

In 1996, Valberg and Crouch combined tumor data from eight chronic inhalation studies in rats. (Valberg and Crouch, 1999.) Exposure-response analysis of the rat data showed no tumorigenic effect for continuous lifetime exposure concentrations less than 600 $\mu g/m^3$ on average. In fact, the maximum likelihood estimate of the cancer slope factor at low DEP concentrations was negative (but not statistically different from zero). This meta-analysis of studies exposing rats to DEP yielded no evidence that DEP exerts a tumorigenic effect at low exposures, even in rats. Thus, the relevant rat data predict that ambient and modest levels of occupational exposures to TDE are consistent with no increases in lung tumor risk.

(ii) Mutagenicity of DEP-Associated Organic Compounds

Organic carbon compounds ("OC") can be extracted and concentrated from diesel PM using very strong, nonaqueous solvents, such as dichloromethane ("DCM"), in combination with agitation, heat, and ultrasonic energy. Among the OC that can be isolated in this matter are several potential mutagens, including polycyclic aromatic hydrocarbons ("PAHs"). Considerable attention has focused on whether the presence of mutagenic OC extractable from diesel PM may be the basis for the lung tumors observed in rats exposed for a lifetime to high levels of DEP.[2]

Levels of lung-cell DNA adducts in laboratory animals following inhalation of DEP or other particles have been used to estimate *in vivo* DNA toxicity. It has been reported (Shirnamé-Moré, 1995) that chronic inhalation of high levels of DEP causes increases in the numbers of DNA adducts in the lung cells of rodents. However, inhalation exposure to high levels of many different types of particles increases the frequency of lung DNA adducts, and the types of adducts formed are not the same as the mutations induced by PAH. This suggests that adduct formation following particle inhalation may be a nonspecific PM response, rather than a specific chemical effect of the PAHs associated with DEP. (Bond, *et al.*, 1990A, 1990b, 1990c); (Randerath, *et al.*, 1995.)

Working with the Health Effects Institute (HEI), Randerath, *et al.* (1995) reviewed the findings of lung cell DNA adducts in rats following inhalation of particles and concluded that "endogenous precursors rather than inhalation of exogenous chemicals gave rise to the observed adducts." HEI concluded that the majority of experiments using whole DEP have shown no *in vitro* mutagenic activity, again suggesting that potentially mutagenic OC adsorbed onto diesel PM are poorly bioavailable. (HEI, 1995.) Further, the fact that lung tumors can be induced in rats exposed by inhalation to >2000 $\mu g/m^3$ ultrafine particles with virtually no adsorbed OC (*e.g.*, TiO_2) supports the conclusion that PM generically, and not the OC bound to DEP, is most likely responsible for the species-specific lung tumors in rats exposed to overloading levels of DEP.

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[2] Reviews of *in vitro* mutagenicity studies of DEP extracts are available elsewhere. (Vostal, 1983; IARC, 1989; Rosenkranz, 1993, 1996; Valberg and Watson, 1999; ACGIH, 2000; Mauderly, 2000.)

(iii) Bioavailability of DEP-Associated Organic Compounds

As already noted, OC adsorbed onto DEP can be extracted efficiently (close to 100%) with very strong organic solvents such as DCM, and those organic-solvent derived extracts have been found to be mutagenic. However, the bioavailability of those OCs in biological fluids in the respiratory tract appears to be very minimal. Studies of ^{14}C-labeled diesel PM incubated in DCM, blood, serum, or saline showed almost 100% OC extraction in DCM, while only 50% in serum, and less than 5% in saline. (King, *et al.*, 1981; McClellan, *et al.*, 1982; Brooks, *et al.*, 1984.) Moreover, in contrast to DCM extracts of DEP, extracts of DEP obtained in serum, lavage fluid, or saline had very low levels of mutagenicity (*i.e.*, comparable to background). (Brooks, *et al.*, 1980.) One hypothesis is that the OC extracted using serum or other biological fluids become inactivated. The potentially low bioavailability of OC adsorbed on the surface of DEP is consistent with the pharmacologic principle that the activity of any drug or compound introduced into the body depends on the solubility of the administered compound in biological fluids. (Vostal, 1983.) When a compound is administered in an insoluble form, the chemical will not reach the target organ, and the response seen for a soluble form cannot be expected to occur.

Most bioavailability studies test the mutagenicity of the fluid phase of organic-solvent or biological-fluid extracts, and not DEP per se. There is less evidence that whole diesel PM (as opposed to solvent extracts of DEP) is mutagenic *in vitro*, indicating that the OCs (and associated PAHs) extracted from DEP are poorly bioavailable in lung fluids. (Randerath, *et al.*, 1995.) In that regard, the bioavailability of PAHs on the surface of DEP was more recently studied by Borm, *et al.* (2005). The Borm, *et al.* results suggest that diesel PM and PAHs are very tightly bound to the particles, and only by using organic solvent extraction and concentration do the PAHs become available at high enough concentrations to form PAH-DNA adducts.

Even, assuming that all of the DCM-extractable mutagenic activity of DEP is bioavailable (which it clearly is not), one can compare DEP-delivered mutagenic activity with that of other sources of mutagens. Specifically, Valberg and Watson used a comparative potency approach to rank the mutagenicity of diesel PM extracts relative to cigarette smoke condensate (CSC). (Valberg and Watson, 1999.) They determined that the quantity of DEP, the extract from which had the same mutagenicity as CSC from one cigarette, ranges from 63 to 181 mg, depending on the source of CSC and the DEP. This suggests that, at ambient urban levels of diesel PM (2 $\mu g/m^3$) and assuming complete bioavailability of the OC associated with diesel PM (an unrealistic assumption), a person would have to breathe DEP in ambient air (20 m^3/day) for up to 12 years to reach the mutagenic level equivalent to CSC from smoking one (1) cigarette. At 5% bioavailability, it would take 80-240 years of ambient DEP inhalation to attain equivalency with one (1) cigarette.

Interestingly, in one of the very few studies of diesel occupations in which a range of diesel PM exposures in a group of 87 railroad workers was compared to mutagenic activity in their urine, no association was found between personal DEP exposure and urinary mutagenicity. (Schenker, *et al.*, 1992.)

The foregoing scientific studies and findings can be summarized, as follows: (1) biological fluids are far less efficient at extracting potentially mutagenic OC from DEP than organic solvents; (2) mutagenic chemicals are tightly adherent to DEP and are not likely to be bioactive *in vivo;* and (3) biologic fluids *(e.g.,* serum, surfactants) may mitigate the mutagenic activity of extracted OC such as PAHs. Thus, the relevant data show that the potential genotoxicity of DEP is unlikely to play a role in any reported increase in relative risk for lung cancer.

(iv) Summary of Laboratory Studies

The apparent mechanism whereby lifetime inhalation of very high concentrations of DEP leads to lung tumors in rats stems from the deposition of high levels of particles in the lungs, which then overloads clearance mechanisms and initiates an inflammatory response to which rats are particularly vulnerable. That species-specific carcinogenic process appears to occur only at very high doses, and appears to be a particle and not a chemical effect. Neither the animal nor the cell culture studies of DEP provide convincing evidence of a mechanism involving a direct exogenous mutagen.

Mutations have been demonstrated in cells that have been directly treated (*in vitro* or *ex vivo* from rodents intratracheally instilled) with OC extracted from diesel PM by strong organic solvents. However, those results are not likely relevant to the DEP tumorigenicity observed in rats, because DEP mutagens are relatively non-bioavailable and low in quantitative activity compared to other sources.

D. Epidemiologic Studies

A major problem in estimating exposure to DEP is that most exposed work areas also include airborne particles from many other combustion sources, including carbon compounds from nondiesel sources (e.g., tobacco smoke, gasoline engine exhaust, other sources of combustion, solvents, pollen, paper, dust, etc.). In particular, the exhausts of engines (both gasoline- and diesel-powered) share similar physical and chemical characteristics with each other and with airborne materials from many other combustion sources. In addition, there is no known marker for distinguishing DEP from other types of carbon-based particles. Thus, it has been difficult, if not impossible, to quantify the portion of an individual's total airborne particulate exposure that derives from engine exhaust, and even more difficult to quantify the portion that is specifically related to DEP.

Because DEP is a complex mixture, it cannot be measured directly. Of the identified surrogates, EC exposure measurements appear to provide the most specific representation of historic DEP exposures. Historically, EC was a relatively good surrogate for DEP because DEP had a relatively high fraction of EC for many occupational environments. However, DEP is typically less than 1% of the mass of total TDE. Thus, EC, although the best of the known surrogates for DEP, is still not ideal since EC cannot fully differentiate DEP exposure from exposures to other combustion sources (especially tobacco smoke).

In 2003, HEI convened a panel of experts to attempt to identify a marker for diesel exhaust. The panel determined that there is, at present, no such marker, and concluded: "Better

measures of exposure to constituents of diesel emissions, with careful attention to selection of the sample studies, are needed. Of particular importance are the selection and validation of a chemical marker of exposure to the complex mix of diesel exhaust emission." (HEI, 2003.)

(i) Crump Analysis of Garshick Studies

Even though historical exposure estimates for DEP are problematic, the Garshick, *et al.* studies of railroad workers have received considerable attention. In that regard, and in response to a request from the U.S. EPA, Dr. Kenny Crump conducted a quantitative risk assessment for TDE based on the data from the Garshick 1988 cohort study. In his reports, Crump made several important findings. (Crump, *et al.,* 1991; Crump, 1999, 2001.)

First, Crump reported evidence that the follow-up in the Garshick studies was incomplete; that is, "a sizable fraction of deaths during the last four years of follow-up evidently were not identified" (apparently due to incomplete transmittal of data from the Railroad Retirement Board). The shortfall of data effectively ended the follow-up at 1976, instead of 1980 as originally intended. Second, in contrast to the Garshick, *et al.* (1988) finding that the relative risk for lung cancer increased with duration of exposure, Crump did not find a plausible dose-response for TDE. Third, while Garshick, *et al.* (1988) found a decreased lung cancer risk with increasing age at 1959, Crump reported opposite trends when U.S. rates were used as the basis of comparison; lung cancer mortality was higher among workers who were older in 1959 (and therefore had less TDE exposure). And fourth, Crump demonstrated that although train crews (exposed) had significantly elevated lung cancer mortality relative to clerks and signalmen (assumed to be unexposed), shop workers (the most highly TDE-exposed group) did not have an elevated risk. The fact that lung cancer mortality in those workers was no different from that of clerks and signalmen argued against a causal effect of diesel exposure in the cohort. Based on their findings, Crump and colleagues recommended to the U.S. EPA that the railroad study reported by Garshick, *et al.* (1988) did not constitute an appropriate basis for a quantitative risk assessment of TDE. (Crump, 2001.) EPA accepted that recommendation in its subsequent health assessment document for diesel emissions. (EPA HAD, 2002.)

(ii) Garshick Cohort Study Update Through 1996

In 2004, in response to the work of Crump, *et al.,* Garshick and colleagues updated the cohort mortality experience to cover the 37 years from 1959 through 1996, during which time there were nearly 44,000 deaths with known cause of death, including 4351 lung cancer deaths (Garshick, *et al.,* 2004). The update confirmed and corrected their incomplete follow-up through 1980, which Crump had critiqued (Crump, *et al.,* 1991; Crump 1999), adding several thousand pre-1981 deaths that inadvertently had been excluded in the original 1959-1980 cohort study. Garshick, *et al.* continued to report an elevated lung cancer relative risk of 1.40 for train crews (engineers, firemen, conductors, and brakemen -- jobs identified as TDE exposed) compared with railroad workers in unexposed jobs (clerks and station agents). Indirect adjustment for smoking attenuated the relative risk to between 1.17 and 1.27. Significantly, the shop workers, who reportedly were exposed to the highest levels of TDE but did not show elevated lung tumor incidence, were omitted from this comparison. Garshick, *et al.* further reported that "lung cancer mortality did not increase with increasing years of work in these jobs," which confirmed the Crump, *et al.* (1999) findings.

As noted, Garshick excluded shop workers from the "exposed group" of conductors and engineers. However, Crump had concluded that "based on all the available evidence, it appears highly likely that the shop workers (90% of whom were machinists and electricians) had the highest diesel PM exposures of any group of workers in the Garshick et al. cohort." Garshick did not refute that conclusion, but rather simply chose to overlook it, despite Crump's conclusion that the fact that "lung cancer mortality in those workers was no different from that of clerks and signalmen argues against a causal effect of diesel exposure in this cohort."

Even so, Garshick, *et al.* did acknowledge in 2004 that their original 1988 conclusion -- that "lung cancer risk increased with increasing years of work in diesel-exposed jobs" -- was in error, and they further agreed with Crump that "subsequent re-analyses of these data, with adjustment for attained age, indicated decreased risk with more years worked." Garshick, *et al.* (2004) also conceded that "analysis in this updated cohort with longer follow-up also indicates that lung cancer mortality is inversely related to total years worked."

Laden, *et al.*, 2006b, more recently published a report using an innovative exposure intensity characterization based on historical data for dieselization of individual railroads and emission factors suggested by the US EPA (1996b). While RRs for lung cancer remained elevated, as expected, there was no evidence of an exposure-response relationship among the railroad worker cohort using the improved estimates of exposure based on the intensity measure.

(iii) <u>Health Effects Institute Review of Railroad Studies</u>

The HEI Diesel Epidemiology Expert Panel (HEI, 1999) also conducted an independent detailed review of the Garshick data and various analyses of those data, including the Crump assessment. The panel's analysis found that within each category of worker, the risk of lung cancer decreased with increasing duration of employment, and further, that the decrease was statistically significant for clerks/signalmen and train workers. The HEI report therefore concluded that:

> These findings are not consistent with a steadily increasing association between cumulative diesel exposure and lung cancer risk. Furthermore, if the difference in risk between train workers and clerks/signalmen was due primarily to differences in exposure to diesel emissions, one would expect the relative risk for train workers compared with that for clerks and signalmen to be reduced or even eliminated after adjusting for exposure. In fact, adjustment for exposure increased this relative risk. Such a systematic pattern of decreasing risk with increasing exposure suggests that some form of bias is present in the data.
>
> * * *
>
> These patterns are not consistent with a monotonically increasing association between cumulative exposure to diesel exhaust and lung cancer risk.

In sum, the current weight of evidence suggests that in the Garshick, et al. studies, any occupational increase in lung cancer among train riders was not due to exposures to TDE or DEP.

(iv) <u>On-Road Transportation Workers (Teamsters Union Studies)</u>

The most relevant published investigation of lung cancer deaths among on-road (non-railroad) transportation workers was conducted using information obtained from the Central States Conference of the International Brotherhood of Teamsters. The investigation included: a case-control study of lung cancer deaths among teamsters during 1982-1983 (Steenland, *et al.*, 1990, 1992); and an exposure-response analysis and risk assessment of the case-control population based on the exposure data (Steenland, *et al.*, 1998).

The Steenland studies and risk assessment reflect the underlying assumption that TDE, as measured by EC, represents the greater part of PM exposure for truckers. There is substantial evidence, however, that such an assumption is not valid. Other sources of EC include gasoline engines, tire and brake wear, stationary combustion sources, and industrial processes. Bailey, *et al.* also concluded that the proportion of TDE relative to other emissions was much lower in these studies than originally estimated. (Bailey, *et al.*, 2003.)

In most, if not all, of the epidemiologic studies of transportation workers that associate TDE with lung cancer, the workers were exposed to mixed (and inseparable) gasoline and diesel exhausts, which, evidence suggests, were predominantly gasoline. The truckers in the studies drove on highways, where most vehicles were gasoline-fueled. Truck drivers, particularly on highways, were (and are) not likely to be exposed to own-truck exhaust emissions, because the exhaust pipe on a diesel truck is above and behind the driver. Indeed, Zaebst, *et al.* found that EC levels inside the truck were not significantly elevated over ambient roadside EC levels, while the in-cab OC levels (nonsmokers) were about 8-fold elevated over outdoor levels, indicating that truck drivers were exposed to significant combustion sources other than diesel exhaust, most likely secondhand tobacco smoke and gasoline engine exhaust. (Zaebst, *et al.*, 1991.) They concluded that if truck drivers experience an increased incidence of cancer, "it may be because they spend more time on the highway and not because the truck they are driving is exposing them to diesel exhaust."

In another more recent study, nondetectable to very low levels of EC were measured inside a diesel-powered school bus tested on an automotive test track. (Borak, *et al.*, 2003.) Those findings suggest that truckers are not likely to be primarily exposed to emissions from their own vehicles, but are instead exposed to emissions from other on-road vehicles. Since the other onroad vehicles during the Steenland, *et al.* study period (1960-1983) were predominantly gasoline-fueled, the truckers were likely exposed predominantly to gasoline exhaust. Indeed, during the 1960s (the critical years of the Streenland study from a latency perspective), diesel fuel represented only 4-7% of the total fuel sales (cars and trucks) (HEI, 1999). Moreover, in the 1960s, gasoline-fueled vehicles had no exhaust after-treatment, and quite likely would have contributed as much or more to mobile source air pollution as diesel vehicles. Accordingly, HEI has cautioned that "the lack of data to reconstruct gasoline exhaust emissions, particularly for years earlier than 1990, will significantly limit attempts to calculate risks from diesel as opposed to other sources, as well as any epidemiologic study of DE." (HEI, 2000.)

(v) Inadequate Latency Period

HEI further concluded that the Steenland studies quite likely suffer from an inadequate latency period, making them unsuitable for reaching any qualitative or quantitative conclusions about an association between TDE exposure and lung cancer. (HEI, 1999.) Specifically, the Steenland researchers assumed that trucks were dieselized by 1960; the case-control study analyzed lung cancer mortality in 1982-1983. However, data submitted to the U.S. EPA suggested that a more accurate date of dieselization is between 1965 and 1970 for heavy-duty (class 8) trucks, and after 1980 for medium-duty (class 5-7) trucks. (Bunn and Slavin, 2001.) Given that the latency period for lung cancer is estimated to be at least 15+ years (Peto, *et al.*, 1977), the Steenland study (1981-1983 mortality period) did not allow a sufficient latency period if the date of dieselization was 1970. Latency would still be inadequate even if the dieselization occurred in 1963. HEI recognized this problem, noting that "the latency period may not be sufficient to demonstrate an excess of lung cancer due to diesel exposure for all workers." (HEI, 1995.)

(vi) Mining Industry and Diesel Exhaust Exposures

If there is an empirical basis for associating TDE with lung cancer in humans, this association should appear most clearly in the underground mining industry, which includes occupations that have the highest potential for TDE exposure. However, while not definitive, underground mining epidemiology studies are generally negative for lung cancer, despite potential confounding in some underground mines by other factors such as radon and silica that would tend to increase lung cancer incidence in the study populations.

Significantly, eight years after the publication of their monograph on diesel exhaust, IARC issued a monograph on the cancer risk for coal miners (IARC, 1989, 1997). In the 1997 monograph, IARC reviewed studies of coal miners and determined that the evidence was *inadequate* for the carcinogenicity of coal dust. Thus, IARC classified coal dust as Group 3 -- "cannot be classified as to its carcinogenicity to humans."

Like diesel PM, the primary constituent of coal dust is carbon. Like diesel PM, coal dust contains organic carbons, some of which are PAHs. Yet for coal miners, the occupational group exposed to elevated concentrations of both coal dust and diesel PM, the 1997 IARC monograph concluded there was "inadequate evidence" for carcinogenicity. It reasonably follows that the IARC conclusion on coal miners is consistent with a lack of carcinogenicity for DEP and TDE as well.[3]

(vii) Meta-Analyses of the Diesel Exhaust Epidemiologic Database

Until very recently, the epidemiologic database for TDE had undergone two major meta-analyses that were conducted to evaluate the relationship between occupational exposure to TDE and lung cancer incidence. (Bhatia, *et al.*, 1998; Lipsett and Campleman, 1999.) A third meta-analysis was published in 2011, and is discussed below.

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[3] It is anticipated that another epidemiological study of underground miners that has been conducted by NIOSH/NCI -- the "Diesel Exhaust in Miners Study" or "DEMS" -- will be published soon. As discussed later in these comments, that study appears to be based on a significantly flawed exposure surrogate methodology.

Bhatia, *et al.* (1998) evaluated 29 TDE epidemiologic studies and selected 23 that complied with their criteria for inclusion in their meta-analysis. They defined exposure to TDE as work in an industry in which diesel engines (vehicles or equipment) were used. They included studies of truckers, railroad workers, bus drivers, other professional drivers, equipment operators, and mechanics. However, they excluded from their analysis studies of miners, due to the potential for exposure to multiple airborne substances in this industry. Bhatia, *et al.* reported a lung cancer relative risk of about 1.33 for all 29 studies combined and for several subcategories of studies.

Lipsett and Campleman (1999) also conducted a meta-analysis of epidemiologic studies to investigate associations between occupational TDE exposure and lung cancer incidence. Their analysis included many of the same studies as those included in the Bhatia, *et al.* analysis, and, like Bhatia, *et al.* they excluded studies of miners. Lipsett and Campleman also reported increased relative risks for lung cancer of about 1.33 when data for all studies were pooled or were grouped into various subcategories.

In assessing the value of meta-analyses, it is important to recall that any meta-analysis is only as strong as the underlying studies and data on which it is based. In the case of TDE, the existing epidemiological database has several important limitations, among which are inadequate latency for the developments of lung cancer in some or all of the study subjects, lack of direct quantitative data to confirm TDE exposure, and lack of consistent evidence of a dose-response relationship. In that regard, Silverman (1998) has noted three main concerns about the available epidemiologic evidence: (i) the magnitude of effect in most studies is low (reported RRs were generally under 1.5); (ii) of the 30 studies that investigated associations between TDE and lung cancer, only two (truckers and railroad workers) (Steenland, *et al.*, 1998; Garshick, *et al.*, 2004) had a sampling of quantitative data on which to base their estimates of historical exposure; and (iii) even in those studies, exposures for past time periods were estimated from more contemporary data collected well after the study time periods. Moreover, given the strong association between smoking and lung cancer, failure to control adequately for smoking can cause significant confounding of the results in the TDE epidemiologic studies.

The meta-analyses at issue relied predominantly on studies in the trucking industry, in which latency periods were inadequate, since many or all of the study subjects' initial exposure to TDE was less than 20 years prior to the follow-up date. The trucker studies also are suspect since there was an increased relative risk of lung cancer among truck drivers before there was widespread utilization of diesel trucks. The cause of that pre-dieselization elevation in risk has never been identified. Consequently, investigators have not been able to develop controls in the TDE epidemiologic results to account for that unidentified cause.

The lack of dose-response findings in the TDE epidemiologic database further suggests that the lung cancer relative risks derived by the Bhatia, *et al.* and Lipsett/Campleman analyses could be related to lifestyle or other exposures of these occupational populations rather than to TDE.

In light of the foregoing limitations inherent in the epidemiologic studies of TDE, Silverman has concluded that "the repeated finding of small effects, coupled with the absence of quantitative data on historical exposure, precludes a causal interpretation. To establish causality will require well designed epidemiologic studies that do not suffer from the weaknesses of

previous studies."

More recently, Olsson, *et al.* published another meta-analysis assessing the association between occupational exposures to TDE and lung cancer from 11 case-control studies in Europe and Canada. (Olsson, *et al.*, 2011.) This pooled analysis claimed to find a RR of 1.31 (CI 1.19-1.43) when comparing the assumed highest exposed quartile with the unexposed control group. The risk ratio decreased by 10-20% when adjustments were made for smoking, resulting in RRs that were not statistically significant for any exposure group except the highest quartile.

Significantly, the primary objective of the 11 pooled studies was not to assess exposures to diesel exhaust, but rather to "study the joint effects of exposure to concurrent occupational lung carcinogens (asbestos, PAHs, nickel, chromium and silica) and smoking." Thus, as with prior meta-analyses, past exposures to diesel exhaust were not derived from any actual air quality measurements, but instead were premised on "a general population job-exposure matrix based on 5-digit ISCO-68 codes." More specifically, three "occupational exposure experts" were given the task of assigning a diesel exhaust exposure score (ranging from 1 to 4) to each of the pooled study subjects based on their assigned job-exposure matrix code. This process resulted in what Olsson, *et al.* described as "a semi-quantitative score of cumulative exposure" to diesel exhaust.

In reporting their results, Olsson, *et al.* conceded that "odds ratios in the highest [exposure] quartile did not attain statistical significance in all subgroup analyses." They also noted that "the prevalence of [diesel exhaust] exposure was higher in current meta-analysis compared to the original studies that had estimated diesel exposure using expert case-by-case assessment," and that their exposure assignment method "did not take into account the changes in the use of diesel engines over time." Thus, the reported RRs could, again, stem from mis-estimates of past occupational exposure levels, since this meta-analysis utilized no measured or estimated concentration levels of diesel engine exhaust whatsoever. Further, it remains just as likely that the reported results were impacted by an incomplete correction for smoking.

In sum, the defects inherent in the earlier meta-analysis and underlying epidemiology studies -- studies which NTP itself found to be of "limited" value in 2000 -- also pertain to the more recent meta-analysis reported by Olsson, *et al.*

(viii) <u>The NIOSH/NCI Diesel Exhaust in Miners Study</u>

The opinion has been raised that the body of epidemiologic evidence on TDE will be significantly strengthened when the analyses from the NCI-NIOSH study of U.S. underground miners -- the Diesel Exhaust in Miners Study ("DEMS") -- are published (Ward *et al.*, 2010). Although those findings will certainly add to the health effects literature, it is important to emphasize that they are also limited by an uncertain retrospective exposure assessment that relies on assumptions and predictions rather than actual DEP exposure measurements. A brief elucidation of that point is warranted.

The original premise for DEMS was to address the shortcomings of earlier epidemiological studies of occupational exposures to diesel exhaust by utilizing a non-metal, non-coal mining cohort where it was postulated that the only significant source of exposure to elemental carbon (EC) would be from diesel engines utilized and operated in the underground

mines. The original intent was to use actual measurements of EC -- contemporary and historical measurements -- taken in the eight study mines, and to build an exposure data base derived from actual emissions measurements covering the entire multi-decade study period, thereby avoiding the exposure surrogate/estimation methods that yielded questionable results in the earlier epidemiology studies of railroad workers and truck drivers. Unfortunately, the original premise and concept of DEMS was never implemented, which, as we have now learned, replicates the problems of the earlier studies and casts serious doubts on the methodology and results of DEMS.

More specifically, as DEMS moved forward subsequent to 2001, the NIOSH/NCI investigators realized that there were insufficient historical measurements of respirable elemental carbon (REC) to reconstruct the exposure estimates for the mine workers being studied. In response, they chose to use carbon monoxide (CO) as a surrogate for REC based on the fact that the mines had consistently measured CO levels in the mines going back to 1975. Specifically, the NIOSH/NCI investigators proceeded to use the actual measurement data from the mine air quality surveys (conducted between 1998 and 2001) and calculated a "weak" correlation factor of 0.41 between CO and REC emissions. They then developed a novel and untested analytic method that utilized total engine horsepower in the mines along with mine ventilation rates to estimate historical trends in CO concentrations in the mines (and among different work areas/job categories within the mines). Of note, the correlation factor between engine horsepower and CO emissions is not described or quantified in the four published papers. Nonetheless, the investigators assumed a linear scaling relationship between CO and REC based on multiple statistical reanalyses and regressions of their admittedly weak correlation data (which actually yielded a non-linear, non-proportional relationship of, at most, 0.58:1, not 1:1) to derive historical trend estimates of REC, even while acknowledging that "the relation between CO and REC might not be strictly proportional." ("In our primary time trend models, we assumed that a relative change in historical CO levels was directly translated to an identical change in REC levels over all the years of the study.")[4]

The NIOSH/NCI investigators used the estimated and modeled levels of REC, derived from estimated levels of CO, as the metric to estimate workplace exposure to diesel exhaust. They then compared lung cancer rates observed in miners from various job categories to estimated diesel (REC) exposure levels to complete the epidemiology studies. Thus, the one anticipated data set of DEMS that was viewed as key to the validity and "definitiveness" of the study results -- actual historical measurements of diesel particulate (REC) in the mines -- was in fact not available or utilized. Instead, DEMS ended up relying exclusively on reconstructed and estimated levels of diesel exhaust, derived from estimated levels of CO and assumed correlations to horsepower and REC. That approach amounts to reliance on the same type of exposure estimate/surrogate data that was seen as a fundamental weakness in the earlier epidemiology studies of diesel exhaust.

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[4] The four previously published papers describing the exposure surrogate methodology utilized and relied on in DEMS are as follows: (i) "DEMS: I. Overview of the Exposure Assessment Process," Ann.Occup.Hyg., Vol. 54, No. 7, pp. 728-746 (2010); (ii) "DEMS: II. Exposure Monitoring Surveys and Development of Exposure Groups," Ann.Occup.Hyg., Vol. 54, No. 7, pp. 747-761 (2010); (iii) "DEMS: III. Interrelations Between Respirable Elemental Carbon and Gaseous and Particulate Components of Diesel Exhaust," Ann.Occup.Hyg., Vol. 54, No.7, pp. 762-773 (2010); and (iv) "DEMS: Estimating Historical Exposures to Diesel Exhaust in Underground Non-Metal Mining Facilities," Ann. Occupy. Hyg., Vol. 54, No. 7, pp. 774-788 (2010).

Thus, the core assumptions for the exposure assessment methodology that serve as the foundation for DEMS are that: (i) CO and PM emissions from different diesel engines correlate sufficiently well; (ii) historical CO emissions correlate sufficiently well with and can be estimated based upon aggregate engine horsepower; and (iii) the overall correlation of CO and PM emissions from different diesel engines is sufficiently proportional and linear to allow for 1:1 scaling over the years of the study. Significantly, none of those assumptions is correct, and data have been obtained (and continue to be obtained) to demonstrate that fact.

Specifically, emissions experts and the relevant peer-reviewed literature have conclusively established that there is no actual correlation between CO emissions and PM (or REC) emissions among different diesel engines. Of note in that regard are three published papers of Dr. Nigel Clark (West Virginia University) and colleagues: (i) "Field Measurement of Particulate Matter Emissions, Carbon Monoxide, and Exhaust Opacity from Heavy-Duty Vehicles," J. Air & Waste Manag. Assoc., 49: PM 76-84 (1999); (ii) "Evaluation of Methods for Determining Continuous Particulate Matter from Transient Testing of Heavy-Duty Diesel Engines," SAE Technical Paper 2001-01-3575 (2001); and (iii) "Comparison of Heavy-Duty Truck Diesel Particulate Matter Measurement: TEOM and Traditional Filter," SAE Technical Paper 2005-01-2153 (2005). Also of note is an earlier published letter to the editor regarding the DEMS exposure methodology: "Comments on the Diesel Exhaust in Miners Study," Ann.Occup.Hyg., Vol. 55, No.3, pp. 339-342 (2011).

The foregoing papers establish a number of extremely important and relevant facts, including that "there is no universal relation between CO and PM" among different diesel engines, and that "the CO/PM relationship is unique for each engine type and perhaps for each engine." (JAWMA, p. PM-79; Fig. 1.) Thus, "the wide range of average CO/PM ratios is too great to allow the inference of PM directly from CO." (Id. at p. PM-80.) Similarly, "data taken using a variety of test schedules, vehicles, engines, and geographic locations have shown that there is generally no reliable or unique relationship between CO and PM integrated over a test cycle." (Id. at PM-83.) For example, "EPA certification data for large heavy-duty off-road diesel engines tested in 2003 indicate that the ratio of CO/PM emission rates varied over a range more than 100-fold." (Ann.Occup.Hyg., Vol. 55, No. 3, p. 340.) Simply stated, there is "no overall (fleet) relationship between CO and PM." (SAE 2005, pp. 1, 9.) Similarly, "studies of diesel equipment in underground mines |have| revealed no consistent relationship between engine power and either CO or EC." (Ann.Occup. Hyg., Vol. 55, No. 3, p. 340.)

In addition, Dr. Nigel Clark and colleagues at West Virginia University have just completed an extensive data review confirming a well-known precept in the diesel engine industry: CO and PM emissions do not correlate among different diesel engines. In fact, the CO/PM correlation for the relevant data sets -- older diesel engines -- was no higher than 0.14, and for some data sets was even negative. Moreover, the slope of the regression lines for differing data sets varied significantly, further underscoring the fact there is no sufficient correlation and linearity between CO and PM emissions from different diesel engines. Dr. Clark's analysis and paper on this issue have been submitted to SAE for publication, and he is currently working on follow-up analyses to assess in detail the nature of the correlation, or lack thereof, between engine horsepower and CO emissions among different diesel engines.

The bottom line, therefore, is this: The original premise for DEMS was abandoned

several years ago in favor of an exposure surrogate methodology that appears to be fundamentally flawed, since it relies on incorrect assumptions regarding the correlation between CO and REC emissions from diesel engines, and between CO emissions and aggregate engine horsepower. Inasmuch as that flawed methodology serves as the foundation of DEMS, the resultant epidemiological results will be, in all probability, similarly questionable, and likely will have other fundamental defects. Thus, it appears that DEMS will not alter the relative sufficiency of the available epidemiological data.

(ix) Conclusions Regarding the Epidemiologic Studies

A number of recent reevaluations of the TDE epidemiologic data have concluded that the existing epidemiological studies are unable to predict potential human health effects from exposure to TDE or to link TDE or DEP to increases in lung cancer. (Muscat and Wynder, 1995; Stöber and Abel, 1996; Cox, 1997; Morgan, *et al.*, 1997.) There are several factors that lead to this conclusion: (1) many, if not most, of the TDE epidemiologic studies suffer from inadequate latency periods; (2) of the positive studies, only weak associations are seen and those could be attributable to residual confounding (particularly by smoking); (3) the epidemiologic database is inconsistent and inconclusive, with a few studies showing a weak association between TDE exposure and lung cancer, and other studies showing no association; (4) there is no exposure-response relationship in most studies, with some studies even showing negative a dose-response; (5) given the negative mutagenicity data for whole TDE and DEP, and a negative animal database for carcinogenicity, biological plausibility is questionable; and (6) the epidemiological studies lack adequate exposure information regarding DEP, without which the relevance of the human studies is unknown.

E. Overall Assessment of DEP

A critical assessment of the currently available laboratory and epidemiological data does not provide a convincing argument for a causal relationship between exposure to TDE/DEP and an increased incidence of lung cancer. The data from laboratory studies of DEP, both *in vivo* and *in vitro*, have only limited relevance in assessing the carcinogenic potential of DEP in humans. Laboratory rats exposed to very high levels of DEP (>2200 $\mu g/m^3$) developed an excess of lung tumors; however, the tumor incidence was consistent with that observed in rats exposed to the same overload levels of other types of fine particles (*e.g.*, TiO_2, talc, and carbon black). Other species (mice and hamsters) exposed at similar, high DEP levels did not show an excess of lung tumors, nor did rats exposed at lower DEP levels. In rats, high exposures to a variety of different particulates (DEP as well as inert TiO_2, talc, and carbon black) resulted in lung overload, lung inflammation, cell proliferation, and eventually tumors. This mechanism is not specific to DEP and did not occur in the rats at DEP exposure concentrations below 2000 $\mu g/m^3$, a concentration level that is 100-fold greater than DEP levels to which railroad and trucking industry workers might be exposed. Thus, the tumorigenic effect of high levels of DEP in rats is now considered to be a nonspecific particle effect that resulted from a species-specific overload mechanism. Such a mechanism has little or no relevance to humans exposed either to low levels in occupational environments or to even lower ambient levels.

Furthermore, mutagenicity studies in which cultures of mammalian or bacterial cells were exposed to organic solvent extracts of DEP are of limited utility for understanding the potential

carcinogenicity of whole DEP. Whole DEP itself has not been found to be mutagenic in most studies. The mutagens extractable from DEP dissolve either minimally or not at all in aqueous based fluids, such as body fluids or cell culture medium. Thus, the adsorbed mutagens are generally not considered to be bioavailable, which could explain why most studies have not shown DEP to be a direct-acting mutagen.

Epidemiologic studies of the transportation industry (primarily trucking and railroad workers) generally show a low elevation in lung cancer incidence (RRs generally below 1.5), but dose-response for TDE exposure is lacking, and the studies are limited by minimal or inadequate latency periods, a lack of quantitative concurrent exposure data, and inadequate or lack of controls for tobacco smoking. Furthermore, there were similar elevations in lung cancer incidence in truck drivers prior to dieselization. Additionally, in-cab PM exposures of trucks drivers have been shown to be comparable to ambient highway exposures. Thus, at least on the road, long-haul truckers are not exposed to any higher DEP levels than the rest of the driving or highway-situated population. Taken together, these findings suggest that lifestyle or an unidentified occupational agent other than DEP might be responsible for the low elevations in lung cancer reported in the transportation studies. In contrast to the transportation industries studies, epidemiologic studies of underground miners, many of whom are exposed to perhaps the highest known human DEP exposures, are generally negative for lung cancer.

All of the foregoing scientific studies and findings demonstrate that there is no sufficient basis to amend or increase the current hazard assessment that NTP has ascribed to DEP. Accordingly, NTP should retain the current classification for DEP in any future Report on Carcinogens.

7. The Key Premises Pertaining To NTP's 2000 Evaluation Of DEP No Longer Apply

In addition to the foregoing conclusion regarding TDE/DEP, NTP's reassessment of DEP will need to account separately and distinctly for NTDE. In that regard, NTP's 2000 evaluation of DEP was premised on a number of key findings and assumptions regarding the nature and composition of DEP. As detailed below, more recent scientific data and observations have demonstrated that those foundational premises (while still insufficient to alter the listing for DEP) simply do not apply to NTDE.

One significant source of new data relating to the nature and composition of NTDE is the Advanced Collaborative Emissions Study ("ACES"). ACES is a multi-party effort, managed by the Health Effects Institute ("HEI") and the Coordinating Research Council ("CRC"), to measure and characterize the emissions from new technology diesel engines (Phases 1 and 2 of ACES), and to conduct a chronic inhalation bioassay in mice (3-month exposures) and rats (lifetime exposures) (Phase 3 of ACES). The core (null) hypothesis of ACES is, as follows: "Emissions from combined new heavy-duty diesel engines, after-treatment, lubrication and fuel technologies designed to meet 2007 NOx and PM emission standards will have very low pollutant levels and will not cause an increase in tumor formation or substantial toxic health effects in rats and mice at the highest concentrations of exhaust that can be used (based on temperature and NO_2 or CO levels) compared to animals exposed to clean air, although some biological effects may occur."

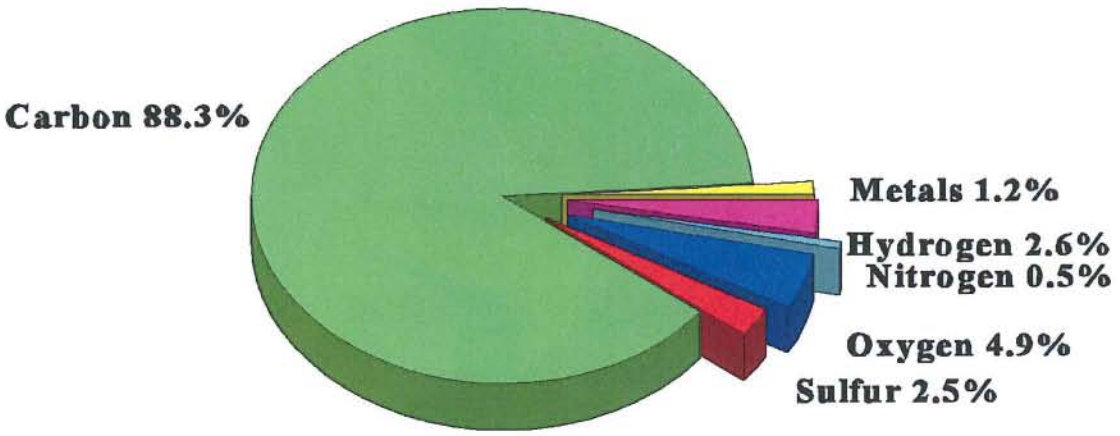
The ACES Phase 1 results were reported in 2011, and are discussed below. The ACES Phase 3 results are expected to be reported in 2013. The ACES data, along with the other data and findings detailed herein, clearly establish that the NTP's previous conclusions regarding DEP cannot be carried over to NTDE.

Premise No. 1:
DEP is emitted at high rates and is dominated by carbon, including a solid carbon core

In 2000, it was assumed that DEP was characterized by a significantly higher content of particulate matter than that from gasoline-fueled vehicles, and that, in general, heavy-duty diesel trucks emitted up to 40 times more particulate than catalyst-equipped gasoline-fueled vehicles. (See IARC Monograph 46, pp. 47, 57, 149; EHC 171, pp. 91, 102, 138.) Similarly, it was claimed that some light-duty diesel engines could emit 50 to 80 times, and some heavy-duty diesel engines 100 to 200 times more particulate mass than typical catalytically-equipped gasoline engines. (RoC, 12th Ed., p. 153 (2011); CARB "Part A" Exposure Assessment (hereinafter, "Part A"), pp. A-1, 8.)

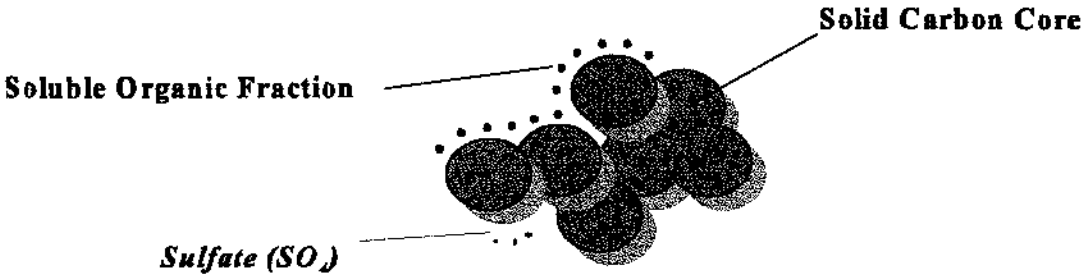
CARB provided a depiction of the composition of DEP (*see* CARB, Part A, Figure III-2, reproduced below), which indicated that diesel particles were comprised (by weight) of carbon (88.3 percent), oxygen (4.9 percent), hydrogen (2.6 percent), sulfur (2.5 percent), metals (1.2 percent), and nitrogen (0.5 percent). (Part A, p. A-11.)

CARB Figure III-2
Carbon is the Primary Element in a TDE Particle
(adapted from Volkswagen, 1989)

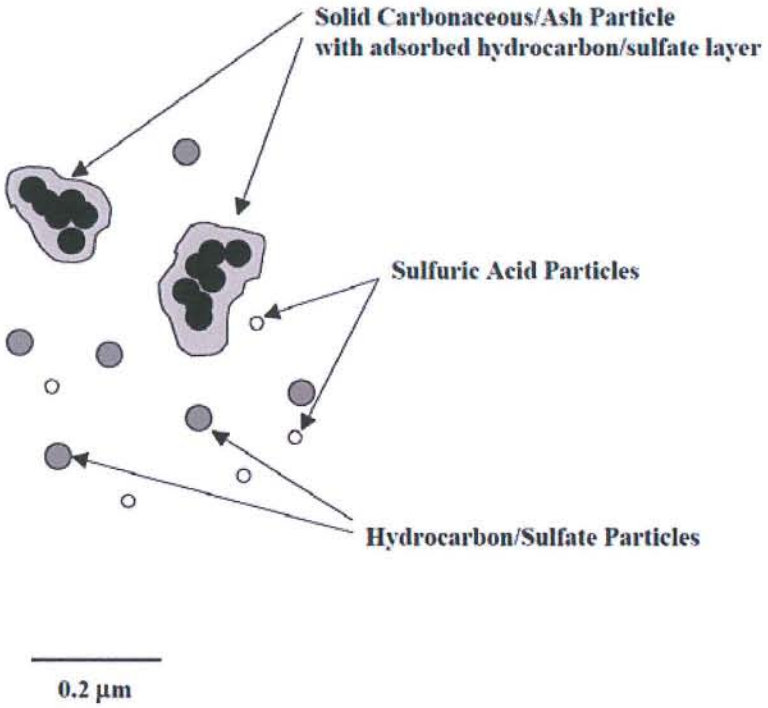


The fundamental premise was that the particles contained in DEP were mainly aggregates of spherical carbon particles coated with organic and inorganic substances (*see* CARB, Part A, Figure III-1, reproduced below). IARC estimated that the composition of the particles was approximately 80 percent elemental carbon. (Monograph 46, pp. 47-48.) CARB similarly estimated that the amount of elemental carbon, or EC, in the average diesel particle typically ranged up to 71 percent. (Part A, p. A-9.) It also was assumed that the inorganic fraction consisted of small solid elemental carbon particles, ranging from 0.01 to 0.08 micrograms, along with sulfur, oxygen, carbon, sulfate (SO_4), CO and NOx. (RoC, 12th Ed., p. 153 (2011).)

CARB Figure III-1
TDE Particles are Mainly Aggregates of Carbon Particles

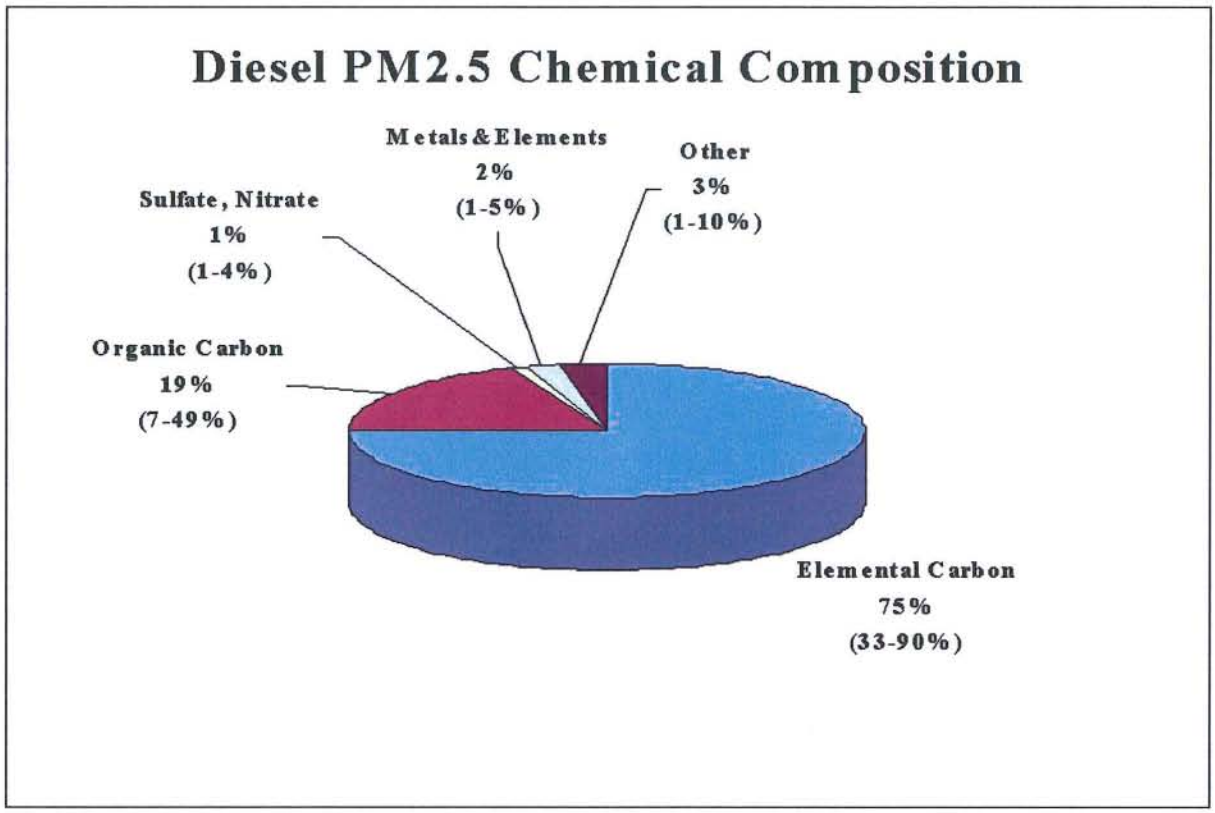


Significantly, in its 2002 Diesel HAD, U.S. EPA also reached similar conclusions regarding the characteristics and composition of DEP. More specifically, EPA noted that DEP are "primary spherical particles consisting of solid carbonaceous (EC) material and ash (trace metals and other elements)," absorbed onto which "are added organic and sulfur compounds (sulfate) combined with other condensed material." (2002 Diesel HAD, p. 2-11.) EPA's schematic diagram of DEP (reproduced from the HAD) is set forth below:



EPA Figure 2-7. Schematic diagram of diesel engine exhaust particles.

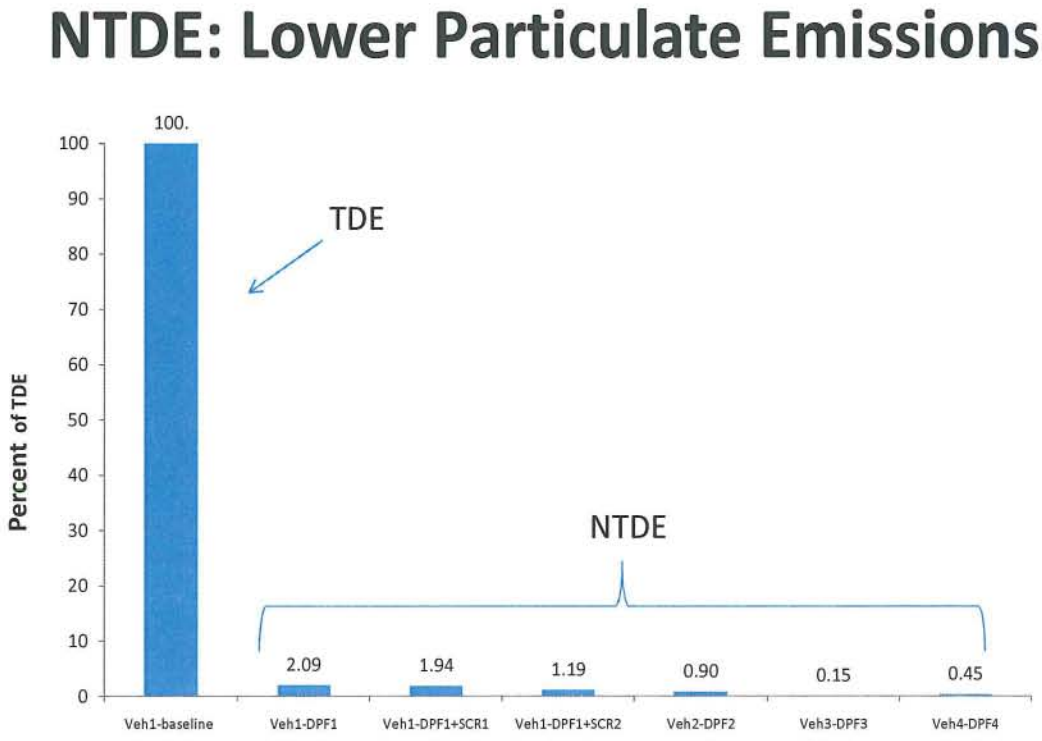
With respect to the composition of DEP, EPA concluded that those particles were typically composed of 75% EC (ranging up to 90%), 20% OC (ranging down to 7%), and small amounts of sulfate, nitrate, trace elements, water, and unidentified compounds. The relevant graphic from the 2002 Diesel HAD is reproduced below:



EPA Figure 2-8. Typical chemical composition for diesel particulate matter ($PM_{2.5}$)

The New Data Demonstrating That Premise No. 1 Does Not Apply to NTDE

The scientific data and findings since 2000 have established that the PM fraction of NTDE is different than what was assumed for TDE. First, the actual PM emission rates from new-technology diesel engines are approximately 0.001 g/bhp-hr -- 90% below the currently applicable standard of 0.01 g/bhp-hr, and more than 99% below the pre-1988 "unregulated" levels. As a result, the PM emission levels from today's heavy-duty diesel engines have been reduced to near-zero, passenger car-like levels. Indeed, in most cases, the PM emission rates for NTDE are well below 0.01 g/mi. (which is equivalent to the PM emission rate for low-emission passenger cars) and are similar to the proposed CARB LEV III PM standard of 3.0 mg/mi for 2017 and later model year passenger cars. (Herner, *et al.*, 2009; Biswas, *et al.*, 2009; ACES Phase 1 Study, CRC Report (June 2009).)



CARB Study: Herner et al., EST 43:5928-5933, 2009, data from Table 2. Transit Buses: UDDS Test Cycle

As depicted in Figure 1.1 below, multiple recent studies of the emissions (g/mile) from heavy-duty transit buses have shown that NTDE particulate mass emissions are not "significantly higher" than other technologies, but instead are more comparable to the PM emission levels from low-emission CNG-fueled vehicles (which emissions are not a toxic air contaminant or "TAC"). (Ayala *et al.*, 2002; Ayala *et al.*, 2003; Biswas, *et al.*, 2009; Gautam *et al.*, 2005; LeTavec *et al.*, 2002; McCormick *et al.*, 1999; Northeast *et al.*, 2000; Norton *et al.*, 1999; Wang *et al.*, 1997; Lanni *et al.*, 2003.) While TDE transit bus PM emissions were 0.75 g/mile, the levels are 10 to 40 times lower for NTDE, CNG and CNG with an oxidation catalyst (0.033, 0.062, and 0.018 g/mile, respectively). This result holds whether testing is done on the Central Business District cycle, or on other emission test cycles.

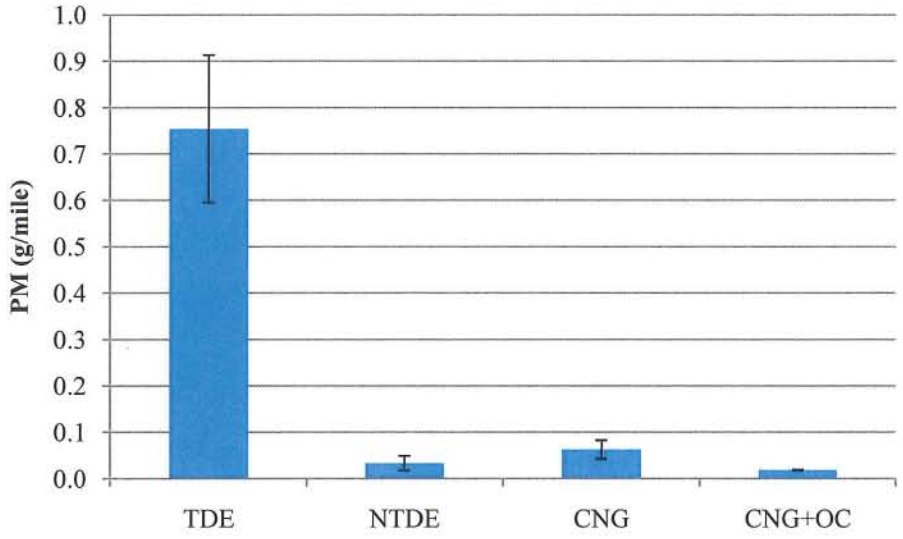


Figure 1-1. The particulate emissions (PM g/mile) for transit buses (TDE, NTDE, CNG and CNG with oxidation catalyst (CNG+OC)) tested under the Central Business District test cycle (means, standard errors plotted) (data from Ayala *et al.*, 2002; Ayala *et al.*, 2003; Gautam *et al.*, 2005; LeTavec *et al.*, 2002; McCormick *et al.*, 1999; Northeast *et al.*, 2000; Norton *et al.*, 1999; Wang *et al.*, 1997; Lanni *et al.*, 2003). NTDE, CNG, and CNG+OC are significantly different from TDE ($p < 0.05$). NTDE is not significantly different from CNG or CNG+OC ($p < 0.05$).

A similar result also applies if NTDE PM emission levels are compared to gasoline-fueled vehicles. To make a comparison with gasoline fueled vehicles, data from passenger cars are used since current transit buses are not fueled with gasoline. As shown in Figures 1.2a through 1.2e below, particulate mass emissions (g/mile) for NTDE are not "significantly higher," but instead are fully comparable to gasoline (and CNG-fueled) vehicles. (Rijkeboer *et al.*, 1994; Ahlvik, 2002.) More specifically, the TDE passenger car PM emissions were found to be 0.13 g/mile, while the levels are 7 to 70 times lower for NTDE, CNG and gasoline vehicles (0.0019, 0.0187, and 0.090 g/mile, respectively).

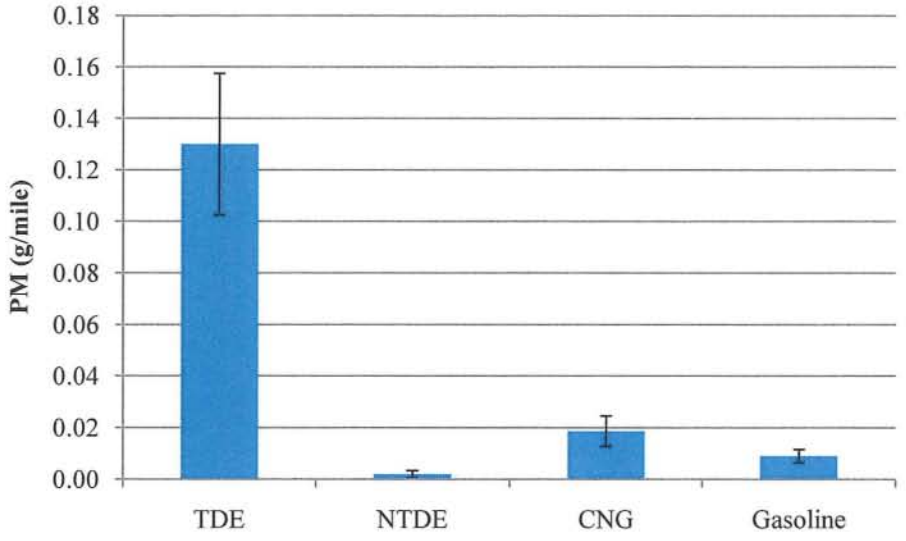
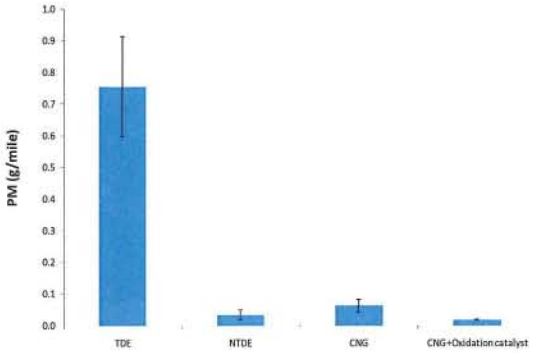


Figure 1.2a. The particulate emissions (g/mile) for passenger cars (TDE, NTDE, CNG and gasoline) tested under various transient test cycles (means, standard errors plotted) (data from Rijkeboer et al., 1994; Ahlvik, et al., 2002). NTDE, CNG, and gasoline are significantly different from TDE ($p < 0.05$). NTDE is not significantly different from CNG or gasoline ($p < 0.05$).

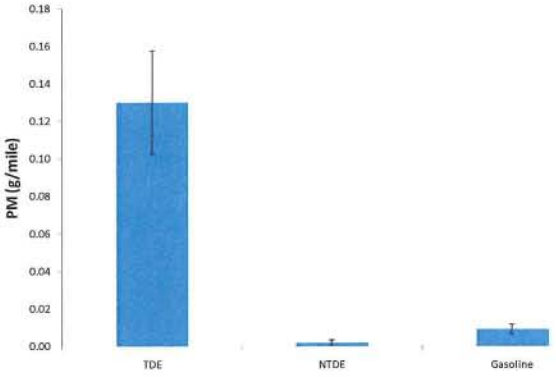
NTDE Particulate Mass Emissions Similar to CNG Fueled Vehicles



Hesterberg et al., EST 42 (17), 6437–6445, 2008, data from Table 1. Transit Buses

Figure 1.2b

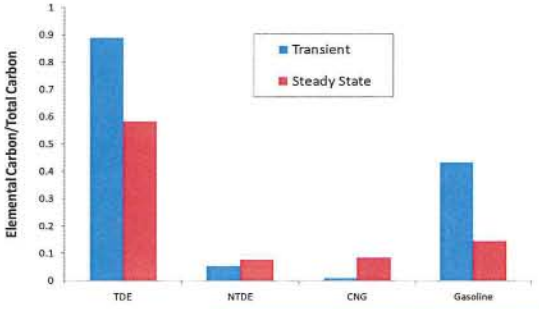
NTDE Particulate Mass Emissions Similar to Gasoline Fueled Vehicles



Ahlvik, Vägverket, Publikation 2002:62 2002, data from Figure 12. Passenger cars

Figure 1.2c

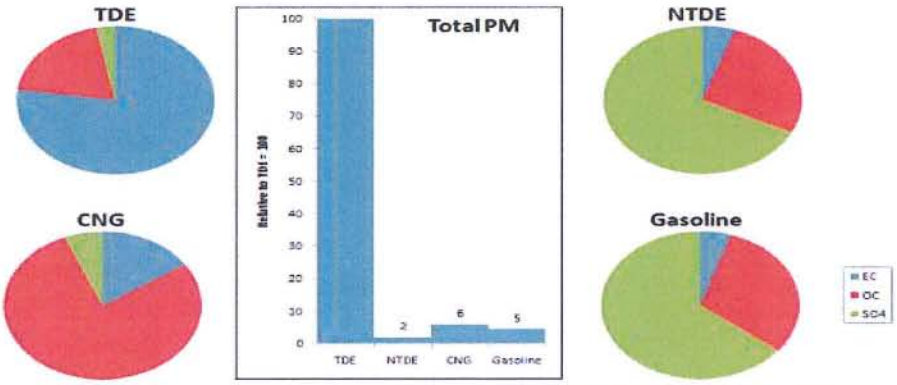
EC/TC Ratio for NTDE PM Similar to CNG and Gasoline Fueled Vehicles



CARB Study: Holmen and Ayala, EST. 2002, 36, 5041–5050, diesel and CNG transit buses. Schauer et al. Aerosol Sci. Technol. 2008, 42, 210-223. Gasoline passenger cars.

Figure 1.2d

PM Composition and Mass Comparisons



TDE, NTDE, CNG: Lanni et al., SAE 2003-01-0300, 2003. Transit Bus. Gasoline, Steady State: Schauer et al., Aerol Sci Tech 42:210-23, 2008. Gasoline vs. TDE PM: Ahlvik 2002

Figure 1.2e

In summary, data developed since 2000 clearly show that the particulate mass emissions rates from NTDE are 20 to 70 times lower than previously presumed, and are statistically indistinguishable from the near-zero PM emission levels seen from low-emission gasoline-fueled and CNG-fueled vehicles (which emissions are not classified as toxic air contaminants ("TAC")). (Hesterberg, *et al.*, 2011.) Thus, the primary emission constituent of concern (DEP)--the emission constituent that is the focus of NTP's nomination for reevaluation -- has been virtually eliminated and reduced to passenger car-like, near-zero levels in NTDE.

In addition, elemental carbon now only represents 13% (not 80% or more) of the miniscule, near-zero amount of DEP emitted from new-technology diesel engines. (Khalek, et al., 2011.) Thus, the soot or carbon core fraction of NTDE is largely nonexistent. The following chart (Figure 1.3) from the results of Phase 1 of the Advanced Collaborative Emissions Study ("ACES"), overseen by the independent Health Effects Institute ("HEI"), helps to demonstrate this important development.

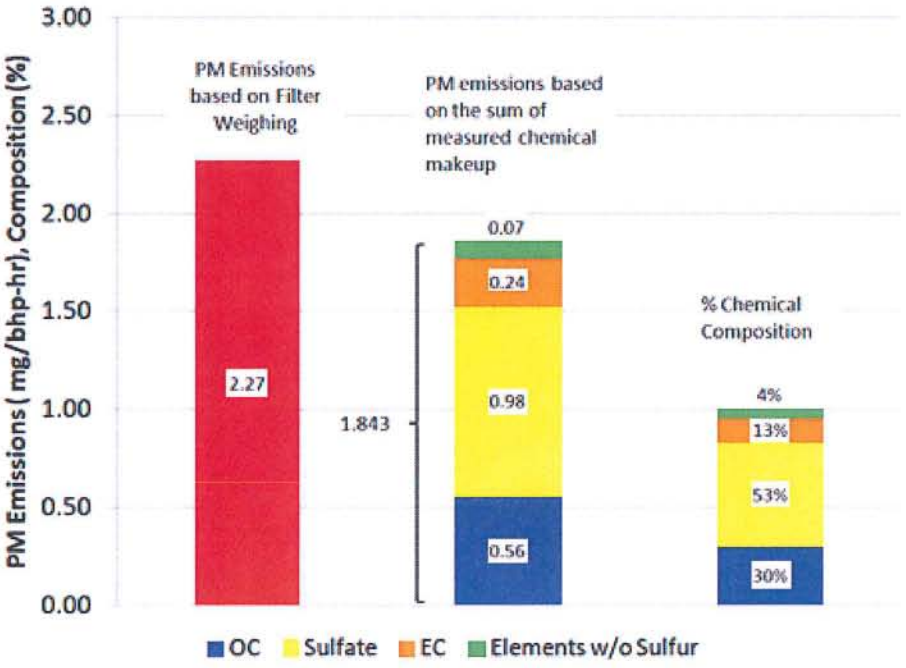


Figure 1.3 (Khalek, et al., Figure 2). Average PM Emissions Rate and Composition for all twelve repeats of the 16-hour cycles using all four 2007 ACES Engines. (Data taken from animal exposure chambers; PM mass emissions from CVS sampling system are 50% lower.)

Other studies have shown that elemental carbon represents just 3%-8% of the total carbon fraction of NTDE. (Holmen, *et al.*, 2002.) In that regard, and as shown in Figure 1.4 below, the ratio of elemental carbon (EC) to total carbon (TC) (TC = EC + organic carbon (OC)) for NTDE particulate is more comparable to the particulate emissions from CNG-fueled and port fuel-injection gasoline engines (which particulates are not classified as TACs). (Holmén and Ayala, 2002; Lev-On *et al.*, 2002; Schauer *et al.*, 2008); Liu *et al.*, 2009a.) Further, the EC/TC ratios for NTDE and CNG are not significantly affected by engine test cycle or workload.

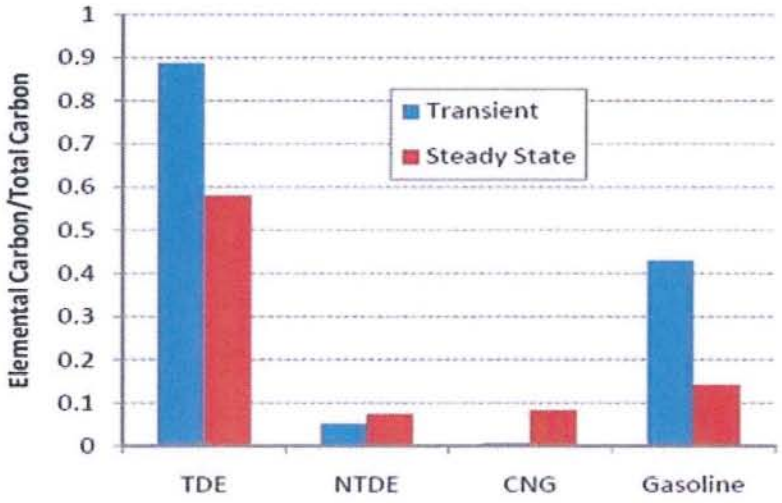


Figure 1.4. The elemental carbon fractions of total carbon from transit bus particulate emissions (TDE, NTDE, and CNG) and passenger car (gasoline) particulate emissions, tested under transient test cycles and steady-state conditions. The transient test cycle for the transit buses was the Central Business District test cycle, while the Unified Driving Cycle was used for the passenger cars. The steady-state data for transit buses and cars are from Holmén and Ayala, and Schauer, *et al.*, respectively.

In addition, the near-zero levels of PM found in NTDE is dominated by sulfate (53%) and organic carbon (30%) -- not a solid carbon core. Sulfate dominates the PM composition of NTDE, and EC constituents have been largely eliminated. (Biswas, *et al.*, 2009.) In that regard, it is important to recognize that sulfate is neither a TAC nor a hazardous air pollutant ("HAP"), and recent findings show that no significant toxicity is associated with sulfate. (Grahame, *et al.*, 2005.)

Similarly, the nanoparticle emissions contained in NTDE are predominantly ammonium sulfates and sulfuric acid, which are fully water-soluble. (Grose, *et al.*, 2006.) Soluble sulfate particles, which will tend to undergo dissolution in the lungs, are of low toxicity. (Schlesinger, *et al.*, 2003; Schlesinger, *et al.*, 2007; Reiss, *et al.*, 2007.)

In addition, due to artifact formation during sampling procedures, and further considering real-world dilution ratios, the actual concentrations of organic carbon emissions from new-technology diesel engines are likely to be just 10% of what is measured through laboratory sampling techniques. (Robinson, *et al.*, 2007.) Ten percent of near-zero is the practical equivalent of zero.

In sum, the early assumptions regarding the emission rates and carbon-dominated composition of DEP simply do not apply to current diesel engine technologies.

Premise No. 2:
Newer diesel engines emit more fine particles

There also was concern back in the 1980s and 1990s that more fine particles, a potential health concern, could be formed as a result of then-emerging new diesel engine technologies.

The New Data Demonstrating That Premise No. 2 Does Not Apply To NTDE

As confirmed by the work of Drs. Kittleson and Khalek (including in the ACES Phase 1 study), the average total number of particles in NTDE (from engines operating on the FTP transient cycle) are 99% lower than from a 2004 technology engine (and 89% lower when operating on a cycle that triggers regeneration events). Thus, the number of particles contained in NTDE has been dramatically reduced and does not raise any unique health concerns.

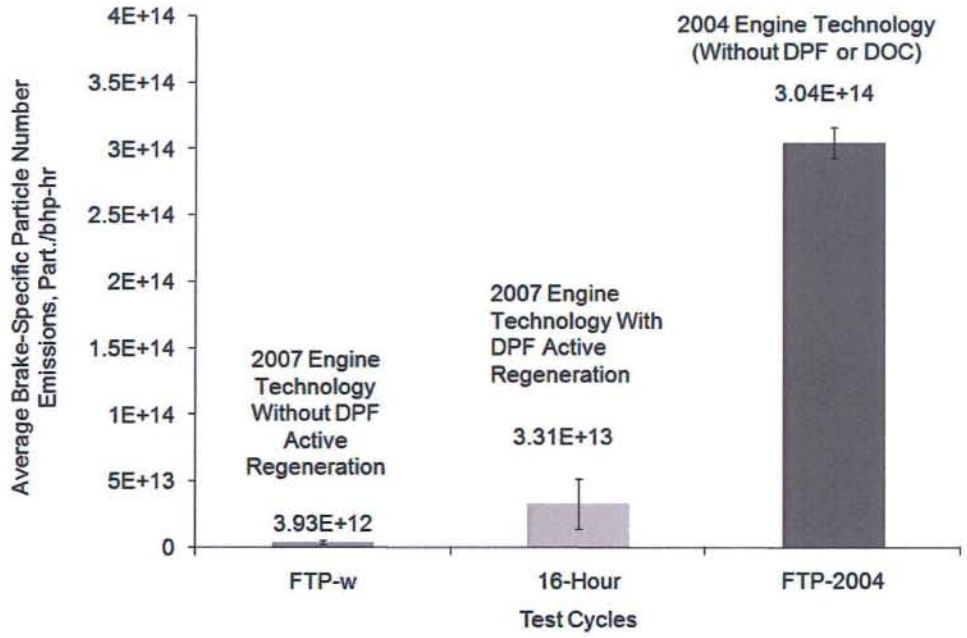


Figure 2.1 (Khalek, et al., Figure 6.) Average Particle Number Emissions Comparison between 2007 ACES Engines with and without C-DPF Regeneration and a 2004 Technology Engine.

In fact, the particle number concentration emissions contained in NTDE are well below typical urban outdoor air concentrations, and amount to a 10,000-fold reduction from unregulated engines. (Barone, Storey, *et al.*, 2010.) Other studies have confirmed that the particle numbers contained in NTDE have been lowered to below ambient background levels. (Kittlelson, *et al.*, 2006.) In fact, particle number emissions from NTDE and CNG-fueled engine exhaust are, on average, equivalent. (Holmen, *et al.*, 2002.)

Additional research since 2000 also has established that the average number of nanoparticles contained in NTDE is more than 100 times less than the number of nanoparticles in the exhaust from unregulated engines, and is equivalent to the number of nanoparticles found in the emissions from CNG-fueled vehicles. (Holmen, *et al.*, 2004.) Further, under higher load

conditions, the particle count from NTDE is essentially undetectable when compared against ambient background particle counts. (Id.) Still other studies have confirmed that the particle number emissions contained in NTDE are at least one order of magnitude lower than a gasoline vehicle. (Bosteels, *et al.*, 2006.)

In another recent study analyzing the impact of fuel sulfur content on PM emissions, lower nuclei-mode particulate emissions were observed when ULSD fuel (<15 ppm) was used in place of low-sulfur (308 ppm) diesel fuel, as shown in Figure 2.2. (Liu, *et al.*, 2007.) Thus, the significant reduction of sulfur content in diesel fuel resulting from the adoption of the ULSD fuel standards (<15 ppm) has further reduced fine particle emissions.

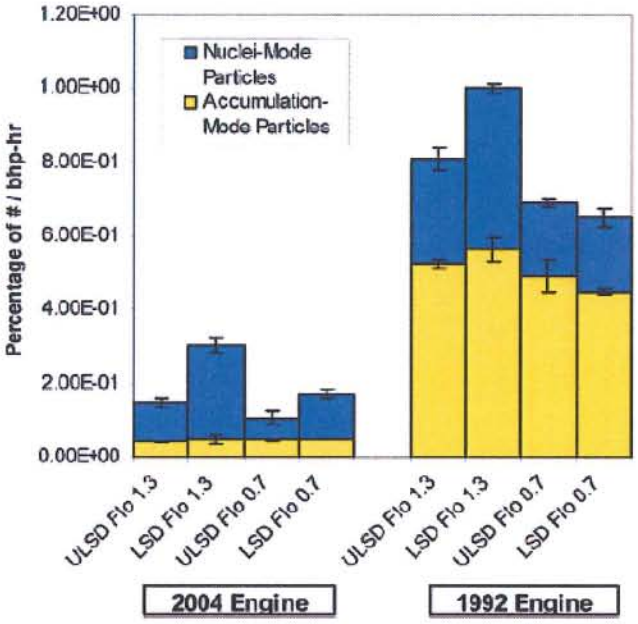


Figure 2.2. (Liu, et al., 2007, Figure 5.) Normalized total PM number emissions during entire FTP cycles for a 1992 TDE and a 2004 engine equipped with an EGR system operating on both ULSD and LSD fuel, with flow rates of 0.7 and 1.3 m3/s.

In sum, contrary to the concern that new diesel technologies (including DPFs) could augment the formation of particles, advanced engine systems operating on ULSD are highly efficient in suppressing if not completely eliminating the PM nucleation mode, and exhibit a 1000-fold reduction (or even more) in nucleation mode particles. (Biswas, *et al.*, 2008.) This, provides additional support for the conclusion that any evaluation that NTP might undertake of DEP will need to consider NTDE separately.

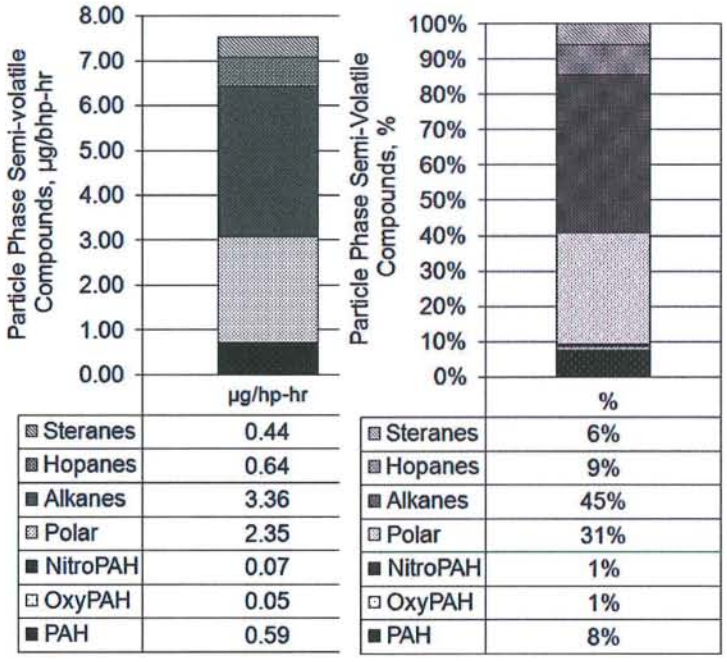
Premise No. 3:
The semi-volatile organic fraction of TDE is significant

NTP also assumed in 2000 that the sponge-like structure and large surface area of TDE particles made them an excellent carrier for organic compounds of low volatility, and that those compounds resided on the particulate surface (as a liquid) or were included inside the particle, or both. (RoC, 12th Ed., p. 154 (2011); Monograph 46, p. 48; EHC 171, pp. 101-103.) (*See also* Part A, p. A-10). Other assumptions were that the majority of the soluble organic fraction

("SOF") was absorbed onto the surface of the solid carbon core, that the SOF accounted for up to 45% of the total particulate mass, and that the SO_4 fraction of diesel exhaust PM could contribute up to 14 percent of the diesel exhaust particle. (*See, e.g.*, Monograph 46, p. 48; CARB Part A, p. A-10.)

The New Data Demonstrating That Premise No. 3 Does Not Apply To NTDE

The ACES Phase 1 study has demonstrated that the semi-volatile phase compounds contained in NTDE have been reduced to extremely low levels, accounting for only 1.4% of the organic carbon fraction. (See Figure 3.1, below.) Of that negligible amount, alkanes (45%) and polar compounds (31%) dominate. PAHs, hopanes and steranes are present in near-zero amounts, ranging from just 6%-9% of the already-miniscule semi-volative phase. NitroPAHs and oxyPAHs are present in even closer-to-zero amounts, a mere 1% of the semi-volatile phase.



	µg/hp-hr
Steranes	0.44
Hopanes	0.64
Alkanes	3.36
Polar	2.35
NitroPAH	0.07
OxyPAH	0.05
PAH	0.59

	%
Steranes	6%
Hopanes	9%
Alkanes	45%
Polar	31%
NitroPAH	1%
OxyPAH	1%
PAH	8%

Figure 3.1. Average Particle Phase Semi-volatile Emissions Rate and Composition for all Twelve Repeats of the 16-hour Cycles using all four 2007 ACES Engines.

Significantly, NTDE achieves better than 99% reductions for a wide variety of PAH compounds, including both semi-volatile low molecular weight three- to four-ring PAHs, as well as medium to higher molecular weight PAHs, which are generally below the detection limit. (Pakbin, *et al.*, 2009; Liu, *et al.*, 2008.) NTDE also achieves 96%-98% reductions in other particulate organic species, including n- alkanes, hopanes, and steranes. (Pakbin, *et al.*, 2009.) Similar reductions of C_1, C_2, and C_{10} through C_{33} particle-phase and semi-volatile organic compound species in NTDE are detailed below in Table 3.2. (Liu, *et al.*, 2010), and in the following figures from the reviews conducted by Hesterberg, et al (2011).

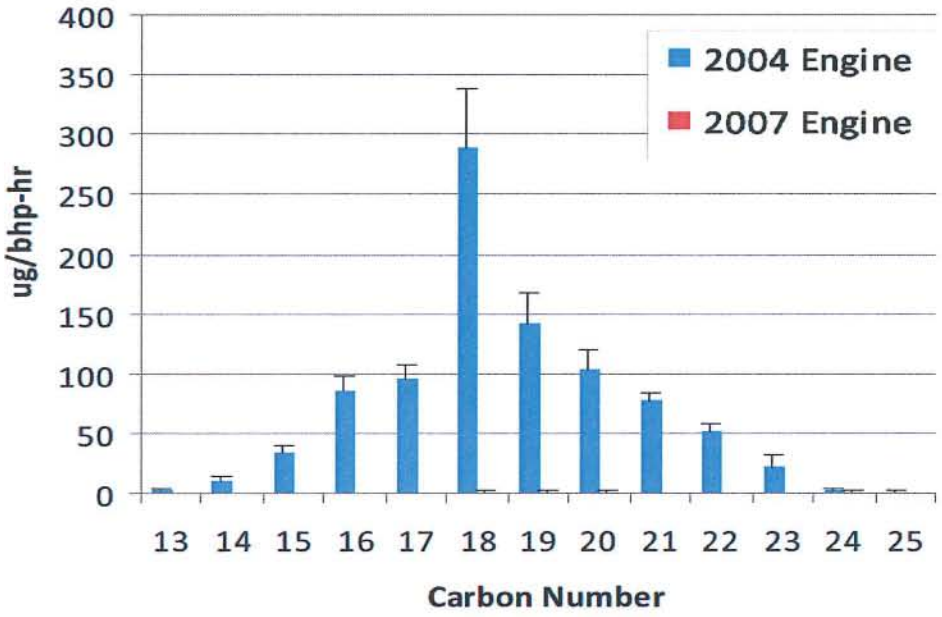
Table 3.2. (Liu, et al., 2010, Table 2.) Organic species emissions comparison from a 2004 HD diesel engine (fuel sulfur content of 308.5 ppm) without aftertreatment, and a 2007 HD diesel engine (fuel sulfur content of 9.2 ppm) equipped with a catalyzed DPF system.

Compound (carbon number)	2004 Engine[a]			2007 Engine[a]			% Reduced
Elemental carbon	49 700	±	3550	150	±	38.2	99.7 ± 7.2
Organic carbon	37 800	±	4360	213	±	101	99.4 ± 11.8
Organic mass	45 300	±	5230	256	±	121	99.4 ± 11.8
n-Alkanes							
n-Undecane (11)	< 0.01	±	2.97	1.04	±	1.76	–
n-Dodecane (12)	<0.01	±	0.795	0.279	±	0.286	–
n-Tridecane (13)	2.25	±	0.859	<0.01	±	0.186	>99.6 ± 46.4
n-Tetradecane (14)	10.4	±	2.64	<0.01	±	0.203	>99.9 ± 27.3
n-Pentadecane (15)	34.4	±	5.52	<0.01	±	0.00	>99.9 ± 16.0
n-Hexadecane (16)	84.6	±	13.4	<0.01	±	0.00	>99.9 ± 15.8
n-Heptadecane (17)	96.5	±	10.7	<0.01	±	0.193	>99.9 ± 11.3
n-Octadecane (18)	68.8	±	12.7	<0.01	±	0.413	>99.9 ± 19.1
n-Nonadecane (19)	52.3	±	10.0	<0.01	±	1.02	>99.9 ± 21.1
n-Eicosane (20)	75.0	±	7.46	<0.01	±	0.931	>99.9 ± 11.2
n-Heneicosane (21)	68.5	±	4.88	<0.01	±	0.348	>99.9 ± 7.6
n-Docosane (22)	48.1	±	4.63	<0.01	±	0.423	>99.9 ± 10.5
n-Tricosane (23)	19.3	±	8.48	<0.01	±	0.00	>99.9 ± 43.9
n-Tetracosane (24)	0.0127	±	2.37	<0.01	±	1.07	–
Branched alkanes							
Norpristane (18)	215	±	34.6	<0.01	±	0.754	>99.9 ± 16.4
Pristane (19)	89.4	±	14.6	<0.01	±	0.0725	>99.9 ± 16.4
Phytane (20)	28.3	±	9.02	<0.01	±	0.768	>99.9 ± 34.6
Saturated cycloalkanes							
Dodecylcyclohexane (18)	4.26	±	2.67	<0.01	±	0.00	>99.8 ± 62.7
Pentadecylcyclohexane (21)	8.92	±	1.91	<0.01	±	0.00	>99.9 ± 21.4
Hexadecylcyclohexane (22)	3.52	±	1.85	<0.01	±	0.00	>99.7 ± 52.6
Heptadecylcyclohexane (23)	3.53	±	1.05	<0.01	±	0.00	>99.7 ± 29.7
Octadecylcyclohexane (24)	1.02	±	1.02	<0.01	±	0.00	>99.0 ± 100
Nonadecylcyclohexane (25)	0.896	±	0.451	<0.01	±	0.00	>98.9 ± 50.3
Aromatics							
Biphenyl (12)	140	±	11.4	47.7	±	14.2	65.9 ± 18.3
2-Methylbiphenyl (13)	13.3	±	2.09	54.3	±	28.6	–
3-Methylbiphenyl (13)	288	±	29.5	152	±	64.0	47.2 ± 32.5
4-Methylbiphenyl (13)	62.5	±	5.52	18.8	±	5.10	69.9 ± 17.0
PAHs, POM, and Derivatives							
Naphthalene (10)	719	±	79.6	122	±	129	83.0 ± 29.0
2-Methylnaphthalene (11)	1290	±	144	82.7	±	52.1	93.6 ± 15.2
1-Methylnaphthalene (11)	543	±	52.5	46.1	±	26.1	91.5 ± 14.5
Dimethylnaphthalenes (12)	1460	±	113	89.0	±	18.6	93.9 ± 9.0

Trimethylnaphthalenes (13)	935	±	45.9	38.8	±	3.95	95.9 ± 5.3
1 Ethyl 2 methylnaphthalene (13)	115	±	14.1	4.25	±	1.18	96.3 ± 13.3
2-Ethyl-1-methylnaphthalene (13)	6.83	±	1.59	0.673	±	0.193	90.1 ± 26.1
Anthracene (14)	7.38	±	1.00	0.862	±	0.385	88.3 ± 18.8
Phenanthrene (14)	78.6	±	11.3	12.3	±	3.62	84.4 ± 19.0
Methylphenanthrenes (15)	85.4	±	9.49	3.30	±	0.460	96.1 ± 11.7
Dimethylphenanthrenes (16)	66.9	±	5.33	1.17	±	0.239	98.3 ± 8.3
Fluorene (13)	131	±	20.6	12.9	±	3.54	90.2 ± 18.4
Methylfluorenes (14)	0.00	±	0.00	10.9	±	3.91	–
Fluoranthene (16)	4.31	±	0.137	1.13	±	0.564	73.8 ± 16.3
Pyrene (16)	11.7	±	1.20	0.979	±	0.649	91.6 ± 15.8
Acenaphthalene (12)	30.5	±	1.88	2.18	±	1.42	92.9 ± 10.8
Acenaphthene (12)	45.5	±	6.55	22.0	±	21.1	51.6 ± 60.8
Chrysene + triphenylene (18)	1.05	±	0.133	0.123	±	0.109	88.3 ± 23.0
Benz[a]anthracene (18)	0.586	±	0.0579	0.0632	±	0.0698	89.2 ± 21.8
Benzo[g,h,i]fluoranthene (18)	0.607	±	0.593	0.258	±	0.270	57.5 ± 142
Benzo[b + k + j]fluoranthene (20)	0.240	±	0.0735	0.00776	±	0.00715	96.8 ± 33.6
Benzo[a]pyrene (20)	0.0797	±	0.0378	0.00613	±	0.00469	92.3 ± 53.3
Benzo[e]pyrene (20)	0.232	±	0.0575	0.00374	±	0.0983	98.4 ± 67.2
Benzo[g,h,i]perylene (22)	0.0724	±	0.0240	0.0168	±	0.00885	76.8 ± 45.4
Nitro-PAHs							
1-Nitronaphthalene (10)	0.361	±	0.0701	0.0858	±	0.0198	76.2 ± 24.9
2-Nitronaphthalene (10)	0.531	±	0.0896	0.0478	±	0.00914	91.0 ± 18.6
Methylnitronaphthalenes (11)	0.719	±	0.110	0.0232	±	0.00393	96.8 ± 15.8
2-Nitrobiphenyl (12)	0.0228	±	0.00974	0.00166	±	0.00087	92.7 ± 46.5
4-Nitrobiphenyl (12)	0.0103	±	0.00644	0.000117	±	0.00009	98.9 ± 63.4
1-Nitropyrene (16)	0.0550	±	0.0154	<0.00025	±	0.00	99.5 ± 28.0
9-Nitroanthracene (14)	0.192	±	0.00914	0.0403	±	0.00931	79.0 ± 9.6
Oxygenated PAHs							
Acenaphthenequinone (12)	29.1	±	2.68	0.945	±	1.49	96.8 ± 14.3
9-Fluorenone (13)	13.9	±	2.29	6.54	±	1.59	52.9 ± 27.9
Xanthone (13)	8.75	±	3.94	0.386	±	0.0908	95.6 ± 46.1
Compound (carbon number)	2004 Engine[a]			2007 Engine[a]			% Reduced
Perinaphthanone (13)	29.7	±	4.33	1.01	±	0.288	96.6 ± 15.5
Anthraquinone (14)	5.16	±	0.886	1.30	±	0.506	74.8 ± 27.0
9-Anthraaldehyde (15)	1.56	±	0.829	0.0388	±	0.0291	97.5 ± 55.0
Benzanthrone (17)	1.89	±	0.109	0.0154	±	0.00973	99.2 ± 6.3
Aliphatic aldehydes							
Formaldehyde (1)	5160	±	2440	<0.01	±	58.1	>99.9 ± 48.4
Acetaldehyde (2)	1480	±	783	<0.01	±	43.1	>99.9 ± 55.8
Hopanes							
17α(H)-22,29,30-Trisnorhopane (27)	0.430		0.0658	<0.01		0.00	97.7 ± 15.3
17α(H),21β(H)-Hopane (30)	1.67		0.0558	0.0109		0.0109	99.3 ± 4.0
22S-17α(H),21β(H)-29-Homohopane (31)	0.925		0.0309	<0.01		0.00	98.9 ± 3.3
22R-17α(H),21β(H)-29-Homohopane (31)	0.545		0.284	<0.01		0.00	98.2 ± 52.1
22S-17α(H),21β(H)-29,30-Bishomohopane (32)	2.11		1.60	<0.01		0.00	99.5 ± 75.8
22R-17α(H),21β(H)-29,30-Bishomohopane (32)	0.288		0.144	<0.01		0.00	96.5 ± 50.0
22R-17α(H),21β(H)-29,30,31-Trishomohopane (33)	5.33		5.33	<0.01		0.00	–
Steranes							
20S-5α(H),14α(H),17α(H)-Cholestane (27)	5.89		4.87	<0.01		0.00	99.8 ± 82.7
20R 5α(H),14β(H),17β(H) Cholestane (27)	0.576		0.0438	<0.01		0.00	98.3 ± 7.6
20S-5α(H),14β(H),17β(H)-Cholestane (27)	0.749		0.0729	<0.01		0.00	98.7 ± 9.7

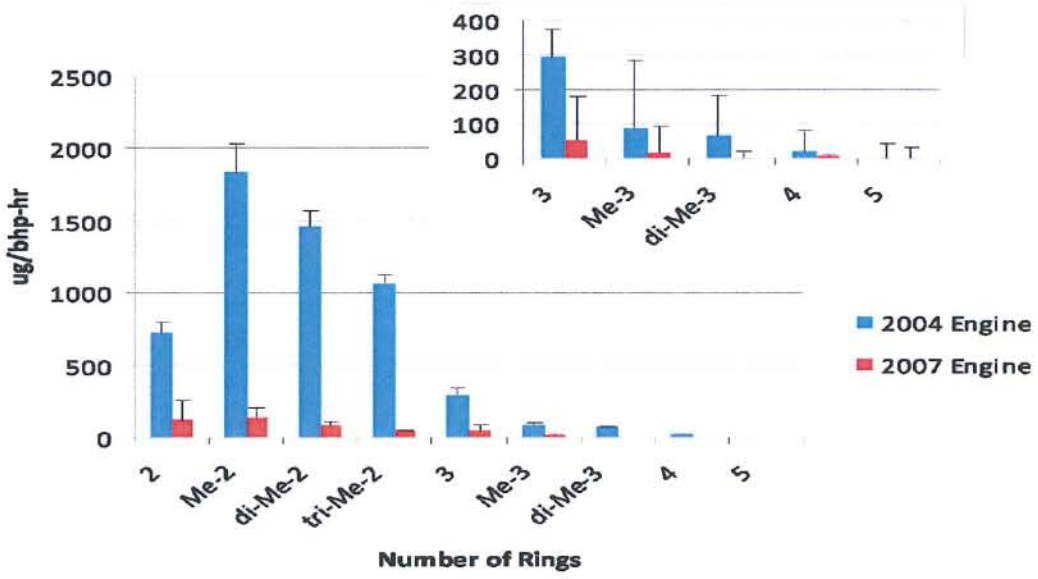
[a] Values are reported in μg (bhp*h)$^{-1}$, uncertainty is given as the standard error of the test results.

Particle-Phase and Semi-Volatile Alkanes and Cycloalkanes



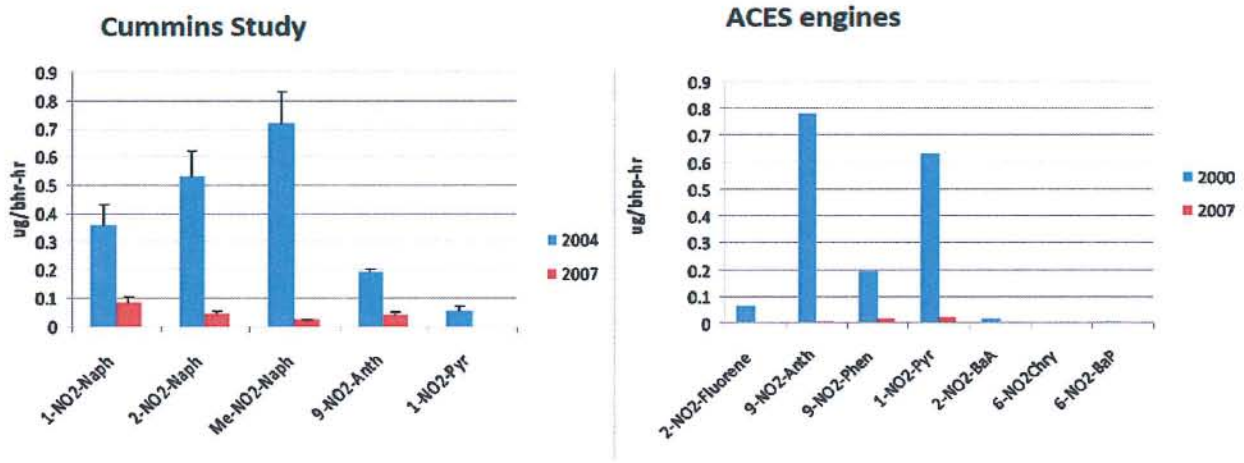
Liu at al., 2010

Polycyclic Aromatic Hydrocarbons (PAH)



Liu et al., 2010

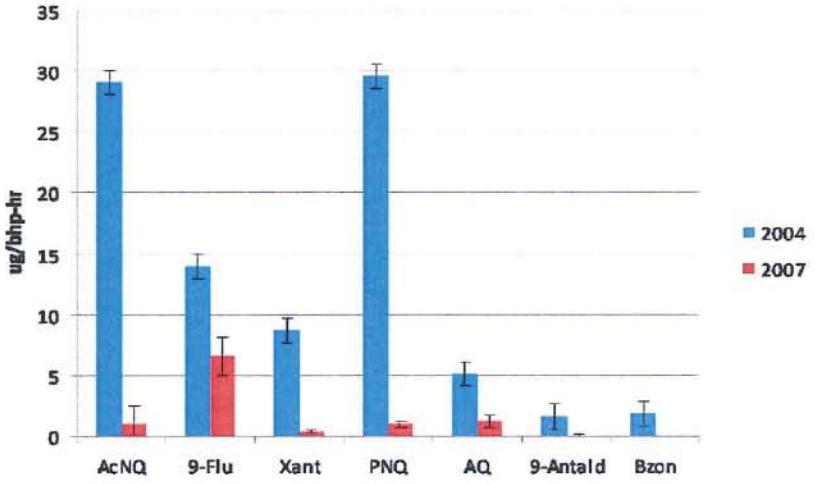
Nitro-PAH



Liu et al., 2010

Khalek et al, 2010

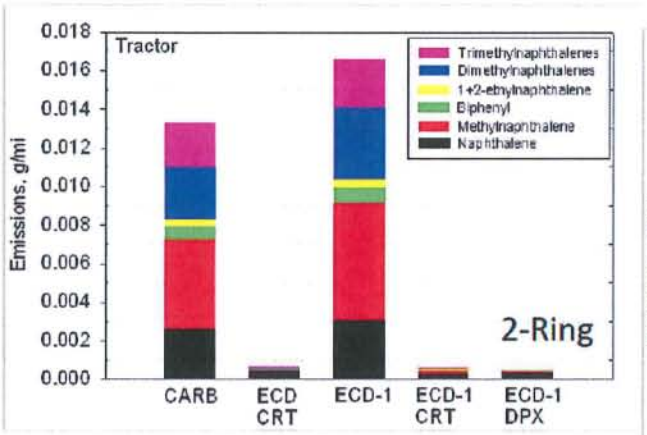
Oxy-PAH

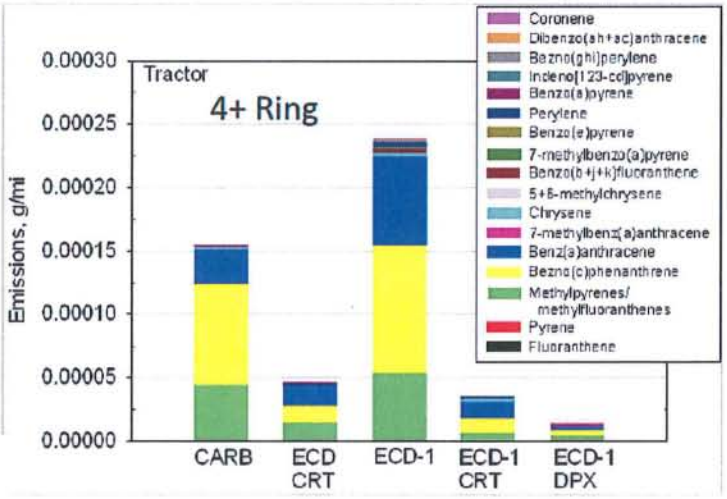


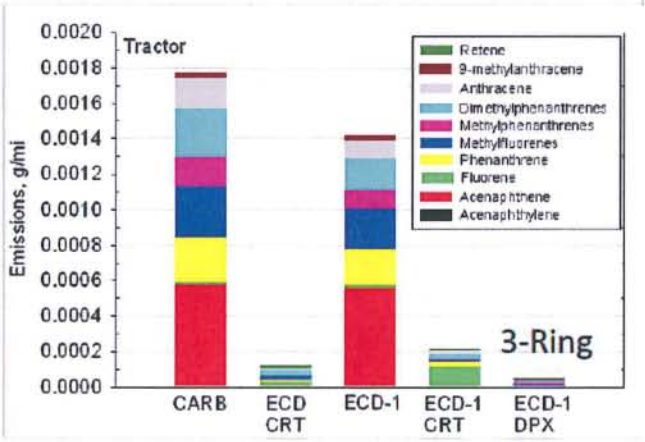
AcNQ:acenaphthenequinone; 9-Flu:9-fluorenone; Xant: xanthone; PNQ:perinaphthanone; AQ: anthraquinone; 9-antal: 9-anthraaldehyde; Bzon:benzanthrone

Liu et al., 2010

PAH Emissions from HDD Vehicles Retrofitted with DPF







Tractor: Grocery truck, 1999

CARB: CA diesel fuel, 114 ppm S

ECD, ECD-1: low S fuel (4.1 and 12.7 ppm)

CRT, DPX: Diesel particulate filters

Lev-On et al., SAE 02FFL-125, 2002

EC Diesel Study

As set forth in the following table of results from the ACES Phase 1 study (Table 3.3), and even using conservative estimates from the various measurement techniques used in the ACES program, NTDE has achieved very substantial reductions (71% to 99%) in the emissions of unregulated pollutants. Moreover, particle-bound trace metals and elements also have been reduced very significantly (by an average of 98%) in NTDE.

Table 3.3. (Khalek, et al., Table 6.) Summary of Average Unregulated Emissions for all Twelve Repeats of the 16-Hour Cycles for all four 2007 ACES Engines all four 2007 ACES Engines, and for 2004 Technology Engines used in CRC E55/E59 (Dioxins were compared to 1998 levels).

	2007[a] Engines Avg., mg/hp-hr	2007[a] Engines Std dev, mg/hp-hr	2007 Engines Avg., mg/hr	2007 Engines Std dev., mg/hr	2004 Engines Avg., mg/hr	2004 Engines Std dev., mg/hr	Avg. % Reduction Relative to 2004 Technology Engines
Single Ring Aromatics	0.76	0.35	71.6	32.97	405.0	148.5	82%
PAH	0.74	0.25	69.7	23.55	325.0	106.1	79%
Alkanes	1.64	0.83	154.5	78.19	1030.0	240.4	85%
Hopanes/Steranes	0.0011	0.0013	0.1	0.12	8.2	6.9	99%
Alcohols and Organic Acids	1.14	0.27	107.4	25.43	555.0	134.4	81%
Nitro-PAH	0.0065	0.0028	0.1	0.03	0.3	0.0	81%
Carbonyls	2.68	1.0	255.3	95.25	12500.0	3535.5	98%
Inorganic Ions	0.98	0.4	92.3	37.68	320.0	155.6	71%
Metals and Elements	0.071	0.032	6.7	3.01	400.0	141.4	98%
OC	0.56	0.5	52.8	47.10	1180.0	70.7	96%
EC	0.24	0.05	22.6	4.71	3445.0	1110.2	99%
Dioxins/Furans	6.6E-07	5.5E-07	6.2E-05	5.2E-05	N/A	N/A	99%[b]

[a] Data shown in brake-specific emissions for completeness. No 2004 brake-specific emissions data are available
[b] Relative to 1998 technology engines

Further, and as detailed in the table set forth below (Table 3.4, prepared from the ACES Phase 1 data), NTDE contains 80%-99% less PAHs. PAHs with more than four rings (except fluoranthene and pyrene) have been reduced below the detection limit, and nitroPAH compounds have been reduced by 99%.

Table 3.4. (Khalek, et al., Table 8.) PAH and nitroPAH Average Emissions for all Twelve Repeats of the 16-Hour Cycles for all four 2007 ACES Engines, and for 2000 Technology Engine Running Over the FTP Transient Cycle.

PAH and nitroPAH Compounds	[a]2007 Engines mg/bhp-hr	2000 Technology Engine mg/bhp-hr	% Reduction
Naphthalene	0.0982000	0.4829	80
Acenaphthylene	0.0003000	0.0524	>99
Acenaphthene	0.0004000	0.0215	98
Fluorene	0.0013000	0.0425	97
Phenanthrene	0.0055000	0.0500	89
Anthracene	0.0004000	0.0121	97
Fluoranthene	0.0003000	0.0041	93
Pyrene	0.0004000	0.0101	96
Benzo(a)anthracene	<0.0000001	0.0004	>99
Chrysene	<0.0000001	0.0004	>99
Benzo(b)fluoranthene	<0.0000001	<0.0003	>99
Benzo(k)fluoranthene	<0.0000001	<0.0003	>99
Benzo(e)pyrene	<0.0000001	<0.0003	>99
Benzo(a)pyrene	<0.0000001	<0.0003	>99
Perylene	<0.0000001	<0.0003	>99
Indeno(123-cd)pyrene	<0.0000001	<0.0003	>99
Dibenz(ah)anthracene	<0.0000001	<0.0003	>99
Benzo(ghi)perylene	<0.0000001	<0.0003	>99
2- Nitrofluorene	0.00000090	0.0000650	99
9-Nitroanthracene	0.00000310	0.0007817	>99
2-Nitroanthracene	<0.00000001	0.0000067	>99
9-Nitrophenanthrene	0.00001530	0.0001945	92
4-Nitropyrene	<0.00000001	0.0000216	>99
1-Nitropyrene	0.00002000	0.0006318	97
7-Nitrobenz(a)anthracene	0.00000020	0.0000152	99
6-Nitrochrysene	<0.00000001	0.0000023	>99
6-Nitrobenzo(a)pyrene	<0.00000001	0.0000038	>99
[a] The significant figures signify the detection limit for in mg/bhp-hr			

More recently, other studies have demonstrated that there is no significant risk of elevated levels of polychlorinated dibenzodioxins or polychlorinated dibenzofurans (PCDD/Fs) emissions over Cu-Zeolite SCR systems. (Laroo, 2010.)

Thus, the emission compounds of potential concern have been reduced to truly negligible near-zero levels in NTDE, and NTDE aftertreatment systems are not catalyzing the formation of other potential contaminants. The net result is that the amounts of both regulated and unregulated compounds contained in NTDE are very similar to those found in the emissions from advanced-technology natural gas engines equipped with catalyzed mufflers. (Hesterberg, *et al.*, 2008.)

All of these data confirm that another of the original foundational premises for NTP's assessment of DEP no longer applies, which provides additional support for the conclusion that NTP will need to assess NTDE separately.

Premise No. 4:
TDE particles carry biologically relevant amounts of potential genotoxins

Another core assumption regarding TDE/DEP was that "a variety of mutagens and carcinogens, such as PAHs and nitro-PAHs, are absorbed by the particulates." (RoC, 12th Ed., p. 154 (2011); EHC 171, p. 101; Monograph 46, p. 48.) In addition, particulate matter had been associated with approximately 50 to 90 percent of the mutagenic potency of whole diesel exhaust. (CARB Staff Report ("ISOR"), p. 6; CARB Board Resolution, p. 3.) Significantly, however, much of the information regarding the genotoxicity of TDE was obtained using diesel exhaust particles or extracts of diesel exhaust particles. (*See, e.g.*, Monograph 46, pp. 120-121; OEHHA "Part B" Health Risk Assessment (hereinafter, "Part B"), p. 1-4.) While recognizing that the bioavailability of those genotoxins had been questioned, regulatory agencies such as CARB concluded that it appeared that the organic chemicals adsorbed onto the particles, particularly the genotoxic components, were likely to be bioavailable in humans. (Part B, p. 1-5.)

The New Data Demonstrating That Premise No. 4 Does Not Apply to NTDE

As detailed above, studies utilizing DEP extracts are of very limited relevance, since the adsorbed mutagens of concern are generally not considered to be bioavailable. In addition, the nature and composition of diesel exhaust particles in NTDE have changed, especially since 2000. The solid carbon core has been virtually eliminated from NTDE. Instead, nanoparticle emissions in NTDE have a sulfate-rich composition because they are primarily associated with the nucleation of sulfates downstream from the aftertreatment systems. (Tobias, *et al.*, 2001.) Thus, especially when considered in light of the near-zero emission levels of the organic compounds found in NTDE (if found at all), the earlier findings relating to DEP and their extracts (which are of limited relevance to begin with) are not germane to NTDE. (Hesterberg, *et al.*, 2011.)

Premise No. 5:
New-technology diesel engines reduce public exposure to potentially harmful emissions

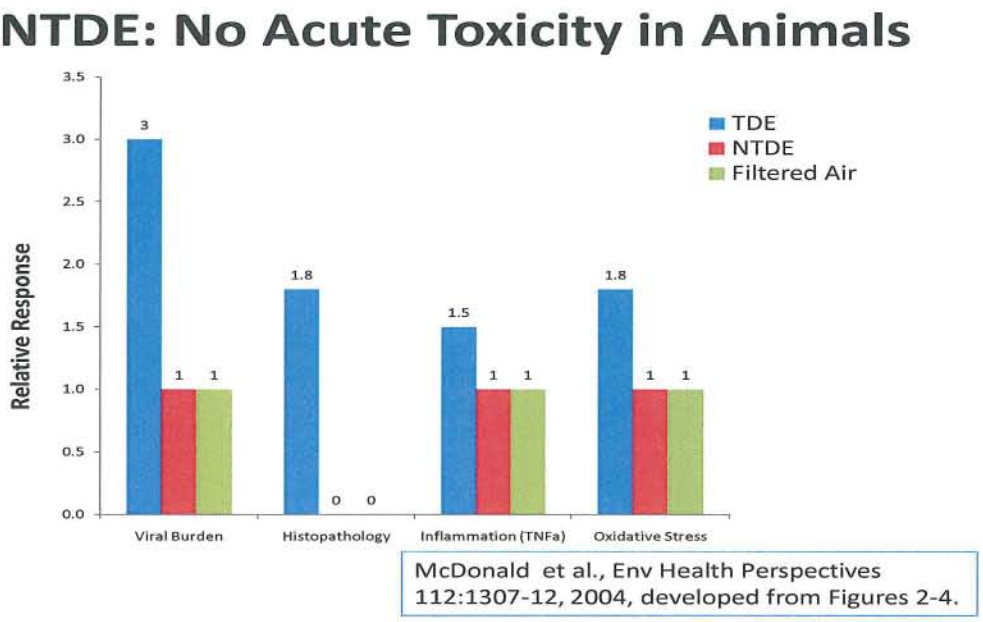
Over the past two decades, many regulatory agencies have encouraged further research to quantify the amounts of specific compounds emitted from a variety of engine technologies, operating cycles, and fuel to characterize better any differences between old and new diesel fuels and technologies. (*See* Scientific Review Panel Cover Letter for the CARB TAC Listing, dated May 27, 1998.) These agencies have similarly stressed (as did EPA in the 2002 Diesel HAD) that recognition should be given to the changes in diesel engine technology and fuel formulations that may reduce public exposure to harmful combustion constituents. (CARB Board Resolution, p. 3.)

The New Data Confirming Premise No. 5

As detailed in these comments, significant research has been conducted since 2000 regarding the progressive changes in diesel technology, fuel and emissions. That research demonstrates that the DEP in NTDE are quantitatively and qualitatively different from what NTP assumed to be the case in 2000.

In addition, two recent human controlled-exposure studies have examined the potential health effects that could be associated with exposures to NTDE. (*See* Barath, *et al.*, 2009; Lundbäck, *et al.*, 2009.) As described in those studies, researchers in Sweden have conducted human clinical experiments of vasometer function and thrombus function using exhaust from a diesel engine retrofitted with a commercially available DPF. Barath, *et al.*, have reported that the use of a DPF reversed the elevations in thrombus formation, while Lundbäck, *et al.*, have reported that the use of a DPF did not cause the type of interference with response to vasodilators that was observed for unfiltered diesel exhaust exposures. (Lucking, *et al.*, 2011.) (*See also* Mills, *et al.*, 2011 (diesel exhaust inhalation does not impact on heart rate variability or induce autonomic dysfunction).)

Similar results have been observed in a laboratory animal study comparing diesel exhaust with and without a DPF. Specifically, McDonald, *et al.*, (2004), investigated the relative toxicity of acute inhalation exposures (6 hours per day over 7 days) to TDE and to NTDE (generated from an engine equipped with a DPF and operated on ULSD) based on a number of sensitive markers of acute lung toxicity in mice, including lung inflammation, RSV resistance, and oxidative stress. The investigators reported that any observed effects for each of the measures of lung toxicity were either nearly or completely eliminated in the case of NTDE.



Recent *in vitro* studies also have investigated the comparatively beneficial effects observed for NTDE. For example, recent studies have shown that NTDE yields a 98% reduction in oxidative potential, and also has been found to have oxidative potential that is similar to advanced ultra-clean gasoline vehicle exhaust, as depicted in Figure 5.2 below. (Cheung, *et al.*, 2009.)

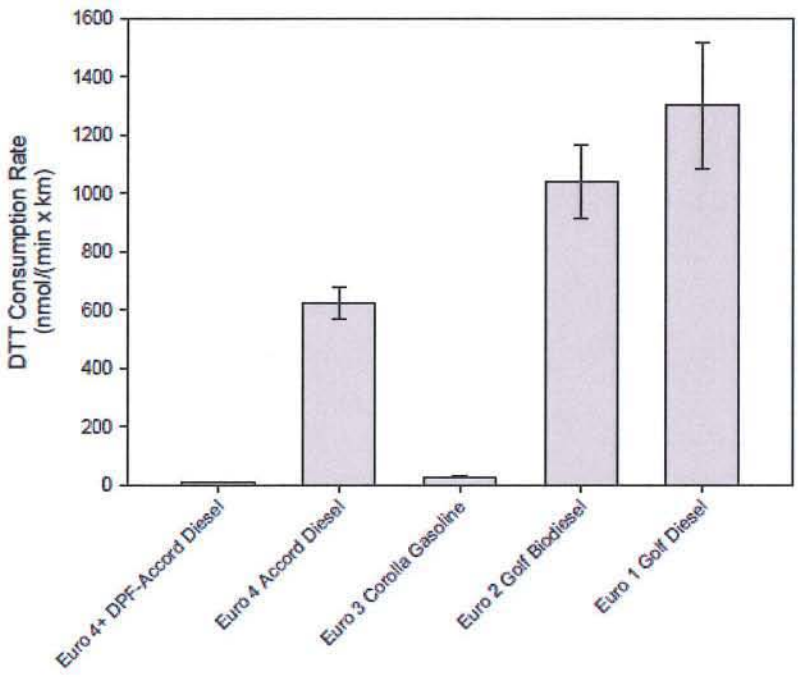


Figure 5.2. Measured oxidative potential, as assessed based on dithiothreitol (DTT) consumption for liquid particle suspensions in a cell-free chemical assay, for different light-duty vehicle types (data from Cheung *et al.*, 2009).

Further, and as depicted below in Figure 5.3, other studies have reported 2 to 3-times higher levels of specific mutagenic activity for the particulate component of CNG exhaust (which is not a TAC) when compared against NTDE. The mutagen emissions for CNG exhaust also are higher. (Okamoto, *et al.*, 2006.)

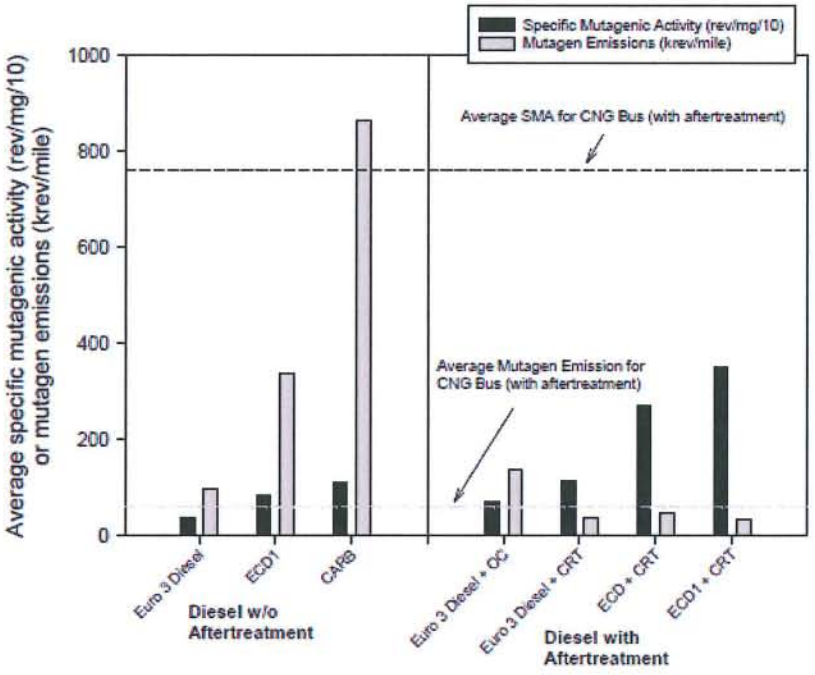


Figure 5.3. Results of Ames bacterial mutagenicity test results from the Finnish VTT study (Nylund *et al.*, 2004) of diesel buses with and without aftertreatment (Euro 3 buses) and from the CARB study (Kado *et al.*, 2005; Kado and Kuzmicky, 2003) of diesel buses with and without aftertreatment operated using three different diesel fuels (ECD, ECD1, and CARB fuels). Data shown are for the *Salmonella*strain TA98 with metabolic activation (+S9) and the particulate fraction only. Average CNG particle-associated mutagenic activity and emissions are from CARB testing (Okamoto *et al.*, 2006) of a CNG transit buses with aftertreatment (a catalyzed muffler).

In conclusion, all of the foregoing data and results establish that the original premises for NTP's characterization of DEP in 2000 no longer apply. NTDE does not contain high rates of PM. NTDE is not dominated by elemental carbon and a solid carbon core. NTDE does not contain significant amounts of TACs and HAPs. NTDE does not contain higher levels of smaller particles. NTDE does not contain significant amounts of semi-volatile organic compounds, and does not contain significant amounts of unregulated pollutants of concern. And, NTDE is not a unique carrier of genotoxic components.

Moreover, there are currently few health effects data of relevance to the chronic-exposure, carcinogenic potential of NTDE, although a chronic inhalation rat bioassay for NTDE is ongoing as part of the collaborative ACES efforts. There are no epidemiologic studies of direct relevance to NTDE and there may not be any for many years, not because populations have not been exposed to NTDE, but rather because historical exposures are entirely for TDE and current exposures continue to be a mixture of TDE and NTDE. In contrast, there are currently available an abundance of emissions characterization data, as well as preliminary toxicological data, relating to NTDE. As noted above, those data demonstrate major reductions in numerous regulated and unregulated exhaust constituents in NTDE, chemical and physical changes to the particles in DEP, and the elimination of some previously observed biological responses. Those data are clearly not sufficient to support a hazard or cancer risk classification for NTDE, and they also provide scientific justification for the independent evaluation of NTDE.

8. Conclusion

In sum, large and growing uncertainties and data gaps remain in the available knowledge base for DEP. Moreover, it is far from certain whether more study, including additional retrospective epidemiologic analyses (such as DEMS), will help to reduce those uncertainties. Consequently, NTP will need to assess carefully the actual quality and relevance of the available epidemiological and toxicological data as they pertain to DEP. Such an assessment, as elucidated above, will demonstrate that the available data remain insufficient to alter NTP's current characterization of the carcinogenic potential of DEP. Furthermore, it should be noted that TDE/DEP exposures will continue to diminish, as older diesel engines are increasingly retrofitted and ultimately replaced with post-2006 engines.

With respect to NTDE, while there may be data gaps regarding its hazard and risk potential, there is available a sizable body of data conclusively demonstrating that today's NTDE should not be viewed as the same substance as yesterday's DEP. The nature and composition of the DEP contained in NTDE are different, quantitatively and qualitatively, from the nature and composition of the DEP that NTP assessed in 2000. This well-established fact is the intended result of paradigm-shifting advancements in the regulation and control of diesel engine emissions since 2000. More importantly, the significant regulatory and technological advancements that have occurred over the past two decades with respect to diesel engine technologies have yielded the air quality and public health benefits that they were designed to achieve. This "win-win" result -- improved ultra-clean technologies and improved ultra-clean emissions -- has resulted in NTDE that requires a separate and distinct evaluation in any efforts that NTP undertakes to update the Report on Carcinogens.

Respectfully submitted,

TRUCK AND ENGINE MANUFACTURERS ASSOCIATION

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