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# Evaluation of carcinogenic hazard of diesel engine exhaust needs to consider revolutionary changes in diesel technology

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ABSTRACT

Diesel engines, a special type of internal combustion engine, use heat of compression, rather than electric spark, to ignite hydrocarbon fuels injected into the combustion chamber. Diesel engines have high thermal efficiency and thus, high fuel efficiency. They are widely used in commerce prompting continuous improvement in diesel engines and fuels. Concern for health effects from exposure to diesel exhaust arose in the mid-1900s and stimulated development of emissions regulations and research to improve the technology and characterize potential health hazards. This included epidemiological, controlled human exposure, laboratory animal and mechanistic studies to evaluate potential hazards of whole diesel exhaust. The International Agency for Research on Cancer (1989) classified whole diesel exhaust as – "probably carcinogenic to humans". This classification stimulated even more stringent regulations for particulate matter that required further technological developments. These included improved engine control, improved fuel injection system, enhanced exhaust cooling, use of ultra low sulfur fuel, wall-flow high-efficiency exhaust particulate filters, exhaust catalysts, and crankcase ventilation filtration. The composition of New Technology Diesel Exhaust (NTDE) is qualitatively different and the concentrations of particulate constituents are more than 90% lower than for Traditional Diesel Exhaust (TDE). We recommend that future reviews of carcinogenic hazards of diesel exhaust evaluate NTDE separately from TDE.


## 1. Introduction

Diesel engines have found increasingly wide application in industry and in the transportation of goods and people around the world from the time of invention of the technology by Rudolph Diesel in the 1890s to the present day. Rudolph Diesel, with an eye to the future, wrote on October 2, 1892 – "This machine is destined to completely revolutionize engine engineering and replace everything that exists" (Mollenhauer and Tschoeke, 2010). His prophecy was only partially realized during the first century of diesel technology development. He could not have anticipated the recent revolutionary advances that have been made in diesel engine and fuel technology in response to more stringent emission regulations. Those advances in technology and the resulting major reductions in diesel engine exhaust emissions are the subject of this paper.

Diesel engine exhaust is a complex mixture of carbon dioxide, oxygen, nitrogen, nitrogen compounds, carbon monoxide, water vapor, sulfur compounds and numerous low and high molecular weight hydrocarbons, and particulate matter. As will be related in this paper, the relative contribution of each of these compounds or classes of compounds have changed with advances in engine and fuel technology. A key concept well established in the internal combustion engine field is that emissions are influenced by both the engine (and exhaust after-treatment system) and the fuel being combusted. Pre-1980 diesel engines fueled with high sulfur content fuel produced exhaust that contained high concentrations of carbonaceous particulate matter with associated high concentrations of polycyclic aromatic hydrocarbons. The exhaust also contained high concentrations of nitrogen oxide ($NO_x$) and gas phase hydrocarbons. That exhaust was of concern because of its impact on visibility and for its potential health hazard. Concern for health impacts and especially, cancer intensified when it was discovered that organic solvent extracts of the exhaust particulate matter were mutagenic in the Ames bacterial assays.

The finding that extracts of diesel exhaust particulate matter contained mutagenic chemicals was viewed as presumptive evidence that exposure to diesel exhaust particulate matter could pose a carcinogenic hazard. This presumptive evidence had three related impacts. First, it stimulated a multi-faceted international research effort to clarify the potential health hazards of exposure to diesel exhaust. This included epidemiological studies, controlled

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human exposure studies, laboratory animal bioassays and mechanistic studies using both *in vivo* and *in vitro* approaches. The research findings were reported in the peer-reviewed literature and periodically integrated and evaluated to characterize human health hazards of exposure to diesel exhaust. Most significantly, health hazard assessments focusing on carcinogenic hazard were conducted by international organizations such as the International Agency for Research on Cancer (IARC) and national organizations such as the National Toxicology Program (NTP) in the United States. Second, the presumptive evidence of possible human health hazard stimulated the issuance of increasingly stringent regulations to limit diesel exhaust emissions and, in turn, ambient air concentrations and human exposures. Third, the regulations stimulated research and development efforts that led to the manufacture and marketing of new technology diesel engines that would meet those more stringent regulations.

In this paper, we briefly recount the key regulatory issues of concern for diesel engines and fuels, focusing on emission limits and the characterization of diesel exhaust with regard to its potential carcinogenicity. This paper focuses on regulations and standards promulgated in the United States. However, similar regulations were also promulgated in Europe and in other economically advanced countries around the world (Bauner et al., 2009). Thus, there has been regulatory pressure from around the globe to develop new technology diesel engines and fuels, which produce markedly lower exhaust emissions. Hesterberg et al. (2005) coined the term, "New Technology Diesel Exhaust" (NTDE) to describe the emissions from post-2006 diesel engines and from earlier model diesel engines retrofitted with exhaust after-treatment devices (filters and catalysts) and using ultra-low sulfur fuels. In contrast, Traditional Diesel Exhaust (TDE) refers to emissions from pre-1988 diesel engines sold and in use prior to the US EPA 2007 Heavy-Duty Diesel Emission Particulate Standards as well as the exhaust from transitional engines marketed from 1988 to 2006, a period of continuous improvements in diesel engine technology.

This paper describes the quantitative and qualitative differences between TDE and NTDE. The diesel exhaust particulate matter aggregates of elemental carbon nanoparticles with associated hydrocarbons, that is a prominent constituent in TDE, is shown in Fig. 1. The emissions of particulate mass in NTDE are substantially lower (less than 1%) than those emitted from 1988 engines. Most importantly, NTDE is virtually free of the elemental carbon particles found in TDE. The specific chemical constituents found in TDE are also substantially reduced in concentration in NTDE. The reductions in concentration are so profound that we recommend that future carcinogenic hazard reviews on diesel engine exhaust and its constituents, such as those to be conducted in the near future by IARC and the NTP, evaluate and classify the potential carcinogenic hazard of NTDE separately from that of TDE, either as whole diesel exhaust or as diesel exhaust particulates.

## 2. New regulations impacting on diesel exhaust emissions

In the United States, the stage was set for the development of improved, low emission diesel technology by passage of the Clean Air Act (CAA) Amendments of 1970 which substantially strengthened the regulatory authority available for dealing with ambient air quality (CAA, 1970). The US Environmental Protection Agency (EPA) was created by Executive Order almost simultaneously with passage of the CAA and began operation on December 2, 1970 (Nixon, 1970). The EPA was delegated the authority to implement the CAA's numerous provisions.

One section of the CAA, as amended, called for the establishment of National Ambient Air Quality Standards (NAAQS) for criteria pollutants, pollutants that come from multiple sources and are found across the United States. The criteria pollutants included particulate matter (PM), hydrocarbons (HC), nitrogen dioxide ($NO_2$), sulfur dioxide ($SO_2$), and carbon monoxide (CO), all of which were prominent constituents in the exhaust of ca. 1970 diesel engines. In addition, photochemical oxidants (with ozone later identified as the indicator) was listed as a criteria pollutant. Ozone is formed in the atmosphere in the presence of sunlight by chemical reactions among $NO_x$ and volatile organic compounds (VOCs), which are emitted in diesel exhaust.

Another section of the CAA provides for the regulation of hazardous air pollutants (HAPs), agents whose emissions are typically related to specific sources, through the setting national emission standards for hazardous air pollutants (NESHAPS). Very slow progress was made in the 1970s and 1980s in setting NESHAPs, in part, due to the challenge of establishing standards for agents that were identified as posing a potential carcinogenic hazard. This prompted a change with the CAA amendments of 1990 to an approach based on first implementing emission limits based on maximum achievable control technology on an industry sector-by-sector basis, for example, the pulp and paper industry (CAA, 1990). This was to be followed by an assessment of any residual risk that needed to be addressed through additional regulations and emission controls.

Other sections of the CAA specifically provide for setting standards for engine emissions including emission standards for diesel

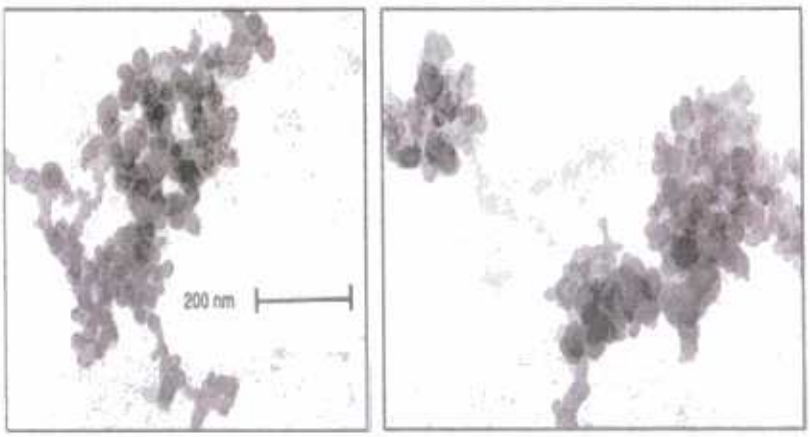


Fig. 1. Scanning electron micrograph of Traditional Diesel Exhaust particulate matter (from Mollenhauer and Tschoeke, 2010). Primary particles with diameters of less than 10 nm that rapidly aggregate to a size distribution that is log-normal and with median diameter of approximately 80–100 nm. The elemental carbon particles adsorb and absorb hydrocarbons, sulfates and trace metals.

engines. These standards are based on concern for the potential health effects of the emissions. However, the specific standards are not linked to achieving a specified, acceptable level of associated health risk, but rather have a strong technology-forcing character. In short, each progressively more stringent emission standard has been viewed as achievable with the advanced technology in hand or, in some cases, with an eye to new technology on the horizon or anticipated to be developed. Indeed, the progressively more rigorous diesel engine emission standards can be viewed as analogous to maximum achievable control technology standards.

Using the legislative framework of the CAA, the EPA has issued a series of regulations (Table 1) that have impacted the development and deployment of new technology diesel equipment and the use of improved diesel fuel. The myriad of regulations promulgated since the earlier IARC (1989) review can be summarized as follows:

(i) Diesel fuel sulfur levels for on-road vehicles have been reduced from 500 ppm and higher to less than 15 ppm.
(ii) Heavy-duty on highway (HDOH) diesel engine PM emission standards have been reduced by 90%, from 0.10 g/bhp-hr to 0.01 g/bhp-hr (Fig. 2).
(iii) HDOH diesel engine $NO_x$ emission standards have been reduced by more than 90%, from 4.0 g/bhp-hr to 0.20 g/bhp-hr (Fig. 3).
(iv) Non-road diesel engine PM emission standards have been reduced by more than 90%, from 0.60 g/bhp-hr to 0.01 (or 0.02) g/bhp-hr.
(v) Non-road diesel engine $NO_x$ emission standards have been reduced by more than 90%, from approximately 5.6 g/bhp-hr (or higher) to 0.30 g/bhp-hr.

The issuance of these increasingly stringent emission standards has been bolstered by changes over the last four decades in the National Ambient Air Quality Standards (NAAQS) for particulate matter (PM) (Table 2), Ozone ($O_3$) (Table 3) and nitrogen dioxide ($NO_2$). Each of the NAAQS consists of four elements: indicator, averaging time, concentration and statistical form; the latter two

**Table 1**
Summary of Key Regulations in the USA that have stimulated the development of improved diesel engine technology and fuels with markedly reduced exhaust emissions (see website of EPOA's Office of Transportation and Air Quality for details (<http://www.epa.gov/otaq/>).

| Year | Regulation |
|---|---|
| 1968 | First "smoke standard" promulgated for on-road heavy-duty diesel engines (HDDE) |
| 1970 | Clean Air Act Amendments passed with provision for establishing National Ambient Air Quality Standards (NAAQS) for criteria pollutants, regulation of hazardous air pollutants and provisions for setting emission limits for sources including diesel-powered equipment |
| 1971 | EPA issues NAAQS for Particulate Matter (PM), Photochemical Oxidants, Hydrocarbons (HC), nitrogen oxides ($NO_x$), Carbon Monoxide (CO) and Sulfur Dioxide ($SO_2$) |
| 1974 | EPA issues regulations for CO and combined HC + $NO_x$ emissions from HDDE |
| 1985 | EPA implements new $NO_x$ regulation (10.7 g/bhp-hr) for on-road HDDE to replace combined HC and $NO_x$ standard |
| 1987 | EPA issues regulations with reduced PM emission limits of 0.2 g/mile and 0.26 g/mile for light duty diesel cars and HDDE, respectively |
| 1991 | EPA issues regulations reducing PM emissions to 0.25 g/bhp-hr for HDDE in trucks and urban buses and reducing $NO_x$ emissions to 5.0 g/bhp-hr |
| 1993 | EPA reduced PM emissions to 0.1 g/bhp-hr and sets highway diesel fuel standards of less than 500 ppm sulfur and 35% by weight of aromatic hydrocarbons |
| 1994 | EPA reduces PM emissions limit to 0.1 g/bhp-hr and 0.07 g/bhp-hr for on-road HDDE for trucks and urban buses, respectively<br>EPA issues TIER 1 emission standards for CO, HC, PM, $NO_x$ and smoke emissions for non-road diesel engines at or above 37 kW. EPA TIER 1 standards for light-duty vehicles phased in 1994–1997 |
| 1997 | EPA establishes new emission limits for model year 2004 and later truck and bus HDDE, targeting $NO_x$ and non-methane HC (NMHC) using two alternative standards (either a combined $NO_x$ + NMHC limit of 2.4 g/bhp-hr, or a $NO_x$ limit of 2.5 gbhp-hr and a NMHC limit of 0.50/bhp-hr<br>EPA promulgates exhaust emission standards for $NO_x$, HC, CO, PM and smoke for newly manufactured and re-manufactured locomotives and locomotive engines<br>EPA issues NAAQS for PM using Particulate Matter 2.5 μm ($PM_{2.5}$) as indicator |
| 1998 | EPA sets emission standards for new diesel engines used in non-road construction, agricultural, airport and industrial equipment and certain marine applications |
| 1999 | EPA sets $NO_x$ and PM emission standards for large marine diesel engines in US waters |
| 2000 | EPA issues "2007 Heavy-Duty Highway Rule," establishing updated emission limits for 2004 and later heavy-duty engines and vehicles and highway diesel fuel (ultra-low sulfur diesel fuel with sulfur at or below 15 ppb)<br>Mine Safety and Health Administration (MSHA) issues final rule establishing diesel particulate matter (DPM) limits for underground metal and non-metal mines (400 μg total carbon/$m^3$ effective July 2002 and 160 μg/$m^3$ effective January 2006 |
| 2002 | EPA issues first emission standards (combined HC + $NO_x$, PM, and CO) for recreational marine diesel engines over 37 kW |
| 2003 | EPA issues final rule for $NO_x$ for new (2004 or later) commercial marine diesel engines (Categories 1, 2 and 3)<br>Clean School Bus USA program initiated to reduce children's exposure to diesel exhaust |
| 2005 | MSHA issues final rule with revisions to its DPM concentration limits for underground metal and non-metal miners, replacing the interim DPM concentration limit with a permissible exposure limit (PEL) of 380 μg/$m^3$ measured as elemental carbon (70 FR 32868) |
| 2006 | Effective year of US EPA's 2001 standard for highway ultra-low sulfur (15 ppm) diesel fuel (ULSD)<br>MSHA publishes a final rule phasing in the DPM final concentration limit of 160 (Total Carbon) μg/$m^3$ over a two-year period based on feasibility with a final commence data of May 20, 2008 |
| 2007 | US EPA 2001 PM emissions standard for new heavy-duty engines 0.01 g/bhp-hr goes into effect, beginning of phase-in of updated standards for $NO_x$ and non-methane hydrocarbons (NMHC) of 0.20 g/bhp-hr and 0.14 g/bhp-hr. Nonroad diesel engines, including locomotive and smaller marine engines now required to use low sulfur (500 ppm) diesel fuel with eventual goal of using ultra-low sulfur (15 ppm) diesel fuel<br>EPA issues a more stringent $PM_{2.5}$ NAAQS, 24-h averaging time, reduced from 65 μg/$m^3$ to 35 μg/$m^3$ and maintain annual standard of 15 μg/$m^3$ |
| 2008 | US EPA finalizes more stringent emissions standards for locomotive and marine diesel engines including Tier 3 and Tier 4 standards intended to reduce PM and $NO_x$ emissions by 80–90% and the first national emission standards for existing marine diesel engines<br>EPA issues more stringent NAAQS for Ozone, reducing 4th highest 8-h average over 3 years from 84 ppb to 75 ppb |
| 2010 | USEPA 2001 updated $NO_x$ and NMHC emissions standards to be in full effect; USEPA finalizes rule adding two new tiers of Category 3 (C3) marine diesel engine emission standards (Tier 2 and Tier 3 standards for $NO_x$, HC, and CO) and revising its standards for marine diesel fuels produced and distributed in the United States; Non-road diesel engines now required to use ultra-low sulfur (15 ppm) diesel fuel |
| 2011 | EPA revises rules for standards of performance for new stationary compression ignition (diesel) internal compression engines differentiating between engines with displacement greater than or equal to 10 l per cylinder and less than 30 l per cylinder and engines with displacement at or above 30 l per cylinder and also engines operating in remote areas of Alaska |
| 2012 | Effective year for requirement that locomotives and smaller marine engines use ultra-low sulfur (15 ppm) diesel fuel |

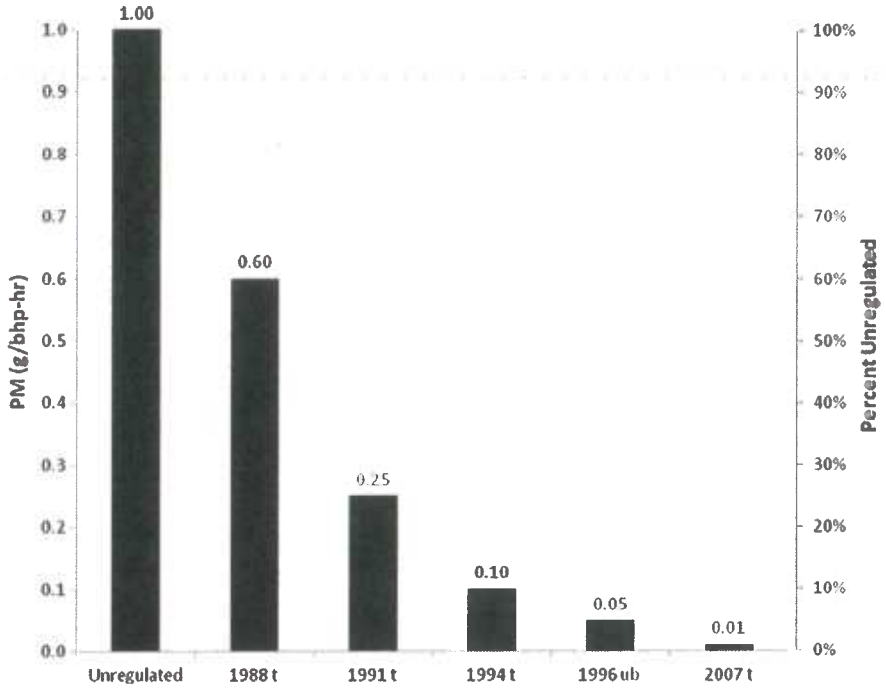


**Fig. 2.** US EPA particulate emission standards for heavy-duty or road diesel trucks (t) or urban buses (ub) in grams per brake-horse power hour (g/bhp-hr) on the left and as % of "unregulated" engine emission on the right. For purposes of use of metric units, 1 hp = 0.7457 kW.

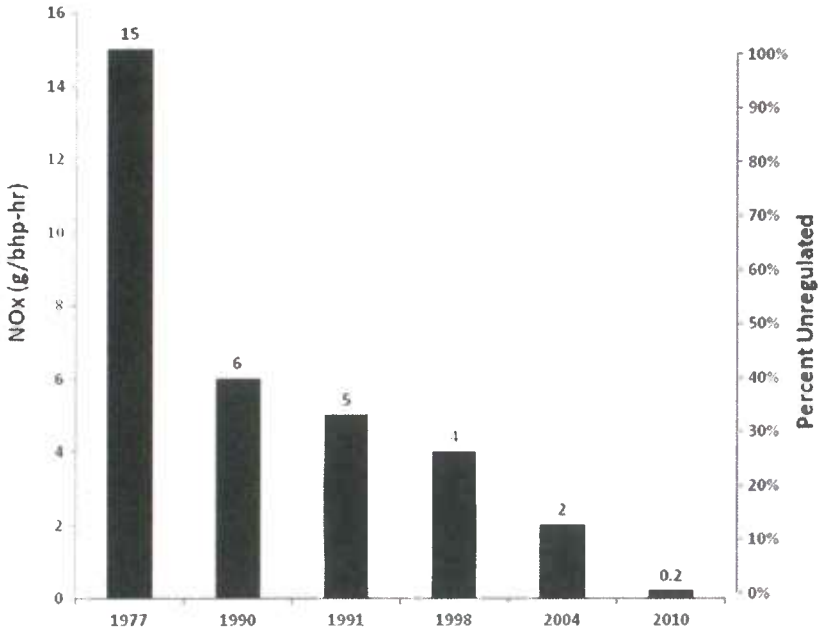


**Fig. 3.** US EPA $NO_x$ emission standards for heavy-duty on-road diesel engines in grams per brake horse power hour (g/bhp-hr) on the left and as % of "unregulated" emissions on the right. For purpose of use of metric units, 1 hp = 0.7457 kW.

elements together determine the stringency of the standard. As may be noted in **Table 2**, the indicator for the initial PM NAAQS set in 1971 was total suspended particulates (TSP) (essentially all particles that are sampled with a high-volume sampler which includes particles up to about 40 μm in aerodynamic diameter). In 1987, the indicator was changed to particulate matter, 10 μm aerodynamic diameter ($PM_{10}$). In 1997, a second PM indicator was added, particulate matter, 2.5 μm aerodynamic diameter ($PM_{2.5}$). In 2006, the $PM_{10}$ NAAQS was revoked.

The particles contained in TDE are less than 2.5 μm. **Kittelson (1998)** reported that TDE is composed of particles in three distinct modes: nucleation (3–30 nm), accumulation (30–500 nm) and coarse (larger than 500 nm) mode. The majority of the particulate mass is in the nucleation and accumulation modes with only 5–20% of the mass in particles greater than 500 nm. Because of their size, the exhaust particles in TDE are present in the TSP, $PM_{10}$ and $PM_{2.5}$ size functions. However, as the indicator for the particulate matter NAAQS shifts from TSP to $PM_{10}$ to $PM_{2.5}$, a constant concen-

**Table 2**
History of the US EPA National Ambient Air Quality Standards for particulate matter during the period 1971–2011 (EPA, 2012a).

| Final rule | Primary/secondary | Indicator | Averaging time | Level[a] | Form |
|---|---|---|---|---|---|
| 1971 36 FR 8186 April 30, 1971 | Primary | TSP[b] | 24-h | 260 μg/m$^3$ | Not to be exceeded more than once per year |
| | | | Annual | 75 μg/m$^3$ | Annual average |
| | Secondary | TSP | 24-h | 150 μg/m$^3$ | Not to be exceeded more than once per year |
| 1987 52 FR 24634 July 1, 1987 | Primary and secondary | $PM_{10}$ | 24-h | 150 μg/m$^3$ | Not to be exceeded more than once per year on average over a 3-year period |
| | | | Annual | 50 μg/m$^3$ | Annual arithmetic mean, averaged over 3 years |
| 1997 62 FR 38652 July 18, 1997 | Primary and secondary | $PM_{2.5}$ | 24-h | 65 μg/m$^3$ | 98th percentile, averaged over 3 years |
| | | | Annual | 15.0 μg/m$^3$ | Annual arithmetic mean, averaged over 3 years[c,d] |
| | | $PM_{10}$ | 24-h | 150 μg/m$^3$ | Initially promulgated 99th percentile, averaged over 3 years; when 1997 standards for $PM_{10}$ were vacated, the form of 1987 standards remained in place (not to be exceeded more than once per year on average over a 3-year period)[e] |
| | | | Annual | 50 μg/m$^3$ | Annual arithmetic mean, averaged over 3 years |
| 2006 71 FR 61144 October 17, 2006 | Primary and secondary | $PM_{2.5}$ | 24-h | 35 μg/m$^3$ | 98th percentile, averaged over 3 years[f] |
| | | | Annual | 15.0 μg/m$^3$ | Annual arithmetic mean, averaged over 3 years[b,g] |
| | | $PM_{10}$ | 24-h[h] | 150 μg/m$^3$ | Not to be exceeded more than once per year on average over a 3-year period |

[a] Units of measure are micrograms per cubic meter of air (μg/m$^3$).
[b] TSP = total suspended particles.
[c] The level of the annual standard is defined to one decimal place (i.e. 15.0 μg/m$^3$) as determined by rounding. For example, a 3-year average annual mean of 15.04 μg/m$^3$ would round to 15.0 μg/m$^3$ and, hence, violate the annual standard (40 CFR part 50 Appendix N).
[d] The level of the standard was to be compared to measurements made at sites that represent "community-wide air quality" recording the highest level, or, if specific requirements were satisfied, to average measurements from multiple community-wide air quality monitoring sites ("spatial averaging").
[e] See 69 FR 45592, July 30, 2004.
[f] The level of the 24-h standard is defined as an integer (zero decimal places) as determined by rounding. For example, a 3-year average 98th percentile concentration of 35.49 μg/m$^3$ would round to 35 μg/m$^3$ and thus meet the 24-h standard and a 3-year average of 35.50 μg/m$^3$ would round to 36 and, hence, violate the 24-h standard (40 CFR part 50 Appendix N).
[g] The EPA tightened the constrains on the spatial averaging criteria by further limiting the conditions under which some areas may average measurements from multiple community-oriented monitors to determine compliance (see 71 FR 61165–61167).
[h] The EPA revoked the annual $PM_{10}$ NAAQS in 2006.

**Table 3**
History of the US EPA National Ambient Air Quality Standards for ozone during the period 1971–2010 (EPA, 2012b).

| Final rule/decision | Primary/secondary | Indicator[a] | Averaging | | Form |
|---|---|---|---|---|---|
| | | | Time | Level[b] | |
| 1971 36 FR 8186 April 30, 1971 | Primary and secondary | Total photochemical oxidants | 1-h | 0.08 ppm | Not to be exceeded more than one hour per year |
| 1979 44 FR 8202 February 8, 1979 | Primary and secondary | $O_3$ | 1-h | 0.12 ppm | Attainment is defined when the expected number of days per calendar year, with maximum hourly average concentration greater than 0.12 ppm, is equal to or less than 1 |
| 1993 58 FR 13008 March 9, 1993 | EPA decided that revisions to the standards were not warranted at the time | | | | |
| 1997 62 FR 38856 July 18, 1997 | Primary and secondary | $O_3$ | 8-h | 0.08 ppm | Annual fourth-highest daily maximum 8-h concentration, averaged over 3 years |
| 2008 73 FR 16483 Mar 27, 2008 | Primary and secondary | $O_3$ | 8-h | 0.075 ppm | Annual fourth-highest daily maximum 8-h concentration, averaged over 3 years |

[a] $O_3$ = ozone.
[b] Units of measure are in parts per million (ppm).

tration of TDE particulate matter in the sampled air represents a larger portion of the sampled PM as the indicator shifts to smaller particles. As a result, each change in the indicator for the PM NAAQS has led to increased pressure on reducing diesel exhaust particulate emissions, since they represent a greater portion of the PM inventory that might potentially be controlled. For example, 1 μg of TDE/m$^3$ as a portion of the annual NAAQS set for TSP (1971) at 75 μg/m$^3$, for $PM_{10}$ (1987) at 50 μg/m$^3$ and for $PM_{2.5}$ (1997) at 15 μg/m$^3$, represents 1.3%, 2.0% and 6.7%, respectively, of the annual standard. The PM NAAQS set in 2006 is currently under review as part of the periodic updating of each NAAQS specified by the CAA. That review has focused on potential additional reductions in the annual $PM_{2.5}$ NAAQS now set at 15 μg/m$^3$ and, perhaps, the 24-h $PM_{2.5}$ NAAQS now set at 35 μg/m$^3$. The review process has been delayed and is now scheduled to be completed in 2013. Any increase in the stringency of the $PM_{2.5}$ NAAQS will bring increased pressure on reducing all sources of $PM_{2.5}$ including diesel exhaust particulate emissions.

In the case of the NAAQS for photochemical oxidants, the indicator and associated measurement methods set in 1971 for photochemical oxidants was changed in 1979 to Ozone. The averaging time was changed in 1997 from the highest 1-h concentration to

the highest 8-h average concentration. The changes in the NAAQS for Ozone have not been as dramatic as for PM. However, the level and statistical form of the 8-h averaging time standard needs to be considered within the context of natural background concentrations of ozone. Wang et al. (2009) used a global chemical transport model (GEOS-Chem) with a 1° times 1° horizontal resolution to quantify daily maximum 8-h average concentrations in the US surface air. They found that eliminating US anthroprogenic emissions of Ozone precursors ($NO_x$) and volatile organic compounds would maintain surface Ozone concentrations in the US below 60 ppb at all times. Zhang et al. (2011) extended the modeling of Wang et al. (2009) using a horizontal resolution of 1/2° times 2/3°. They found background ozone (4th highest 8-h average) concentrations exceeding 60 ppbv in the Intermountain Western US and suggested this region would require special consideration if the Ozone NAAQS were revised to the 60–70 ppbv range as has been proposed. The NAAQS for Ozone is currently under review as part of the periodic 5-year review cycle specified by the CAA. McClellan (2011) has provided perspective on the Ozone NAAQS review which has focused on reductions from 75 ppb, the highest 8-h average NAAQS set in 2008, to 60–70 ppb, with attainment based on the fourth highest daily maximum 8-h concentration, averaged over 3 years. That review should be completed in 2013 or 2014. Needless to say, the increased stringency of the Ozone NAAQS, and the potential for an even more stringent standard will place more pressure on reducing $NO_x$ and VOC emissions from all sources, including diesel engines.

The original NAAQS for $NO_2$ was set in 1971 with $NO_2$ as the indicator, an annual averaging time, a level of 53 ppb and a form based on the annual arithmetic average. The $NO_2$ NAAQS was re-evaluated in 1985 and 1996 and retained without revisions. In 2010, the $NO_2$ NAAQS was revised significantly. The primary annual $NO_2$ NAAQS was retained and a new 1-h averaging time standard was introduced with the level set at 100 ppb. The form was set at the 3-year average of the 98th percentile of the yearly distribution of 1-h daily maximum $NO_2$ concentrations. The 1-h standard places emphasis on reducing $NO_2$ emissions from on-road vehicles, including diesel-powered vehicles, in an effort to reduce ambient $NO_2$ levels near roadways.

The CAA (1970, 1990) delegates to the individual states responsibility for air quality programs to monitor the criteria air pollutants and, most importantly, to put in place programs to assure that the individual NAAQS are attained. The details of those programs are beyond the scope of this paper. Suffice it to note, the individual states that have areas whose air quality does not meet or attain the individual NAAQS must create state implementation plans (SIPs). The SIPs must outline a strategy for bringing non-attainment areas into attainment with each of the NAAQS. The activities developed and described in the SIPs extend to planning for changes in the deployment and use of technologies such as diesel engines whose emissions may impact on air quality.

By way of background, regulatory efforts to reduce emissions from gasoline-fueled vehicles preceded the major regulatory initiatives for diesel-fueled engines. The EPA clean fuel program established standards in 1973 that gradually reduced the amount of lead in gasoline (Colucci, 2004). The lower lead content reduced health risks in two ways. First, it directly reduced the exhaust emissions of lead, a known neurotoxicant. Second, elimination of lead in gasoline was critical to enabling the use of advanced after-treatment technologies such as 3-way catalytic converters that reduce the emissions of CO, $NO_x$ and hydrocarbons in exhaust from gasoline-fueled vehicles. The presence of even trace levels of lead in the fuel and, in turn, in the exhaust poisoned the catalyst in the exhaust treatment system rendering them ineffective. The CAA amendments of 1990 and EPA regulations banned lead in gasoline after 1995. If those changes had not been made, air quality improvement would not have occurred and the literature on gasoline exhaust related health effects might have been quite different in 1988 and today.

The reduced emissions from gasoline-fueled vehicles and associated reductions in human health hazards were already being viewed in 1988 as a technological success story. However, additional improvements in gasoline engine technology, reduction of the sulfur content of gasoline, and reformulation of gasoline have resulted in further reductions in emissions from gasoline-fueled vehicles. Colucci (2004) and Twigg (2005) have provided a historical review of this extraordinary technology success story, emphasizing the critical role of three-way catalytic converters to markedly reduce exhaust emissions of hydrocarbons, carbon monoxide and nitrogen oxides from gasoline-fueled engines. Indeed, in a manner analogous to our discussion of TDE and NTDE, it is appropriate to separately consider traditional gasoline exhaust (TGE) and modern gasoline emissions (MGE). This shift from TGE to MGE occurred rapidly starting in the 1970s with removal of lead from gasoline and progressive reductions in the sulfur content of gasoline allowing the introduction of 3-way catalysts in the exhaust system. The 1988 IARC review of gasoline engine exhaust was largely based on TGE. The June 2012 review of gasoline engine exhaust should consider the distinction between TGE and MGE.

All of the regulations noted in Table 1, taken together, resulted in the need for and implementation of fundamental changes and advancements in the design, performance, sophistication and efficiency of diesel engine systems and the fuels upon which they operate in order to meet the regulations. This, in turn, has yielded profound changes in the concentrations and chemical composition of the exhaust from diesel engines since the last IARC carcinogen hazard classification review was conducted in 1988 (IARC, 1989). The net result is a technological success story similar to that achieved earlier for gasoline-fueled vehicles.

## 3. New technology diesel developments since the mid-1980s

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 since 1989 (Fig. 4). What started as evolutionary advances transitioned to revolutionary advances that markedly reduced and changed diesel engine emissions. 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 with ultra-low sulfur content, improved diesel engine components, catalyzed exhaust after-treatment systems, and electronic sensing and control systems (Bauner et al., 2009; Charlton et al., 2010; Colucci, 2004; Dollmeyer et al., 2007; Johnson, 2010, 2011; Tschoeke et al., 2010).

The fully integrated systems approach of the new technology has resulted in more than order-of-magnitude emission reductions and, in many cases, the virtual elimination of the emitted compounds, including the hallmark elemental carbon nanoparticles with associated hydrocarbons, that were of concern at the time of IARC's evaluation of Traditional Diesel Exhaust in 1988 (Khalek et al., 2011; Liu et al., 2008a,b, 2009a,b, 2010).

The myriad of technological advancements that have been developed over the past two decades through the integrated approach to reduce diesel emissions can be summarized as follows:

(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;

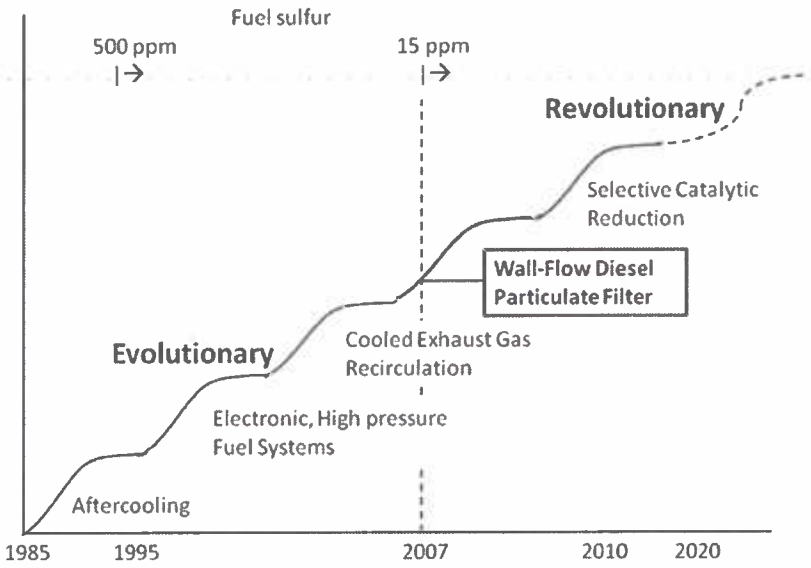


**Fig. 4.** Schematic rendering of evolutionary development of advanced diesel technology followed by revolutionary advances occurring with introduction of ultra-low sulfur (<15 ppm) fuel and wall flow diesel particulate filters.

(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 $NO_x$ 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, defined in the USA as having less than 15 ppm sulfur, has allowed for the deployment of wall-flow diesel particulate filters ("DPFs"), and the use of catalysts which have fundamentally changed the composition of diesel particulates while reducing their emissions to near-zero levels.

Taken together, the foregoing new-technology diesel engine system components (specifically oxidation catalysts, fully integrated electronic control systems, and wall-flow DPFs capable of achieving the 0.01 g/bhp-hr PM standard) and the use of ULSD have resulted in new-technology diesel engines. As we describe later, the resultant New Technology Diesel Exhaust (NTDE) is fundamentally different, both quantitatively and qualitatively, from the "uncontrolled" Traditional Diesel Exhaust (TDE) that was the subject of the 1988 IARC evaluation process.

## 4. Periodic health assessments of diesel exhaust

Another impetus for the development of diesel regulations and technology came from the periodic health assessments conducted by international and national organizations (Table 4). The most influential carcinogenic hazard assessments are those conducted by the International Agency for Research on Cancer (IARC). The IARC process will be described in detail in the next section. The IARC review held in 1988 and published in 1989 classified whole diesel exhaust in Group "2A, probably carcinogenic to humans," based on evidence from exposure evaluations, epidemiological investigations, laboratory animal studies and supporting information (IARC, 1989). The same IARC Working Group evaluated whole gasoline exhaust and classified it in "Group 2B, possibly carcinogenic to humans." The basis for those overall evaluations will be discussed later. The carcinogenic hazard classification for diesel technology was also noted by the International Program on Chemical Safety (IPCS) in its Environmental Health Criteria Report (No. 171) for diesel fuels and exhaust emissions (IPCS, 1996). The California Air Resources Board (CARB) listed "particulate emissions from diesel-fueled engines" as a toxic air contaminant (TAC) based on its carcinogenicity (CARB, 1998a–d). The 9th report on carcinogens (NTP, 2000), prepared by the National Toxicology Program (NTP), listed "diesel exhaust particulates" as "reasonably anticipated to be a human carcinogen (NTP, 2000). The US Environmental Protection Agency, in its Health Assessment Document for Diesel Engine Exhaust, classified diesel engine exhaust as "likely to be carcinogenic to humans" (US EPA, 2002).

It is important to note that the IARC evaluation and, later, that of the US EPA, was for "diesel engine exhaust" while CARB and NTP evaluated "particulate emissions from diesel-fueled engines" and "diesel exhaust particulates," respectively. The focus of CARB and the NTP was on elemental carbon particles with associated hydrocarbons present in TDE such as those shown in Fig. 1, particles that have been virtually eliminated from NTDE. As will be reviewed later, TDE is a complex mixture of gases, semi-volatile chemicals and particulate matter with adsorbed and absorbed chemicals. In contrast, NTDE consists largely of gases with extraordinarily low concentrations of particulate matter that is altered in composition compared to TDE.

All of these hazard assessment reports noted that diesel engine technology was changing and that when advances were made it would be appropriate to review the general applicability of the health hazard conclusions based on traditional technology to the newly emerging technology developed. IARC expressly noted that "changes are expected in the future" (IARC, 1989). The EPA Health Assessment Document (US EPA, 2002) specifically stated – "The health hazard conclusions are based on exhaust emissions from diesel engines built prior to the mid-1990s…." "As new and

**Table 4**
Summary of diesel exhaust/diesel exhaust particles hazard assessments conducted by regulatory agencies and authoritative bodies (Adapted from HEI, 2002).

| Regulatory agency/authoritative body, date | Summary of key findings |
|---|---|
| NIOSH (1988) | • Animal evidence "confirmatory" for carcinogenesis<br>• Human evidence "limited"<br>• Diesel exhaust classified a "potential occupational carcinogen"<br>• No quantitative risk assessment for DE carcinogenicity |
| IARC (1989) | • Rat data "sufficient" for carcinogenicity<br>• Human epidemiology data "limited"<br>• Diesel exhaust classified as a "probable human carcinogen" (Group 2A)<br>• No quantitative risk assessment for DE carcinogenicity |
| WHO (1996) | • Rat data support carcinogenicity<br>• Based on human epidemiology data, conclude that DE is "probably carcinogenic"<br>• Epidemiology studies considered "inadequate for a quantitative estimate of human risk"<br>• Rat data used for quantitative risk assessment |
| California EPA (1998) | • Rat data "have demonstrated" carcinogenicity of diesel exhaust particles<br>• Causal association of diesel exhaust and lung cancer in epidemiology studies is a "reasonable and likely explanation"<br>• Designated diesel particulate matter a "toxic air contaminant"<br>• Human epidemiologic data used in quantitative risk assessment |
| NTP (2000) | • Diesel exhaust particulates classified as "reasonably anticipated to be a human carcinogen" based on elevated lung cancer in occupational groups exposed to diesel exhaust, and supporting animal and mechanistic data<br>• No quantitative risk assessment for DE carcinogenicity |
| US EPA (2002) | • Diesel emissions classified as "likely to be carcinogenic to humans"<br>• Strong, but less than sufficient, epidemiologic evidence<br>• Evidence of carcinogenicity of diesel exhaust particles in rats and mice by non-inhalation routes of exposure<br>• Supportive data demonstrating mutagenic and/or chromosomal effects of DE and its organic constituents<br>• No quantitative risk assessment for DE carcinogenicity |
| ACGIH (2003) | • DEP withdrawn from Notice of Intended Changes (NIC) in "2003 TLVs and BEIs: Threshold limit values for chemical substances and physical agents and biological exposure indices" (DEP formerly proposed as an A2 "suspected human carcinogen" in 1995 NIC with a recommended threshold limit value (TLV) of 150 $\mu g/m^3$; in 1999, ACGIH revised its proposal, lowering the recommended TLV to a value of 50 $\mu g/m^3$)<br>• No quantitative risk assessment for DE carcinogenicity |

cleaner diesel engines, together with different diesel fuels, replace a substantial number of existing engines, the general applicability of the health hazard conclusions will need to be re-evaluated."

The IARC has announced it will review the classification of "diesel and gasoline engine exhausts and some nitroarenes" at a meeting to be held June 5–12, 2012 in Lyon, France (IARC, 2012a). This will be the first carcinogenic hazard assessment for diesel exhaust conducted since substantial advances have been made in technology that have profoundly reduced diesel exhaust emissions and fundamentally changed their composition, resulting in NTDE that will need to be evaluated separately from TDE. It can be anticipated that other authoritative bodies such as the WHO, US EPA, CARB and NTP will also review their previous hazard classification actions on diesel engine exhaust. Indeed, the NTP has already announced its intention to review the classification of "diesel exhaust particulates" for inclusion in the 13th report on carcinogens (NTP, 2012). To a variable degree, those organizations are likely to take account of the actions of IARC at its June 2012 meeting while still fulfilling their own independent mandates.

## 5. IARC evaluation of carcinogenic hazards

Cancer, a family of diseases characterized by new and uncontrolled growth of tissue, has long been of concern to humans because of its frequent occurrence, particularly late in life. It is estimated that in industrialized societies with populations that have a long lifespan, about 40% of individuals will develop cancer sometime during their life and about one in four individuals will die with cancer (Ayres et al., 2010). Lung cancer is one of the most common cancers with a large portion of cases attributed to cigarette smoking. The role of various chemical and biological agents and different lifestyles in causing cancer has received substantial attention stimulated by the view that if the causes of cancer could be identified, then exposure to the substances could be reduced or, perhaps, even eliminated.

Not surprisingly, IARC after its establishment in 1965 received frequent requests for information on known or suspected carcinogens (IARC, 2006). In response, the IARC in 1969 initiated a program on the evaluation of the carcinogenic risk of chemicals to humans, a program that involves the production of critically evaluated monographs on a wide range of agents. The scope of the IARC monographs soon broadened to include groups of related chemicals, complex mixtures, occupational exposures, physical and biological agents and lifestyle factors. This broad scope was recognized in 1988 with the title of the document series changed to "IARC Monographs on the Evaluation of Carcinogenic Risk to Humans."

The preamble to each IARC monograph includes a statement of the scientific principles used to evaluate and classify various agents as to their potential for causing cancer in humans (IARC, 2006). As the preamble notes – "A Cancer 'hazard' is an agent that is capable of causing cancer under some circumstances, while a cancer 'risk' is an estimate of the carcinogenic effects expected from exposure to a cancer hazard." The Monographs are an exercise in evaluating cancer hazards despite the historical presence of the word 'risks' in the title (IARC, 2006). As an aside, evaluation of health risks requires knowledge of the intensity and duration of exposure to an agent and the potency of the hazardous agent for causing the health effect of concern, for example, cancer. The Preamble makes note of the historical use of "strength of evidence" in evaluating carcinogenicity and then proceeds to state – "it should be understood that Monograph evaluations consider studies that support a finding of a cancer hazard as well as studies that do not."

The IARC convenes a separate working group of experts to develop each volume of the monographs. The working group members generally have published significant research related to the carcinogenicity of the agents being reviewed. The Monograph evaluation and classification process only uses papers that have been published and accepted for publication in the openly available scientific literature. Each Monograph consists of six sections: (a) exposure data, (b) studies of cancer in humans, (c) studies of cancer

**Table 5**
IARC carcinogenic hazard classification scheme (based on Preamble, IARC, 2012a, 2012b).

| Group | Overall evaluation | Strength of evidence |
|---|---|---|
| 1 | Carcinogenic to humans | Sufficient evidence of carcinogenicity in humans<br>or<br>Exceptionally, less than sufficient evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals |
| 2A | Probably carcinogenic to humans | Limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals<br>or<br>Inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans<br>or<br>Exceptionally, limited evidence of carcinogenicity in humans<br>or<br>An agent may be assigned to this category if it clearly belongs, based on mechanistic consideration, to a class of agents for which one or more members have been classified in Group 1 or Group 2A |
| 2B | Possibly carcinogenic to humans | Limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals<br>or<br>Inadequate evidence of carcinogenicity in humans, but there is sufficient evidence of carcinogenicity in experimental animals<br>or<br>Inadequate evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals together with supporting evidence from mechanistic and other relevant data<br>or<br>An agent may be classified solely on the basis of strong evidence from mechanistic and other relevant data |
| 3 | Not classifiable as to its carcinogenicity in humans | Inadequate evidence in humans and inadequate or limited evidence in experimental animals<br>or<br>Inadequate evidence in humans but sufficient evidence in experimental animals, but strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans<br>or<br>Agents that do not fall into any other group may be placed in Group 3 |
| 4 | Probably not carcinogenic to humans | Evidence suggesting lack of carcinogenicity in humans and experimental animals<br>or<br>Inadequate evidence of carcinogenicity in humans but evidence suggesting lack of carcinogenicity in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data |

in experimental animals, (d) mechanistic and other relevant data, (e) summary, and (f) evaluation and rationale.

The exposure data section contains general information on each agent. This includes the composition of the agent, analysis and detection methods, production and use, and occurrence and exposure. It is noteworthy that the preamble explicitly notes "Whenever appropriate, other information, such as historical perspectives – may be included." This will be especially important for the upcoming evaluation of diesel exhaust in view of the marked changes in diesel engine exhaust that have occurred with recent technological advances, which changes are the focus of this review.

Studies of humans always have a central role in the IARC evaluation and classification process. This includes multiple types of epidemiological studies – cohort studies, case-control studies, correlation (or ecological) studies and intervention studies.

Studies of cancer in laboratory animals have also traditionally had a key role in evaluating and classifying agents as to their human carcinogenic potential. In fact, the preamble (IARC, 2006) notes – "All known human carcinogens that have been studied adequately for carcinogenicity in experimental animals have produced positive results in one or more animal species" (Tomatis et al., 1989; Wilbourn et al., 1986). Studies of the carcinogenic potential on agents in laboratory animals are of special significance when epidemiological evidence is not available on the agent.

In the various IARC monographs prepared in recent decades, the section on Mechanistic and other relevant data have been an increasingly important part of each monograph (IARC, 1991, 2005, 2006; Vainio et al., 1992,1995). This includes information on toxicokinetics and mechanisms of carcinogenesis including physiological changes, changes in cell function and molecular changes such as genetic alterations.

The summary section of each monograph draws together in a concise manner the information on (a) exposure data, (b) cancer in humans, (c) cancer in experimental animals, and (d) mechanistic and other relevant data.

The final element of each monograph on an agent is the evaluation and rationale section. This section evaluates the strength of the evidence for carcinogenicity arising from human and experimental data using standard terms. In addition, the strength of the mechanistic evidence is also characterized.

The key descriptive phases for each kind of evidence are: sufficient evidence of carcinogenicity, limited evidence of carcinogenicity, inadequate evidence of carcinogenicity, and evidence suggesting lack of carcinogenicity. The basis for selecting from among those four descriptors is given in the preamble (IARC, 2006). At the final step in the evaluation and classification process an overall evaluation is made of the carcinogenicity of the agent to humans. The IARC carcinogenic hazard classification scheme is summarized in Table 5.

The reviews and classifications are published in monographs that are widely used around the world as the most authoritative sources of information on the cancer causing potential of various agents and exposure circumstances. IARC recently published monograph volume 100 consisting of 6 parts (IARC, 2011a–d, 2012a,b). The monographs are summarized in six papers published in Lancet: pharmaceuticals (Grosse et al., 2009); biological agents (Bouvard et al., 2009); arsenic metals, fibres and dusts (Straif et al., 2009); radiation (El Ghissassi et al,. 2009); chemical agents and related occupations (Baan et al., 2009), and tobacco, areca

nut, alcohol, coal smoke and salted fish (Secretan et al., 2009). As of January 1, 2012, IARC has reviewed 942 substances and exposure circumstances with 107 classified in Group 1 (carcinogenic to humans), 59 in Group 2A (probably carcinogenic to humans), 267 in Group 2B (possibly carcinogenic to humans), 508 in Group 3 (not classifiable) and 1 in Group 4 (probably not carcinogenic to humans) (IARC, 2012b).

## 6. IARC 1988 review of diesel exhaust, gasoline exhaust and some nitroarenes

In convening a working group of experts, IARC frequently takes advantage of their expertise to review several related agents or substances at the same time. That was done in the June 14–21, 1988 meeting when diesel and gasoline engine exhaust and some nitroarenes were evaluated (IARC, 1989). It was natural to review the information on exhaust from diesel and gasoline–fueled engines at the same time, since those are the dominant liquid hydrocarbon fuels used around the world. Some nitroarenes were included in the 1988 review because during the mid-1980s considerable attention was being given to this class of compounds as mutagenic and putative carcinogenic agents within engine exhaust emissions.

By way of background, it is useful to recount some of the deliberations that took place at the beginning of the 1988 review. One of us (Roger O. McClellan) participated in that review as Chair of the animal studies subgroup. Two viewpoints were advanced by different participants as the working group began the review session in Lyon, France. Some participants expressed the view that it might be appropriate to consider as a broad class internal combustion engine exhaust, combining the evidence for both diesel engines and gasoline engines. Those advancing this approach noted that many chemical compounds found in engine exhaust were common to both types of engine exhaust and that some epidemiological evidence was based on populations for which the exposures could not be specified as being primarily from diesel or gasoline engines; the exposures were mixed. Points favoring the separate evaluation of diesel and gasoline engine exhaust were the existence of clear quantitative and qualitative differences in the exhaust from the two types of engines. It was also noted that the carbonaceous component and associated chemicals emitted by diesel engines were of particular concern (recall Fig. 1). Moreover, it was apparent from a cursory review of the long-term animal studies with diluted whole engine exhaust that the results from studies with the diesel exhaust were different from those with gasoline engine exhaust exposure. Those who favored lumping the two types of engines countered by noting that both extracts of diesel exhaust particles and condensates/extracts of gasoline engine exhaust yielded positive results in *in vitro* studies. It is noteworthy that some of the gasoline engine condensate/extract studies were conducted with TGE and some with MGE. Samples of gasoline engine exhaust studied at the US EPA as part of their comparative potency project (Albert et al. 1983; Lewtas et al., 1983) were from a mal-tuned gasoline–fueled vehicle. It was necessary to mal-tune the engine in order to obtain sufficiently large samples of particulate material from a gasoline fueled engine to use in the biological studies.

In the end, the decision was made in 1988 to provide separate evaluations of the different kinds of evidence, when available, for whole diesel engine exhaust, gas-phase diesel engine exhaust, extracts of diesel engine exhaust particles, whole gasoline engine exhaust, and condensates/extracts of gasoline engine exhaust and engine exhaust (unspecified as from diesel or gasoline engines), and to provide overall evaluations for diesel engine exhaust and gasoline engine exhaust as shown in the two left hand columns of Table 6. We will discuss the four columns on the right side of Table 6 later.

As is customary in IARC evaluations, the working group considered the information available on the composition of engine exhaust and exposure data as background for evaluating the health effects information. We will discuss key conclusions drawn in that section of the monograph (IARC, 1989) later when we compare and contrast TDE and NTDE.

The core of every IARC evaluation is the carcinogenicity data available from human studies and laboratory animal studies. The first step in the evaluation process for both epidemiological and laboratory animal studies is to consider the quality of the various studies. In a second step, the studies characterized as well-designed and well-conducted are evaluated for the strength of the evidence for an association between exposure and carcinogenic outcome.

The human data evaluation in 1988 focused on five cohort studies and five case-control studies that evaluated the risk of lung cancer and exposure to diesel exhaust, and three cohort studies and four case-control studies that evaluated the risk of bladder cancer and exposure to diesel exhaust. In all cases, the human exposure involving TDE had begun as early as the 1940s, a time when diesel engines were beginning to find increasing application in the transportation of goods and people. Inadequacies in the exposure characterization were a major limitation to varying degrees in all of the epidemiological studies evaluated in 1988. There also were significant difficulties in identifying gradients in exposure–response relationships. The Working Group's summary evaluation of the epidemiological evidence was that "there is limited evidence for the carcinogenicity in humans of diesel engine exhaust." The same Group concluded that – "there is inadequate evidence for the carcinogenicity in humans of gasoline engine exhaust."

The 1988 review of experimental animal data focused on five well-conducted studies in which two different strains of rats were exposed chronically to low dilutions (high exhaust concentrations) of whole diesel exhaust. Four of the studies involved exhaust from light-duty diesel engines and one involved exhaust from a heavy-duty diesel engine. Three of the studies with light-duty diesel engine exhaust and the study with heavy-duty diesel engine exhaust showed a tumorigenic effect in the rats. Based on the terminology described earlier in this paper, those studies would now be considered as having been conducted with TDE. In contrast, the diesel exhaust exposure studies conducted with other species (mice and Syrian Hamsters), frequently conducted in parallel with the rat studies did not show a tumorigenic effect. Two studies were reported in which rats were exposed to filtered diesel exhaust which removed the particles. Neither study reported a tumorgenic response.

Two of the laboratories, the Fraunhofer Institute in Hanover, Germany and the Battelle Memorial Institute in Geneva, Switzerland, conducted studies with animals exposed to low dilutions (high concentrations) of whole gasoline engine exhaust in parallel with the diesel exhaust exposure studies. Published results from only one of these studies were available at the time of the IARC review. It is noteworthy that information is now available from chronic inhalation studies with rats exposed to whole-gasoline engine exhaust from engines without catalytic treatment of exhaust (TGE) and from engines with catalytic treatment of exhaust (MGE) (Brightwell et al., 1989; Heinrich et al., 1986). The exposure to gasoline engine exhaust, either without or with catalytic treatment, did not produce a tumorigenic response.

It is useful to consider the complete evaluation offered by the working group (Table 6) (IARC, 1989). The finding of "inadequate evidence for carcinogenicity in experimental animals of gas phase diesel engine exhaust (particles removed)" is especially noteworthy since, as will be described later, NTDE is essentially free of

**Table 6**
IARC (1989) evaluation of carcinogenicity of exhaust emissions and projected 2012 IARC evaluation.

| | 1988 IARC evaluation* | | 2012 IARC evaluation | | | |
|---|---|---|---|---|---|---|
| | Traditional gasoline | Traditional diesel | Traditional gasoline | Modern gasoline technology | Traditional diesel | New technology diesel |
| Exhaust Composition | Modest data on <1988 engines | Modest Data on <1988 engine | Limited new data | Distinguish between traditional and modern technology | Substantial new data on 1988–2004 technology | Substantial new data on new technology and fuels |
| Exposure Information | Modest data <1988 conditions | Limited data on <1988 conditions | Limited new data | Limited data | Limited data on exposure post-1988 | No data – technology just introduced |
| Animal carcinogenicity studies | *Inadequate evidence* | *Sufficient evidence* | Limited new data | Distinguish between traditional and new technology | New data on mode of action | No data – studies in progress |
| Epidemiological carcinogenicity studies | *Inadequate evidence* | *Limited evidence* | Limited new data | No data | Additional studies related to traditional technology | No data |
| Overall evaluation | Group 2B, possibly carcinogenic to humans | Group 2A, probably carcinogenic to humans | ? | ? | ? | ? |

* In addition to the evaluations for diesel engine exhaust and gasoline engine exhaust, IARC provided the following evaluations: • There is *inadequate evidence* for the carcinogenicity in experimental animals of gas-phase diesel engine exhaust (with particles removed). • There is *sufficient evidence* for the carcinogenicity in experimental animals of extracts of diesel engine exhaust particles. • There is *sufficient evidence* for the carcinogenicity in experimental animals of condensates/extracts of gasoline engine exhaust.

particles. Indeed, the exhaust after-treatment systems with catalyst and particulate traps results in NTDE that is quite similar in composition and concentration to the exhaust from 3-way catalyst equipped gasoline engines (MGE). Recall that the IARC Panel concluded – "There is inadequate evidence for the carcinogenicity in experimental animals of whole gasoline engine exhaust."

The overall evaluations of the working group in 1988 were "Diesel engine exhaust is probably carcinogenic to humans (Group 2A)" and "Gasoline engine exhaust is possibly carcinogenic to humans (Group 2B)." Based on the definitions provided earlier in this paper, we view the diesel exhaust reviewed as TDE and the gasoline exhaust reviewed as TGE and MGE. It is apparent that the overall evaluation for diesel engine exhaust was heavily influenced by the epidemiological findings (limited evidence) and the findings in the experimental studies with rats (sufficient evidence). The monograph made note of the changes in the lungs of rats exposed to the highest concentrations of diesel exhaust including altered clearance when exposures were above about 300 mg-hr per week. However, it was not until after the 1988 Review that it was generally recognized that prolonged exposure of rats to high concentrations of several kinds of poorly soluble particles (not just diesel soot particles) impaired clearance mechanisms, produced lung burdens of particles in excess of that projected from lower level exposures, produced chronic pathology and, most significantly, resulted in an excess of lung tumors (McClellan, 1996). We will return to the issue of lung overload and occurrence of lung tumors in rats exposed for long periods of time to high concentrations of TDE in a later section when we discuss the IARC 2012 review.

## 7. Carcinogenic hazard evaluations of specific chemicals versus complex mixtures from changing technology

The vast majority of IARC evaluations (IARC, 2012a,b), excluding biological agents, can be placed in two categories; (a) specific chemicals, or (b) exposures to emissions of a specific technology. The two kinds of evaluations have some significant differences. A chemical, such as benzene or formaldehyde, is the same chemical today as it was a decade or a century ago. The uses of the chemical may change over time but its basic chemical properties do not change. However, knowledge of the carcinogenic hazard may change over time as a result of additional research and advances in scientific knowledge. Knowledge of human exposure may also change as a result of new measurements and changes in work place practices including control of exposure to the specific agent. Indeed, work place practices were likely influenced by the previous IARC classification of the carcinogenic hazard of the specific chemical.

The situation for a complex agent such as diesel engine exhaust, gasoline engine exhaust, or man-made products such as glass wool fibers is different than that of a specific chemical. The physical properties of these complex agents may be purposefully changed over time with technological advances, including advancements made to reduce the hazardous properties of the agent. As discussed later, the concentrations of particulate matter in TDE have been steadily reduced over the last half century as diesel engine technology and fuels improved. However, those evolutionary reductions and changes in TDE pale by comparison with the recent revolutionary reductions in concentrations and changes in the composition of NTDE compared to TDE. For purposes of carcinogenic hazard evaluation, it is clear that TDE and NTDE are not equivalent; they need to be separately evaluated, a point to be amplified on later.

The importance of separate evaluations and classifications for TDE and NTDE extends to the impact of those evaluations on future use of diesel technology. The detailed evaluation and potential reclassification of TDE is beyond the scope of this review. However, it can be noted that the previous classification, Group 2A (probable human carcinogen), for diesel exhaust could be reaffirmed or changed based on the current scientific evidence. Irrespective of the specific carcinogenic hazard classification, a classification of Traditional Diesel Exhaust in Group 1, 2A or 2B will serve as a continuing stimulus to limit TDE particulate emissions and reduce ambient concentrations of PM. On the other hand, if NTDE were to be considered as equivalent to TDE, a decision that we think would be inappropriate, such an approach could undermine the incentive for shifting from TDE to NTDE, all to the detriment of many decades of effort to improve diesel engine technologies, fuels, air quality, and ultimately public health.

The IARC has previously faced a similar situation in evaluating the carcinogenic hazard of agents impacted by technological change. An example was the IARC review of man-made vitreous fibers (IARC, 2002). This was a re-evaluation of man-made mineral fibers that had occurred earlier (IARC, 1988). Between the initial review and the second review, the man-made vitreous fiber

industry had conducted extensive research to better understand the determinants of fiber induced respiratory tract tumors in rats as a basis for understanding the potential human carcinogenic hazards of various man-made fibers (Hesterberg et al., 2012a). A key finding from that research program was that man-made fibers, which were durable and poorly soluble, had a high potential for causing lung tumors in rats with chronic inhalation exposure. In contrast, chronic inhalation exposure of biosoluble man-made fibers, even at high concentrations, did not result in an increased incidence of lung tumors. Building on this critical scientific finding, the glass fiber manufacturers made major changes in the production process for glass wool fibers shifting to production of biosoluble glass fibers, except for certain highly specialized product lines which required very durable fibers.

The IARC (2002) monograph acknowledged the changes in synthetic vitreous fibers and concluded that insulation glass wool continuous glass filaments, rock (stone) wool, and slag were "not classifiable as to their carcinogenicity to humans (Group 3)." The traditional special purpose fibers and Refractory Ceramic Fibers that were biopersistent in the respiratory tract when inhaled were retained in Group 2B. As reviewed in Hesterberg et al. (2012a), the IARC decisions influenced the European Communities approach to handling synthetic vitreous fibers (EU, 1997; Bernstein, 2007), the National Toxicology Program's modification of its listing for glass wool in the 12th report on carcinogens (NTP, 2011a) and the California Environmental Protection Agency modification of its listing of glass wool fibers (OEHHA, 2011). It is readily apparent that IARC's cancer hazard classifications have impact on subsequent actions by other agencies.

## 8. Advanced collaborative emissions study

As new diesel technology began to be developed by individual companies in response to increasingly stringent emission-control regulations, it became apparent that broad acceptance of the new technology would be enhanced by a complementary collaborative effort that focused on characterization of engine emissions and potential health impacts. Ultimately, with strong support from industry, what has become known as the advanced collaborative emissions study (ACES) program emerged. ACES is a cooperative, multi-party effort managed in a coordinated manner by two well-respected non-profit science-based organizations, the Health Effects Institute (HEI) and the Coordinating Research Council (CRC). The overall effort has been guided by an ACES Steering Committee, which is advisory to HEI and CRC. It includes representatives of the US EPA, US Department of Energy (DOE), California Air Resources Board, American Petroleum Institute, National Resources Defense Council, National Institutes of Occupational Safety and Health, Engine Manufacturers, Emission Control Manufacturers, the Petroleum Industry and others. Most importantly, the ACES effort has been guided by an independent Oversight Committee comprised primarily of academic scientists. This independent Oversight Committee had a central role in the design of the ACES study. It is important to note that a different HEI committee will be involved in reviewing and commenting on reports prepared by the ACES research program investigators.

The HEI is a non-profit entity chartered in 1980 as an independent research organization to provide high-quality, impartial, and relevant science on the health effects of air pollution (HEI, 2012a). Indeed, the creation of HEI traces to uncertainties in the late 1970s over the potential health effects of vehicle emissions, including diesel engine emissions. The HEI typically receives half of its core funds from the US Environmental Protection Agency and half from the world-wide motor vehicle industry. Other public and private organizations periodically support special HEI activities such as the ACES program. HEI does not have its own research facilities, but provides financial support to scientists in universities and research organizations to conduct research oriented to achieving HEI's research objectives.

The CRC is a non-profit organization that directs and manages studies on the interaction between automotive/other mobility equipment and petroleum products (CRC, 2012). It traces its origins to a Committee of the Society of Automotive Engineers and became an independent organization in 1942. It does not have any research facilities; instead it sponsors research at universities and other research organizations to achieve its scientific objectives. Both the HEI and CRC have achieved world-wide recognition for sponsoring research on important air quality issues and for the rigorous review and subsequent publication of that research in the peer reviewed, open scientific literature.

The organization, management and funding of ACES are described in the Preface to one of the initial HEI reports on the program (Mauderly and McDonald, 2012). That document summarizes the three phases of the ACES program as follows:

- "Phase 1: Extensive emissions characterization of four production-ready heavy-duty diesel (HHDD, i.e. gross vehicle weight larger than 33,000 lbs) engines and control systems designed to meet the 2007 standards for reduced PM. This phase was conducted at Southwest Research Institute (SwRI) in 2007 and 2008 and was the basis for selecting one HHDD engine/aftertreatment system for health testing in Phase 3.
- Phase 2: Extensive emissions characterization of a group of production-intent engine and control systems meeting the 2010 standards (including more advanced NO controls to meet the more stringent 2010 $NO_x$ standards). This phase is to be conducted at SwRI during 2011 and 2012.
- Phase 3: Health effects assessment in rodents using one selected 2007 compliant engine system. This phase started in 2008 with the installation of a specially-designed emissions generation and animal exposure facility at the Lovelace Respiratory Research Institute (LRRI) and is being conducted in two Phases. Phase 3A included setting up the engine, characterizing the engine performance and emissions to make sure it was operating as intended, and generating and characterizing the exposure atmospheres in the animal inhalation chambers at three dilution levels. Phase 3B includes a 90-day inhalation study in mice and a chronic inhalation study in rats with health measurements at several time periods."

In this paper, we repeatedly refer to results from the ACES Phase I engine emissions characterization effort. Thus, it is appropriate to briefly describe that activity. A research team, under the leadership of Imad Khalek at the Southwest Research Institute (SwRI) was selected to carry out the Phase 1 engine emission characterization activities under contract to CRC. A description of the characterization effort is found in Khalek et al. (2011) with additional details contained in Khalek et al. (2009), the extensive report on the ACES Phase 1 effort issued by the CRC.

Four different engine manufacturers provided 2007 model year production engines for the characterization studies conducted at SwRI. All four engines were from product lines developed to meet the USEPA's stringent 2007 emissions standards; particulate matter, 0.01 g/bhp-hr; and nitrogen-oxides, 1.20 g/bhp-hr. The nitrogen oxides emissions standard was reduced to 0.20 g/bhp-hr for the 2010 model year. The specific engines tested were a Caterpillar C13 (430 hp), a Cummins ISX (455 hp), a Detroit Diesel Corporation Series 60 (455 hp) and a Mack MP7 (395 hp) manufactured by Volvo. It was anticipated that at the end of the Phase 1 characterization effort at SwRI one of the engines would be identified for transfer to the animal toxicology laboratory to

produce the exhaust emissions used in the Phase 3 health studies. Further, it was decided that it would be desirable to conduct characterization studies on the emissions from a companion engine so that two nearly identical engines would be available for the health studies.

From the outset, it was agreed that the Phase 3B health studies would involve exposures to diluted exhaust of 16 h/day, 5 days/week for up to 30 months. This was done to maximize the exposure of the animals and, thus, maximize the potential for observing adverse effects. As a result, the ACES Phase 3B rat study will be longer than the two-year duration of typical NTP studies (NTP, 2011a). The use of the 30-month duration protocol was used in the early studies of TDE reported by Mauderly et al. (1989). Further, it was understood that it would be important to have the engine operating under a rigorous variable load duty cycle. This led to a decision to create a 16-h engine test cycle that would also be used in the characterization studies at SwRI. This allowed for a direct link between the Phase 1 characterization effort and the use of the engines and the same test cycle at the animal toxicology facility that would conduct the health studies. The details of that test cycle and its development are described in Clark et al. (2007).

The 16-h cycle includes four 4-h segments consisting of Federal Test Procedure (FTP) segments mixed with segments of the CARB 5-Modes driving cycles. It was designed to be representative of modern truck usage and included a broad range of engine loads and speeds reflecting both urban and rural (highway) driving. The 16-h cycle also added useful information on emissions during particle filter regeneration, which may not occur during shorter test cycles. Regeneration typically occurs once or twice during each integrated 16-h cycle. The Phase 1 engine exhaust characterization research was conducted with engines using ultra-low sulfur fuel meeting fuel standards for 2007 and beyond. Specifically, it contained 4.5 ppm sulfur, 26.7 vol.% aromatics, carbon content of 86.32 wt.%, hydrogen content of 12.92 wt.%, oxygen by difference of 0.76 wt.%, density of 855.6 g/h, API gravity at 60 °F of 33.8 density at 15 °C of 855.6 g/l and a Cetane Number of 47.5.

The HEI selected the Lovelace Respiratory Research Institute (LRRI) to conduct the core investigations of the potential health effects of NTDE. The LRRI research team has been actively involved in studying diesel engine emissions and other air quality issues since the late 1970s (McClellan et al., 1982, 1986; McClellan, 1987). The Institute's research included conduct of one of the earliest chronic inhalation bioassays in rats (Mauderly et al., 1989) and a concurrent study in mice reported later (Mauderly et al., 1996). The rats and mice were exposed to diluted whole exhaust produced by a 5.7 L light-duty diesel engine manufactured by General Motors and operating on a fixed bed dynamometer utilizing a variable load cycle. We view the diesel exhaust studied by Mauderly and colleagues in the early 1980s as TDE. Key parameters of those early studies are shown in Table 7.

The development of modified engine/exposure facilities to accommodate a heavy-duty engine and the core ACES chronic toxicity study at LRRI was initiated under the leadership of J.L. Mauderly and, after his retirement, continued under the leadership of J.D. McDonald. The core studies are chronic inhalation exposure bioassays in rats and mice exposed to three dilutions of whole diesel exhaust from an engine operating on a dynamic 16-h load cycle and fueled by ULSD fuel to simulate real world conditions. The study has the objective of testing the ACES program core (null) hypothesis – *"Emissions from combined new heavy-duty diesel engines, after-treatment, lubrication and fuel technologies designed to meet the 2007 $NO_x$ 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 concentration 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 3A effort carried out at Lovelace included preparation of the facilities for operation of one of the heavy-duty on-road diesel engines compliant with the 2007 USEPA emission standards (Mauderly and McDonald, 2012). In addition, the diluted emissions delivered to the animal exposure chambers were characterized without animals in the chambers to provide a linkage to the extensive engine emissions characterization done at SWRI under ACES Phase 1 (Khalek et al., 2009, 2011). The emissions characterization carried out at LRRI provided a basis for determining the plausible upper bound of exposure concentrations for critical constituents for the animal exposures and, thus, the desired dilution of whole exhaust. The ACES Oversight Committee had determined that the $NO_2$ concentration needed to be limited to a Maximum Tolerated Dose (MTD) of $NO_2$ based on an earlier HEI-sponsored chronic inhalation exposure study of $NO_2$ alone reported by Mauderly et al. (1989, 1990). The MTD is the highest daily dose (or more correctly, exposure concentration and duration) that does not cause overt toxicity (McConnell, 1996). The use of an MTD in a chronic study such as ACES provides a maximum likelihood of detecting an excess of late-occurring effects, such as cancer, in the animals exposed to the test agent compared to the occurrence in sham-exposed control animals.

The earlier study of $NO_2$ by Mauderly et al. (1989, 1990) involved exposure of male F344/Crl rats to 9.5 ppm $NO_2$ for 7 h/day, 5 days/week for up to 2 years (see Table 7). This equates to 66.5 ppm-hr/day of exposure. They made extensive measurements of multiple indicators of biological changes after 12, 18 and 24 months of exposure. Key histopathological findings were "mild hyperplasia of epithelium in terminal bronchioles and an extension

**Table 7**
Comparison of key parameters for chronic inhalation studies in rats exposed to Traditional Diesel Exhaust (Mauderly et al., 1987), nitrogen dioxide (Mauderly et al., 1989, 1990), carbon black (Nikula et al., 1995) and New Technology Diesel Exhaust (Mauderly, 2010; McDonald et al., 2012).

| Parameter | Chronic exposure study | | | |
|---|---|---|---|---|
| | TDE | Carbon black | $NO_2$ | NTDE |
| Rat strain | F344 | F344 | F344 | Hscl Rcc: Wistar |
| Duration | 30 months | 24 months | 24 months | 30 months |
| Exposures | 7 h/day, 5 days/wk, 35 h/wk | 16 h/day, 5 days/wk, 80 h/wk | 7 h/day, 5 days/wk, 35 h/wk | 16 h/day, 5 days/wk, 80 h/wk |
| Lowest dilution | 10:1 | – | – | 25:1 |
| Particulate matter ($\mu g/m^3$) – Exp. Conc. | 7080 (247,400 $\mu g/m^3$-hr/wk) | 6500 (520,000 $\mu g/m^3$-hr/wk)<br>2500 (200,000 $\mu g/m^3$-hr/wk) | – | 9.7 (776 $\mu g/m^3$-h/wk) |
| $NO_x$ (ppm) – Exp. Conc. | 10.7 | – | – | 6.9 |
| $NO_2$ (ppm) – Exp. Conc. | 0.7 (4.9 ppm-hr/day) | – | 9.5 (66.5 ppm-hr/day) | 4.0 (64 ppm-hr/day) |
| NO (ppm) – Exp. Conc. | 10.0 | – | – | 2.9 |
| Hydrocarbons (ppm) – Exp. Conc. | 13. | – | – | 0.1 |
| Lung lesions | Yes | Yes | Yes | To be determined |
| Excess lung tumors | Yes | Yes | No | To be determined |

of bronchiolar epithelial cell types into proximal alveoli, giving the appearance of "respiratory bronchioles." Terminal bronchiolar walls were slightly thickened and eosinophilic. A slight inflammatory infiltrate of mixed cell type was occasionally found in alveoli adjacent to thickened bronchioles. The lesions progressed little with time, with the exception of a slight progression of the epithelialization of proximal bronchioles. The inflammatory response remained minimal" (Mauderly et al., 1990).

The pulmonary lesions noted in the $NO_2$ exposed rats are the hallmark lesions associated with reactive oxidant gases including Ozone ($O_3$) (Plopper et al., 1978, 1979). As reviewed by Evans (1984), the ability of these oxidant gases to affect the cells of the lung is influenced by their concentration, aerodynamics, solubility, reactivity, dilutions and the species as the air passes through the nasal passages, oropharynx and the large airways and ultimately, reaches the terminal or respiratory bronchioles. The substantial literature on $O_3$ has been critically reviewed by the US Environmental Protection Agency in the criteria documents (EPA, 1996, 2006) prepared as part of the National Ambient Air Quality Standard setting process.

The National Toxicology Program (NTP) and Health Effects Institute (HEI) have sponsored studies in which F344/W rats and $B6C3F_1$ mice, of both genders, were exposed to ozone starting at 6 weeks of age for up to 125 weeks (rats) and 130 weeks (mice). The exposure concentrations were 0.12, 0.5 and 1.0 ppm $O_3$ for 6 h/day, 5 days/week. The highest concentration was viewed as being the highest concentration that could be tolerated with prolonged exposure. The details of the studies are documented in reports by the NTP (1994) and HEI (Boorman et al., 1995; Harkema and Mauderly, 1994; Catalano et al., 1995). These reports and additional more detailed reports are available on the HEI website. The survival of both rats and mice were generally similar for all groups and there was no increase in neoplasms in either rats or mice associated with $O_3$ exposure. The most pronounced histological changes, hyperplasia and metaplasia, were observed in the nasal tissue of both species. Alveolar epithelial metaplasia and interstial fibrosis of the lung was also observed at the two highest $O_3$ concentrations. These pulmonary lesions are the hallmark oxidant gas-induced changes described by Plopper et al. (1978, 1979) and Evans (1984). Nasal and pulmonary effects were not observed at the 0.12 ppm level.

Mauderly (2010) provides an overview of the ACES program, including the inhalation exposure studies in laboratory animal studies. A detailed HEI report of the ACES Phase 3A is available (Mauderly and McDonald, 2012). The ACES Phase 3B animal health studies have already been initiated at LRRI. Those studies were briefly described by Mauderly (2010) and are described in detail in the recent HEI report (HEI, 2012b; McDonald et al., 2012). Preliminary observations on mice and rats exposed for 4 and 13 weeks were reported by McDonald (2012) to the California Air Resources and by Doyle-Eisele et al. (2012) at the 2012 meeting of the Society of Toxicology. The Preface to the HEI (2012b) report provides the additional details on the organization and design of the ACES laboratory animal studies. The animal studies involve exposure (16 h/day, 5 days/week) to graded concentrations of exhaust from a pair of engines identified based on the SwRI characterization work.

The engine at LRRI is fueled with USEPA 2007 compliant ultra-low sulfur fuel (<15 ppm sulfur). The commercial diesel fuel used in the initial Phase 3A and 3B research contained 3–5 ppm sulfur, 26.5–28.1 vol.% aromatics and a cetane index of 49.5–51.0. Three exposure levels with targeted $NO_2$ concentrations of 4.2, 0.8 and 0.1 ppm, and clean air control are being studied. The resulting dilution ratios of clean air to raw exhaust are approximately 25:1, 115:1 and 840:1.

At this juncture, it is useful to briefly recount the exposure conditions in the earlier study of TDE conducted by Mauderly et al. (1987) in which F344 rats exposed to a high concentration of diesel exhaust for up to 30 months had an increased prevalence of lung tumors (see Table 7). The exhaust for that study was from a 1980 Model 5.7 L General Motors engine operated on a dynamometer with a variable load repeating the US Federal Test Procedure urban certification cycle. The fuel contained 30% aromatics and 0.3% sulfur. The exhaust particles had a mass median aerodynamic diameter of about 0.25 μm and about 12% was solvent extractable organic compounds. The exhaust for the lowest dilution level (highest concentration of exhaust constituents) was diluted 10:1. At the lowest dilution and, thus, the highest exposure level, the exposure atmosphere contained: particulate mass, 7080 $\mu g/m^3$; carbon monoxide, 30 ppm; nitric oxide, 10 ppm; nitrogen dioxide, 0.7 ppm; hydrocarbon vapor, 13 ppm; and carbon dioxide, 0.7%. Two higher dilutions of 20:1 and 200:1 (and, thus, lower concentrations of exhaust constituents) were also studied with particulate mass concentrations of about 3500 and 350 $\mu g/m^3$.

As noted earlier, the lowest dilution ratio, and, thus, the highest exhaust constituent concentration for the ACES Phase 3B studies with NTDE, was selected to achieve what was thought to be the highest level that could be used without having excessive adverse effects solely from the level exposure to $NO_2$, a prominent constituent in the whole diesel exhaust (see Table 7). The HEI report by Mauderly and McDonald (2012) contains detailed results on the characterization of the exposure chamber atmosphere in ACES (see Tables 22, 23 and 24 of that report). Suffice it to note here that the targeted concentrations of $NO_2$ were achieved and the expected concentrations of other key constituents were observed. Specifically, from McDonald et al. (2012) for the high, medium and low exposure levels the results for the rat chambers were as follows: chamber inlet PM (by gravimetric measurement) – 13, 4 and 2 $\mu g/m^3$; NO – 5.1, 1.5, and 0.15 ppm; $NO_2$ – 3.6, 0.95 and 0.11 ppm; and $NO_x$ – 8.6, 2.4 and 0.26 ppm. At the lowest dilution and, thus, highest exposure level, the other key emission constituents present included: carbon monoxide, 10.5 ppm; non-methane hydrocarbons, 0.3 ppm, and $SO_2$, 20.6 ppb. One to two regeneration events occurred during each 16-h cycle indicating the engine was operating as would be expected if it were on an on-road tractor.

As part of the Phase 3B effort with NTDE, a large scale study was conducted with strain C57BL/6 mice with exposure durations of either 1 or 3 months. Each exposure group and the control group included 132 mice with equal numbers of each gender. The three month exposures of the mice were carried out in February to June 2010. The observations included hematology, serum chemistry, bronchioalveolar lavage, complete necropsies, lung epithelial cell proliferation and detailed histopathology. These observations will provide a complete characterization of any potential exposure-related biological effects. Results of that study were summarized by McDonald (2012) and Doyle-Eisele et al. (2012) and will be reported in detail in McDonald et al. (2012).

The core of the ACES Phase 3B effort with NTDE is a large scale study conducted with Wistar rats (strain HsdRecHan:Wist) to test the ACES core hypothesis concerning potential carcinogen effects of exposure to NTDE. As explained in the description of the ACES Phase 3B effort (McDonald et al., 2012), this strain of rat was purposefully selected as an alternative to the F344 rats used in the earlier Lovelace studies. At the time the Phase 3B rat studies were being planned, the National Toxicology Program (NTP) was in the process of evaluating a change from NTP's traditional use of the F344 strain to some other strain (King-Herbert and Thayer, 2006; King-Herberg et al., 2010). That evaluation was prompted by several factors including reductions in litter size that occurred over several decades in the NTP's breeding colony of F344 rats. In

addition, other factors such as the high background incidence of mononuclear cell leukemia in rats of the F344 strain complicated the interpretation of test agent induced effects. Ultimately, the independent ACES Oversight Committee recommended the use of the Wistar rat (strain HsdRECHan:Wist), a strain widely used in assaying for carcinogenic effects. Details concerning this decision are included in the Preface to the HEI (2012b) report and the HEI Review Committee's Commentary accompanying the report of McDonald et al. (2012).

The rat exposures were started in May 2010. Each of the 3 exposure level groups and control group includes 280 rats (equal number of each gender). Twenty rats are to be sacrificed at 1, 3, 12 and 24 months of exposure for observations such as those described for mice. In addition, pulmonary function evaluations are being performed. Results of observations on mice and rats at 4 and 13 weeks were reported by McDonald (2012) and Doyle-Eisele et al. (2012). Results of observations in the rat study through 12 months of exposure will be reported in detail in McDonald et al. (2012). McDonald (2012) gave an overview of the results of the ACES animal inhalation studies to the California Air Resources Board in early 2012. The key observations reported were as follows. The majority of the analyses showed no difference between diesel exhaust exposure and clean air controls. Mild/minimal exposure concentration-related hyperplasia was observed in diesel exhaust exposed rats after 3 months of exposure, but not in mice. This hyperplasia increased at 12 months, but was still considered of mild/minimal severity. Statistically significant findings were noted for several indicators of pulmonary stress and inflammation in rats and mice, although fewer changes were noted in mice. Pulmonary function assessments in rats showed slight differences in NTDE exposed rats compared with clean air exposed controls. It is important to note that 200 rats from each group will be available for long-term observations of lung tumors and other disease endpoints with exposures continuing for at least 24 months. A decision will be made no later than at 23 months of exposure as to the merits of continuing the exposures for 30 months. This would be similar to the approach used by Mauderly et al. (1987) in studying TDE. This contrasts with the practice of others, such as the National Toxicology Program, that conducts long-term bioassays that are typically 24 months in duration and usually have much smaller group size (NTP, 2011b).

In addition to the core studies in mice and rats at LRRI, with extensive observations by LRRI scientists, the HEI has provided funding to four other research teams to conduct complementary evaluations of specimens provided by LRRI to each team. These studies include evaluating blood from exposed animals for micronucleus formation (Jeffrey Bennis, Litton Laboratories, Rochester, NY), examining tissues for evidence of vascular inflammation and fibrosis (Daniel Conklin, University of Louisville, Louisville, KY), evaluation of genotoxicity (Lance Hallberg, University of Texas-Galveston, Galveston, TX) and evaluation of cardiovascular function (Qinghua Sun, The Ohio State University, Columbus, OH). An HEI (2012b) report on the results of the ACES animal studies with exposures of up to 12 months duration has been prepared by the investigators under the direction of HEI, been peer-reviewed by a special HEI Review Committee and is available on the HEI website. The report includes separate sections prepared by McDonald et al. (2012), Bemis et al. (2012), Hallberg et al. (2012) and a commentary by the HEI review committee.

In considering the findings through 1 year of exposure for the ACES Phase 3B rat study, it is important to recall that Mauderly et al. (1989, 1990) found modest respiratory tract pathology in rats chronically exposed to 9.5 ppm $NO_2$ for 7 h/day (see Table 7). This equates to 66.5 ppm-hr $NO_2$ exposure/day, and as noted earlier, was viewed as a Maximum Tolerated Dose (MTD) for a long-term study cancer bioassay, such as ACES. The highest exposure concentration in the ACES study is 4.0 ppm $NO_2$ which with 16-h of exposure per day equates to 64 ppm-hr of exposure/day, only slightly lower than the 66.5 ppm-hr/day studied by Mauderly et al. (1989, 1990). In using the daily exposure metric (concentration–time) to set the MTD, it was assumed that the factor of about two difference in exposure rate, expressed as ppm concentration, would not have a major influence on the effectiveness of the $NO_2$ producing effects. Thus, it was anticipated that the rats at the highest exposure level in the ACES study would have $NO_2$-induced respiratory tract effects, i.e. the hallmark oxidant gas-induced lesions described by Plopper et al. (1978, 1979) and Evans (1984) and similar to those observed by Mauderly et al. (1989, 1990) in their study of $NO_2$ alone. Indeed, such effects have been reported by McDonald (2012), Doyle-Eisele et al. (2012) and McDonald et al. (2012). It is important that these respiratory tract effects not be inappropriately interpreted as being related to the trace levels of particulate matter in the NTDE. The HEI Review Panel (HEI, 2012a,b) agreed with the investigator's suggestion that the histologic changes in the lungs in the current study are consistent with responses to $NO_2$. However, the effects of other gaseous components of DE cannot be ruled out.

Bemis et al. (2012) used blood samples from the animals exposed at Lovelace to investigate micronucleus formation in reticulocytes as a measure of genetic damage. No exposure related effects were observed in rats or mice exposed for 1 or 3 months. Hallberg et al. (2012) used the comet assay and the ELISA Assay for 8-hydroxy-deoxyguanosine adducts (8-OHdG) in lung tissue from rats and mice exposed for 1 or 3 months to evaluate potential genetic damage. Neither assay revealed exposure-level related effects. In addition, they used a thiobarbituric acid reactive substance (TBARS) assay to assess oxidative stress and damage in the form of lipid peroxidation in the hippocampus regions of the brains of NTDE-exposed rats and mice. No NTDE-exposure related effects were observed. The HEI review committee (HEI, 2012a,b) agreed that no genotoxic effects were associated with exposures of up to 3 months duration.

## 9. Quantitative and qualitative differences in NTDE compared to TDE

In the following sections, qualitative and quantitative differences in the physical and chemical characteristics of NTDE and TDE are reviewed. For each parameter, the situation with regard to TDE is described as it existed at the time of the earlier IARC (1989) review giving special attention to particular parameters mentioned in the monograph. Some parameters reviewed below were not discussed in the IARC Monograph, but have been raised by others after the 1988 review as being important to the potential association of TDE with health effects. The discussion of TDE is then followed by presentation of detailed findings on NTDE.

### 9.1. Traditional Diesel Exhaust particulate matter

In the earlier monograph (IARC, 1989), TDE was characterized as having a significantly higher concentration 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. IARC estimated that the composition of the particles was approximately 80% elemental carbon.

In a later analysis, the California Air Resources Board (CARB, 1998a–d) estimated that some light-duty diesel engines could emit 50–80 times, and some heavy-duty diesel engines 100–200 times more particulate mass than typical 3-way catalyst-equipped

**Table 8**
Average regulated emissions summary for four FTP composite cycles (1/7*cold-start + 6/7*hot-start), One per ACES Phase 1 2007 engine (Khalek et al., 2011).

| | 1998 EPA standard (g/bhp-hr) | 2007 EPA standard (g/bhp-hr) | 2007 Average emissions (g/bhp-hr) | % Reduction relative to 2007 standard | % Reduction relative to 1998 standard |
|---|---|---|---|---|---|
| PM | 0.1 | 0.01 | 0.0014 ± 0.0007 | 86 | 99 |
| CO | 15.5 | 15.5 | 0.48 ± 0.33 | 97 | 97 |
| NMHC[e] | 1.3[a] | 0.14 | 0.015 ± 0.024 | 89 | 97[d] |
| $NO_x$ | 4.0[b] | 1.2[c] | 1.09 ± 0.15 | 9 | 73 |

[a] EPA limit was based on total hydrocarbon including methane.
[b] EPA limit went to 2.4 g/hp-hr in 2004.
[c] Average value between 2007 and 2009, with full enforcement in 2010 at 0.20 g/hp-hr.
[d] Value is calculated based on Avg. THC value of 0.034 g/hp-hr using the ACES Phase 1 data.
[e] NMHC is reported as the difference between measured THC and methane.

gasoline engines. CARB similarly estimated that the amount of elemental carbon (EC), in the average diesel particle, typically ranged up to 71%. CARB indicated that TDE particles were comprised (by weight) of carbon (88.3%), oxygen (4.9%), hydrogen (2.6%), sulfur (2.5%), metals (1.2%), and nitrogen (0.5%). The fundamental premise was that the particles contained in TDE were mainly aggregates of spherical elemental carbon particles coated with organic and inorganic substances. It was also assumed that the inorganic fraction consisted of small solid carbon particles, ranging from 0.01 to 0.08 μm in size, along with sulfur, oxygen, hydro carbons, sulfate ($SO_4$), CO and $NO_x$.

The Diesel Health Assessment Document (HAD), prepared by the US EPA (2002), reached conclusions similar to those of IARC and CARB regarding the characteristics and composition of TDE. More specifically, the document noted that TDE particles 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" (Recall Fig. 1). EPA concluded that the diesel exhaust 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 earlier monograph (IARC, 1989) included a table that summarized emission data on various diesel and gasoline engines (1980–1985 era) operated on the Federal Test Procedure cycle. The total particulate phase emissions for a heavy-duty diesel vehicle, a light-duty diesel vehicle, a gasoline vehicle without catalytic converter and a gasoline vehicle with catalytic converter were 1036, 246, 62 and 11 mg/km, respectively. The diesel engines of that era operating on high sulfur content fuel can be viewed as producing TDE. The gasoline vehicle operated without a catalytic converter can be viewed as producing TGE and the gasoline vehicle operated with a catalytic converter can be viewed as producing MGE. However, it should be emphasized that gasoline engine and fuel technology continued to evolve post-1980s (Colucci, 2004).

In the sections that follow on the characterization of NTDE, comparisons are made to TDE when data are available. In addition, to provide added perspective some comparisons are made to emissions from modern gasoline and compressed natural gas (CNG) vehicles. The comparisons to gasoline-fueled vehicles are relevant to the forthcoming IARC review which will evaluate both gasoline engine exhaust and diesel engine exhaust as to their human carcinogenic hazard classification.

### 9.2. NTDE emissions are lower than TDE

The results of the detailed ACES characterization study of four engines (compliant with the 2007-EPA emission standards) by Khalek et al. (2011) show that the PM emissions as well as the other three regulated emissions (CO, NMHC, and $NO_x$) were well below the applicable 2007 standards and remarkably lower than the 1998 standard (Table 8) (Khalek et al., 2011). Indeed, the PM emissions were an 86% reduction relative to the 2007 standard and a 99% reduction relative to the 1998 standard (Recall Fig. 2). It is clear that the PM emission levels from new technology heavy-duty diesel engines have been reduced to near-zero levels not unlike those from modern gasoline-fueled, 3-way catalyst equipped (MGE) passenger cars. 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 gasoline-fueled passenger cars) and are similar to the proposed California Air Resources Board Low Emission Vehicle (LEV) III PM standard of .003 g/mi for 2017 and later model year passenger cars (Herner et al., 2009; Khalek et al., 2011) (Fig. 5).

As reviewed in Hesterberg et al. (2011), multiple recent studies of the emissions (g/mile) from heavy-duty transit buses operated with Diesel Particulate Filters have shown that NTDE particulate mass emissions are not "significantly higher" than observed for other technologies, but instead are similar to the PM emission levels from low-emission CNG-fueled (Ayala et al., 2002; Ayala et al., 2003; Gautam et al., 2005; Lanni et al., 2003; LeTavec et al., 2002; McCormick et al., 1999; Northeast, 2000; Norton et al., 1999; Wang et al., 1997) (Fig. 6). While TDE transit bus PM emissions were 0.75 g/mile, the levels for NTDE, are less than 5% of that for TDE. This result holds whether testing is done on the Central Business District cycle, or on other emission test cycles.

A similar result also applies if NTDE PM emission levels are compared to gasoline-fueled vehicles as reviewed in Hesterberg et al. (2011). 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 Figs. 7 and 8), particulate mass emissions (g/mile) for NTDE are quite similar to modern gasoline (and CNG-fueled) vehicles (Ahlvik, 2002; Rijkeboer et al., 1994). The passenger car with TDE PM emissions was found to emit 0.13 g/mile, while the levels are substantially lower for NTDE, CNG and modern gasoline vehicles (0.0019, 0.0187, and 0.090 g/mile, respectively). From a statistical standpoint, the NTDE, CNG, and modern gasoline passenger vehicles are significantly different from the TDE vehicles, while the NTDE passenger cars are not significantly different from the modern gasoline or CNG vehicles (Fig. 9).

In summary, data developed since 1989 clearly show that the particulate mass emissions rates from NTDE are substantially lower than those for TDE, and are statistically indistinguishable from the near-zero PM emission levels seen from modern low-emission gasoline-fueled 3-way catalyst equipped vehicles and CNG-fueled vehicles. Thus, the primary emission constituent of concern (PM) – the emission constituent that served as the focus of IARC's 1989 evaluation of diesel engine exhaust – has been virtually eliminated and reduced in NTDE to the near-zero levels of modern gasoline-fueled vehicles equipped with 3-way catalysts.

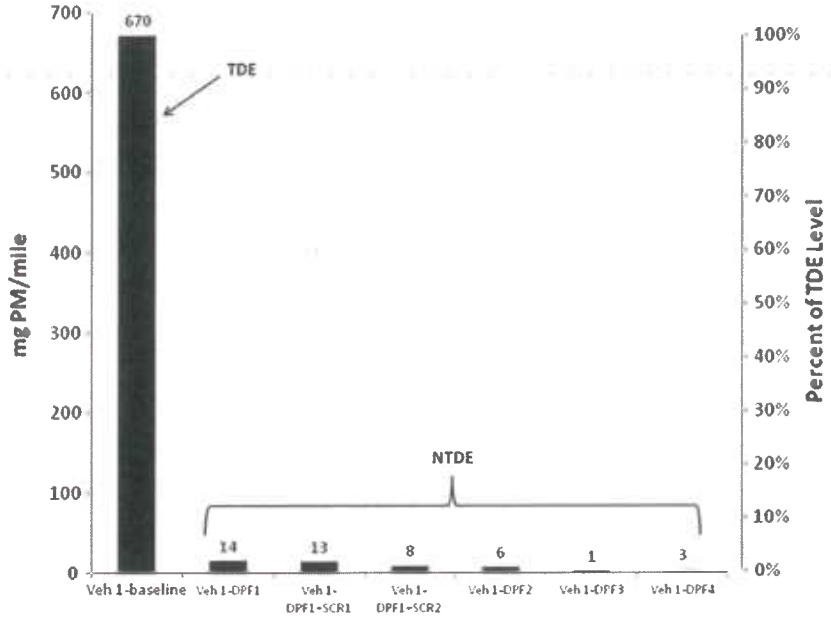


**Fig. 5.** Particle mass emissions for Traditional Diesel Exhaust (TDE) vehicle and six vehicles with New Technology Diesel Exhaust (NTDE) configured with Diesel Particulate Filters (DPF) and Selective Catalytic Reduction (SCR) systems (Data from Herner et al., 2009). Expressed as mg/km on left and as percent of TDE on right. The number at the top of each bar is particle mass emissions in mg/mile.

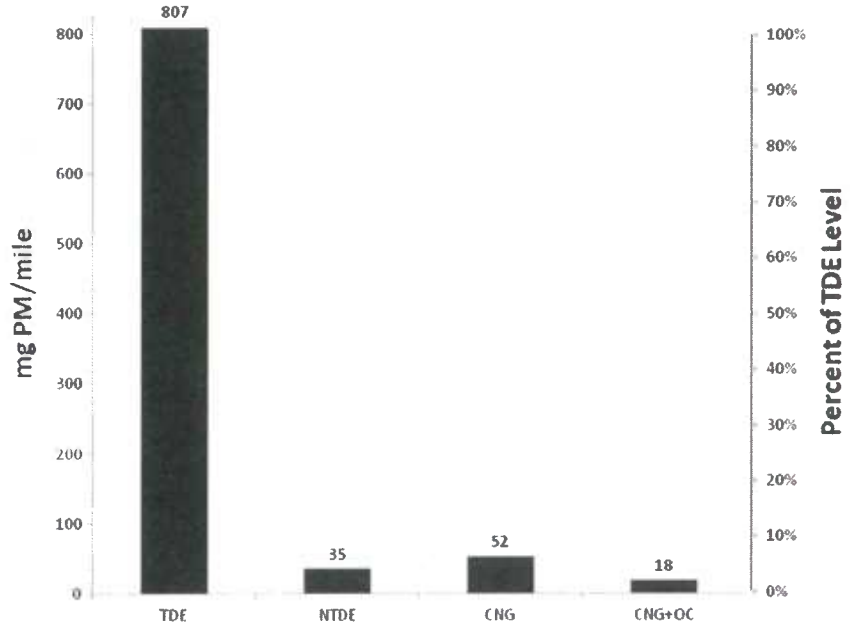


**Fig. 6.** Particulate emissions for transit buses fueled with diesel fuel (NTDE) or compressed natural gas (CNG) and operated with or without an oxidation catalyst (OC). Emissions in mass/mile on the left and as % of TDE on the right (Data from Hesterberg et al., 2008).

### *9.3. NTDE particulate matter has different composition than TDE*

Recall that the particulate matter in TDE was primarily elemental carbon (frequently on the order of 80%). In contrast, the near-zero amount of PM emitted from new-technology diesel engines evaluated in the ACES program contain only 13% elemental carbon (Khalek et al., 2011). Thus, the soot or elemental carbon core fraction of NTDE as shown in Fig. 1 is largely nonexistent.

Other studies have shown that elemental carbon represents only a small portion of the total carbon (TC) fraction of NTDE. For NTDE, elemental carbon (EC) represented 17% of the total carbon (TC) (TC = EC + organic carbon (OC). For particulate emissions from CNG-fueled and port fuel-injection gasoline engines, elemental carbon represented only 3% and 5%, respectively, of the total carbon (Holmén and Ayala, 2002; Lev-On et al., 2002; Schauer et al., 2008; Liu et al., 2009a). Further, the portion of TC present

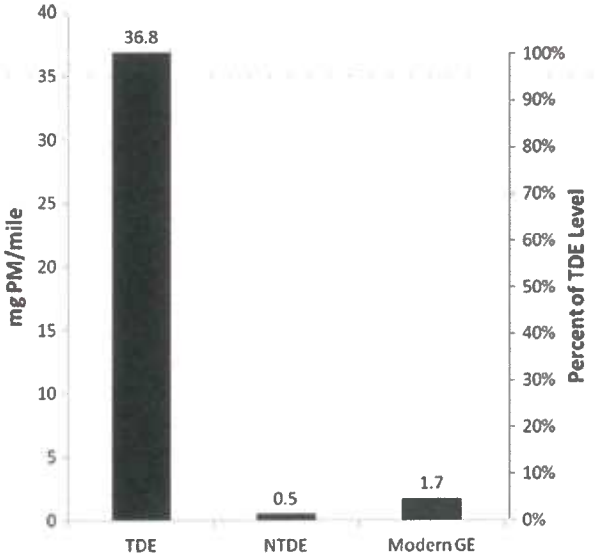


**Fig. 7.** Particulate emissions (PM) expressed in mg PM/mile on left and % Traditional Diesel Exhaust (TDE) on right for passenger cars with different engine technologies (data from Ahlvik, 2002).

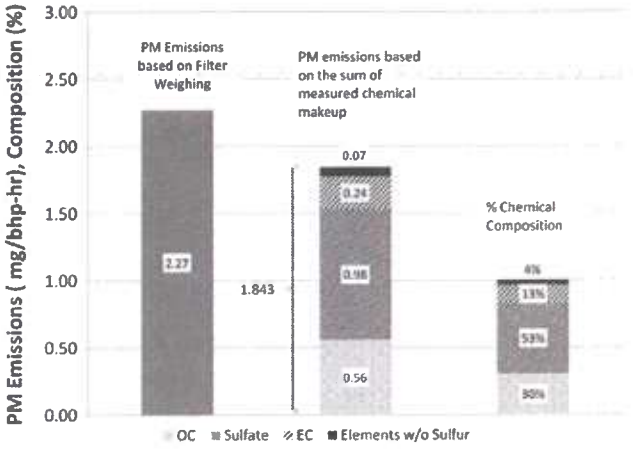


**Fig. 9.** Average PM Emissions Rate and Composition for all twelve repeats of the 16-h cycles using all four ACES Engines (Data taken from animal exposure chambers without animals present; PM mass emissions from constant volume sampler system are 50% lower) (Khalek et al., 2011).

as EC for NTDE and CNG are not significantly affected by engine test cycle or workload. In contrast, the portion of TC present as EC for TDE increases markedly (from approximately 60% to 90%) as the workload increases from the steady-state cycle to the transient Central Business District cycle.

In contrast with the PM contained in TDE that served as the basis for the earlier 1989 IARC evaluation, the near-zero levels of PM found in NTDE are dominated by sulfate (53%) and organic carbon (30%) – not a solid carbon core (Fig. 10). The EC has been largely eliminated (Biswas et al., 2009; Kittelson et al., 2006b). To provide added perspective, Fig. 10 also shows composition data for a modern gasoline-fueled vehicle equipped with a 3-way catalytic converter in the exhaust line (Ahlvik, 2002).

Kittelson et al. (2006b) conducted a study in which they varied the sulfur content of the diesel fuel from 2 to 44 ppm. They found that the nitrate, volatile organics and carbon fractions were relatively constant for all the sulfur levels while the sulfate fraction increased monotonically with increasing fuel sulfur concentration (Fig. 11). It is noteworthy that the elemental carbon fraction was extraordinarily low when the sulfur content of the fuel was 2 or 9 ppm, sulfur concentrations that would result in the fuel being compliant with EPA's 2007 diesel fuel standard.

Grose et al. (2006) has shown that the nanoparticle emissions contained in NTDE are predominantly ammonium sulfates and sulfuric acid, which are fully water-soluble. Soluble sulfate particles, which will tend to undergo dissolution in the lungs, are of low toxicity (Grahame and Schlesinger, 2005; Reiss et al., 2007; Schlesinger and Cassee, 2003; Schlesinger, 2007).

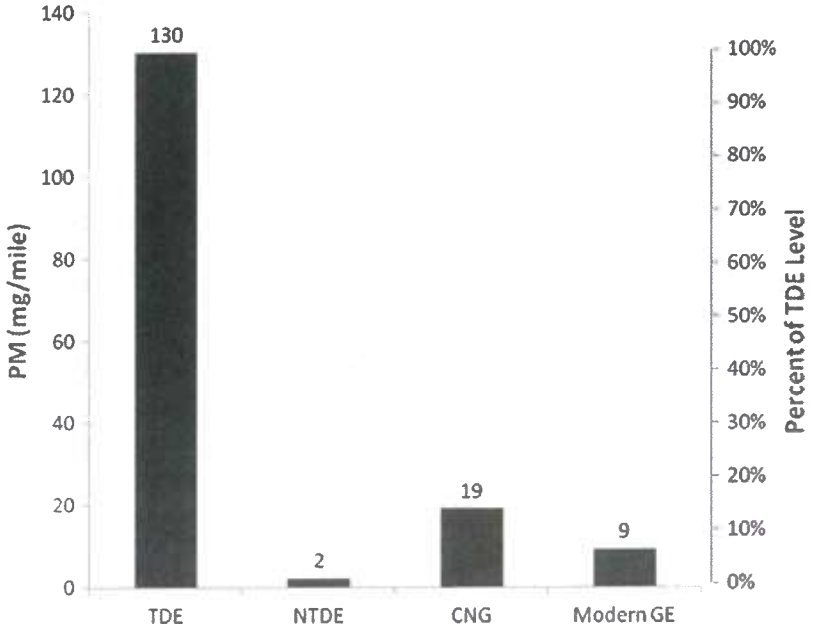


Fig. 8. Particulate Matter (PM) emissions, expressed as mg PM/mile on left and % Traditional Diesel Exhaust (TDE) on right, for Passenger Cars. Data from **Ahlvik (2002)** and **Rijkeboer et al. (1994)** as reviewed by **Hesterberg et al. (2011)**.

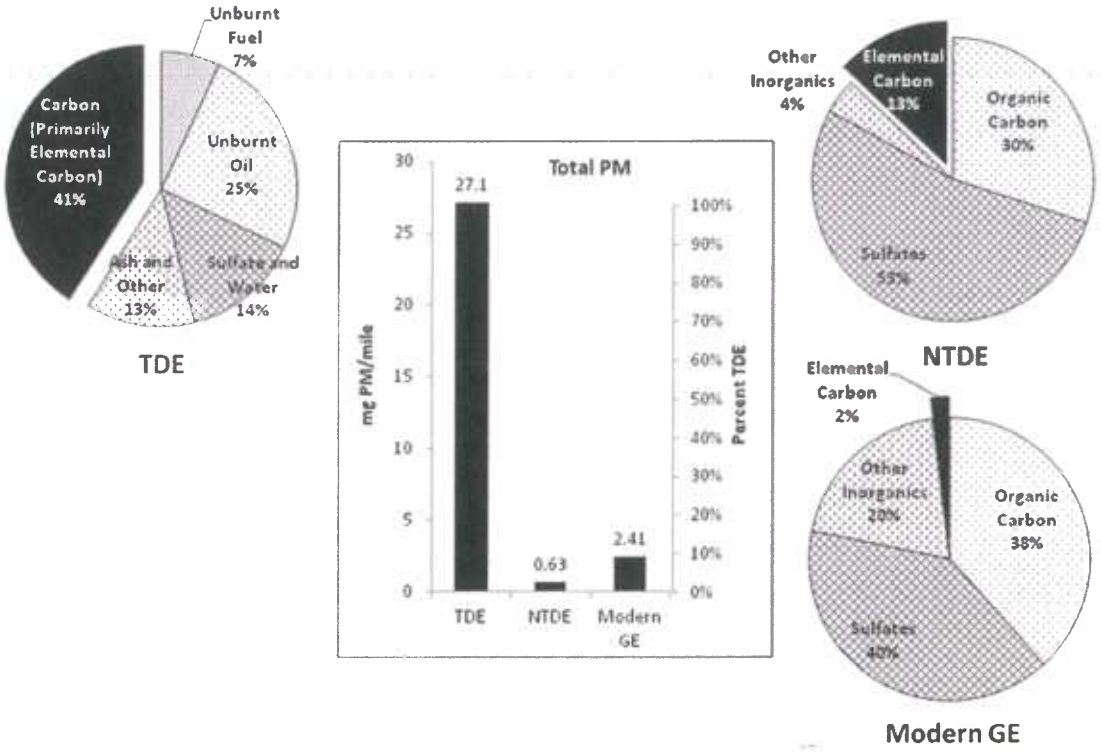


**Fig. 10.** Composition of Particulate Matter from Traditional Diesel Exhaust (TDE) (Kittelson, 1998), New Technology Diesel Exhaust (NTDE) (Khalek et al., 2011) and Modern Gasoline Exhaust (MGE) (Cheung et al., 2009).

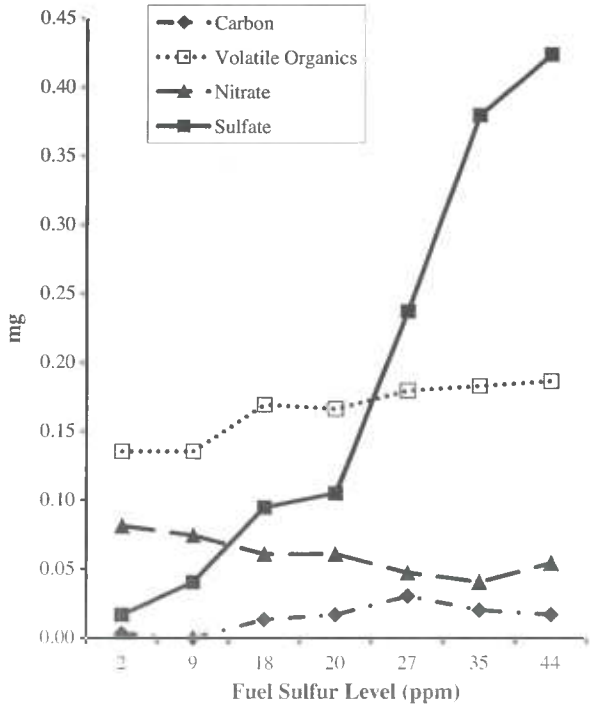


**Fig. 11.** Measured particulate matter emissions (carbon, volatile organic compounds, sulfate and nitrate) continuously regenerating diesel particulate filter from a heavy duty diesel engine as a function of fuel sulfur content (Adapted from Fig. 3 in Kittelson et al., 2006b).

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).

In sum, compared against TDE, NTDE represents a 99.7% reduction in EC, a more than 93% reduction in OC, and a greater than 90% reduction in PAHs (Liu et al., 2008a). The content of any remaining nucleation mode particles in NTDE is dominated by sulfate, and, to a lesser extent, volatile organics, which disappear through evaporation (Biswas et al., 2008). Accordingly, another assumption relating to TDE – that diesel PM is dominated by high levels of organic carbon compounds and a solid carbon core – is fundamentally inapplicable as it pertains to NTDE.

Another key premise in the earlier review (IARC, 1989) relating to evaluating the health effects potentially attributable to TDE is that it contains "many PAHS" and "at least 10 times more nitroarenes than gasoline engines." The monograph identified 60 agents in engine exhaust (not specified as to being found in diesel or gasoline engine exhaust or both) that had been evaluated by IARC. The CARB (1998a–d) identified over 40 components of TDE that had been listed as toxic air contaminants (TAC) or hazardous air pollutants (HAP) by US EPA and other agencies.

The speciated emission components of NTDE are, again, fundamentally different from what was assumed to be present in TDE. Khalek et al. (2011) found that the 40 TACs previously thought to be in TDE were reduced in NTDE by up to 99% or are present in zero-equivalent amounts (including amounts at or below the detection limit), or both (Table 9). These results – like all of the other results reported from the ACES Phase 1 program – are very significant since they were obtained with engines operating on an exceedingly rigorous 16-h test cycle (including urban, creep, transient and cruise mode conditions). The cycle was specifically designed to generate higher-end emission levels (Clark et al. 2007) as compared to emissions from engines operated over the 20-min FTP transient engine-certification test cycle.

**Table 9**
California Air Resources Board Toxic Air Contaminants: average emissions for all twelve repeats of the 16-h cycles for all four 2007 ACES engines, and for 1994 to 2000 technology engines running over the FTP transient cycle (Khalek et al., 2011).

| TAC No. | Compound | 1994–2000 Technology engines[d] (mg/bhp-hr) | 2007 Technology engines[a] (mg/bhp-hr) | % Reduction |
|---|---|---|---|---|
| 1 | Acetaldehyde | 10.3 | 0.61 ± 0.27 | 93 |
| 2 | Acrolein | 2.7 | <0.01 | >99 |
| 3 | Aniline | [c] | 0.000150 ± 0.000075 | [c] |
| 4 | Antimony compounds | [c] | <0.001 | [c] |
| 5 | Arsenic | [c] | <0.0002 | [c] |
| 6 | Benzene | 1.82 | <0.01 | >99 |
| 7 | Beryllium compounds | [c] | <0.0003 | [c] |
| 8 | Biphenyl | [c] | 0.013780 ± 0.001716 | [c] |
| 9 | Bis[2-ethylhexyl]phthalate | [c] | [b] | [c] |
| 10 | 1,3-Butadiene | 1.7 | <0.01 | >99 |
| 11 | Cadmium | [c] | <0.00003 | [c] |
| 12 | Chlorine (chloride) | 0.18 | <0.007 | >96 |
| 13 | Chlorobenzene and derivatives | [c] | [b] | [c] |
| 14 | Chromium compounds | [c] | 0.0007 ± 0.0003 | [c] |
| 15 | Cobalt compounds | [c] | <0.0001 | [c] |
| 16 | Cresol isomers | [c] | 0.02727 ± 0.01233 | [c] |
| 17 | Cyanide compounds | [c] | <0.05 | [c] |
| 18 | di-*n*-Butylphthalate | [c] | [b] | [c] |
| 19 | Dioxins and dibenzofurans | 0.000066 | 0.00000066 ± 0.000000055 | 99 |
| 20 | Ethylbenzene | 0.49 | 0.05 ± 0.04 | 90 |
| 21 | Formaldehyde | 25.9 | 1.90 ± 1.01 | 94 |
| 22 | Hexane | 0.14 | <0.01 | >93 |
| 23 | Inorganic lead | 0.0009 | <0.0001 | >89 |
| 24 | Manganese | 0.0008 | <0.00022 | >73 |
| 25 | Mercury | [c] | <0.00016 | [c] |
| 26 | Methanol | [c] | 0.07 ± 0.13 | [c] |
| 27 | Methyl ethyl ketone | [c] | <0.01 | [c] |
| 28 | Naphthalene | 0.4829 | 0.0982000 ± 0.0423000 | 80 |
| 29 | Nickel | 0.01 | 0.0002 ± 0.0001 | 98 |
| 30 | 4-Nitrobiphenyl | [c] | <0.00000001 | [c] |
| 31 | Phenol | [c] | 0.00905 ± 0.00414 | [c] |
| 32 | Phosphorus | [c] | 0.0130 ± 0.0064 | [c] |
| 33 | POM (Polycyclic Organic Matter), including PAHs and derivatives | See Table 11 | See Table 11 | See Table 11 |
| 34 | Propionaldehyde | 1.8 | 0.01 | >99 |
| 35 | Selenium | [c] | <0.0001 | [c] |
| 36 | Styrene | 0.73 | <0.01 | >99 |
| 37 | Toluene | 0.64 | 0.26 ± 0.28 | 59 |
| 38 | Xylene isomers and mixtures | 2.2 | 0.35 ± 0.10 | 85 |
| 39 | *o*-Xylene | 0.99 | 0.13 ± 0.07 | 87 |
| 40&41 | m&p-Xylenes | 1.21 | 0.20 ± 0.08 | 83 |

[a] The significant figures signify the detection limit in mg/bhp-hr.
[b] Not measured.
[c] Not available.
[d] Standard deviation data were not provided by references 15 and 16.

Similarly, a comparison of a 2004 model year engine and a 2007 model year engine equipped with a catalyzed DPF after-treatment system and a crankcase ventilation coalescer has shown that NTDE contains dramatically reduced levels of many of the compounds that could be identified and quantified in the 2004 model year engine. That included compounds such as formaldehyde and acetaldehyde for which concentrations were dramatically reduced (Liu et al., 2009b). Many of the compounds were below the limits of detection (Table 10). The catalyzed exhaust after-treatment system and crank case ventilation coalescer are typical of those used in commercial 2007 on-road heavy-duty units. As shown in Figs. 12–14 when the emissions of the 2007 engine with contemporary emission controls were compared to the emissions from the 2004 engine, there was a marked reduction in polycyclic aromatic hydrocarbons (PAHs), nitro-PAHs, and oxygenated-PAHs (Liu et al., 2010).

Thus, NTDE simply does not contain the levels of specific elements that prompted regulatory analyses and concerns at the time of IARC's evaluation of TDE in 1989.

### 9.4. Semi-volatile organic fraction of NTDE is different than TDE

The earlier monograph (IARC, 1989) also assumed that the sponge-like structure and large surface area of the elemental carbon 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. Other assumptions were that the majority of the soluble organic fraction (SOF) was adsorbed onto the surface of the EC core, that the SOF accounted for up to 45% of the total particulate mass, and that the sulfate fraction of diesel exhaust PM could contribute up to 14% of the diesel exhaust particle.

The ACES Phase 1 study (Khalek et al., 2011) 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 (Fig. 15). 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-volatile phase. NitroPAHs and oxyPAHs are present in even closer-to-zero amounts, a mere 1% of the semi-volatile phase.

Significantly, when compared to TDE, NTDE has 99% reductions in 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 (Liu et al., 2008a; Pakbin et al., 2009). NTDE also has 96–98% reductions compared to TDE in other particulate

**Table 10**
Organic species emissions comparison from a 2004 HD diesel engine (fuel sulfur content of 308.5 ppm) without after-treatment, and a 2007 HD diesel engine (fuel sulfur content of 9.2 ppm) equipped with a catalyzed DPF system (Liu et al., 2010).

| Compound (carbon number) | 2004 Engine | 2007 Engine | % Reduced |
|---|---|---|---|
| Elemental carbon | 49700 ± 3550 | 150 ± 38.2 | 99.7 ± 7.2 |
| Organic carbon | 37800 ± 4360 | 213 ± 101 | 99.4 ± 11.8 |
| Organic mass | 45300 ± 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 |

(continued on next page)

**Table 10** (*continued*)

| Compound (carbon number) | 2004 Engine | 2007 Engine | % Reduced |
|---|---|---|---|
| Xanthone (13) | 8.75 ± 3.94 | 0.386 ± 0.0908 | 95.6 ± 46.1 |
| 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),21ß(H)-hopane (30) | 1.67 ± 0.0558 | 0.0109 ± 0.0109 | 99.3 ± 4.0 |
| 22S-17α(H),21ß(H)-29-homohopane (31) | 0.925 ± 0.0309 | <0.01 ± 0.00 | 98.9 ± 3.3 |
| 22R-17α(H),21ß(H)-29-homohopane (31) | 0.545 ± 0.284 | <0.01 ± 0.00 | 98.2 ± 52.1 |
| 22S-17α(H),21ß(H)-29,30-bishomohopane (32) | 2.11 ± 1.60 | <0.01 ± 0.00 | 99.5 ± 75.8 |
| 22R-17α(H),21ß(H)-29,30-bishomohopane (32) | 0.288 ± 0.144 | <0.01 ± 0.00 | 96.5 ± 50.0 |
| 22R-17α(H),21ß(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),14ß(H),17ß(H)-cholestane (27) | 0.576 ± 0.0438 | <0.01 ± 0.00 | 98.3 ± 7.6 |
| 20S-5α(H),14ß(H),17ß(H)-cholestane (27) | 0.749 ± 0.0729 | <0.01 ± 0.00 | 98.7 ± 9.7 |

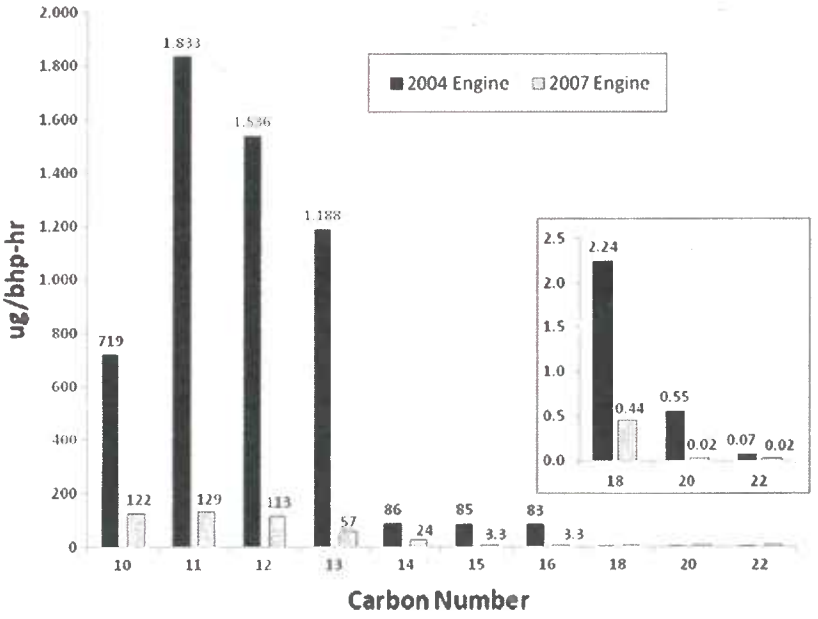


**Fig. 12.** Reduced concentrations of polycyclic aromatic hydrocarbons in emissions from 2007 diesel engine with contemporary emission controls compared to emissions from a 2004 engine without contemporary emission controls (Liu et al., 2010).

organic species, including n- alkanes, hopanes, and steranes, when compared to TDE (Pakbin et al., 2009). Similar reductions of C1, C2, and C10–C33 particle-phase and semi-volatile organic compound species in NTDE were noted by Liu et al. (2010) (Table 10).

All of these data confirm that the finding for the semi-volatile fraction of TDE do not hold for NTDE.

*9.5. NTDE contains lower amounts of unregulated pollutants than TDE*

The earlier monograph (IARC, 1989) assumed that TDE might contain a significant amount of several unregulated pollutants of concern. The ACES Phase 1 study measurements for a number of classes of compounds of interest are shown in Table 11 (Khalek et al., 2011). Even using conservative estimates from the various measurement techniques used in the ACES program, NTDE has substantial reductions (71–99%) in the emissions of unregulated pollutants when compared against 2004-technology engines. Moreover, particle-bound trace metals and elements also have been reduced very significantly (by an average of 98%) in NTDE (Khalek et al., 2011). It is important to recall that earlier TDE engines (typical of 1960–1980) likely had much higher emissions than the ca. 2000 engines with improved TDE profiles. Thus, the reductions compared to earlier engines and fuels would be even more profound.

As detailed in Table 12 (Khalek et al., 2011), NTDE contains substantially less PAHs than found in emissions from earlier model year engine technologies. As noted, 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%.

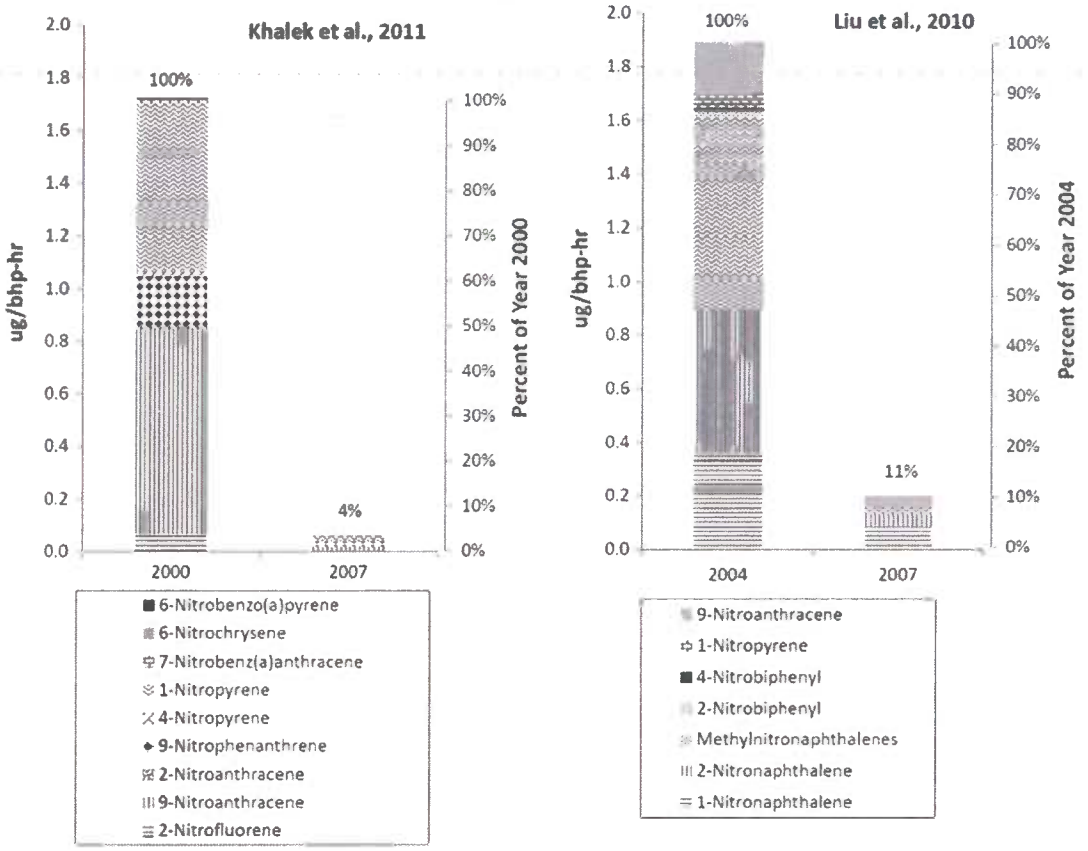


**Fig. 13.** Concentration of nitro-polycyclic aromatic hydrocarbon in 2007 model engine with contemporary emission controls compared to 2004 model engines without contemporary emission controls (left), Liu et al. (2010) and 2007 model (ACES engines) compared to 2000 mode engines (right) (Khalek et al., 2011).

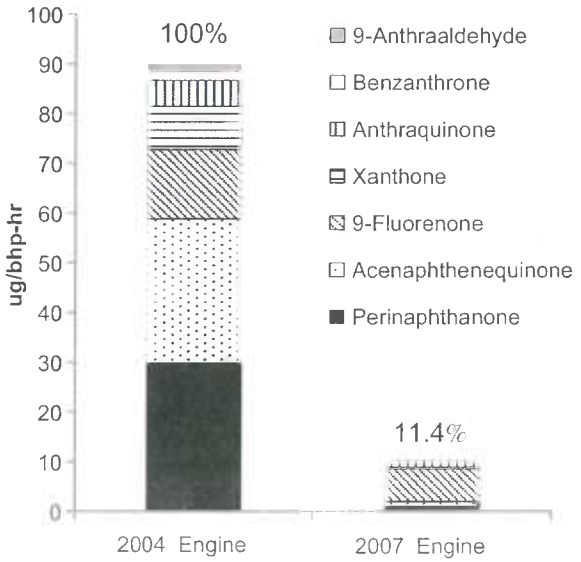


**Fig. 14.** Concentration of oxygenated polycyclic aromatic hydrocarbons from 2004 model engine without exhaust after-treatment compared to 2007 model with contemporary controls. AcNQ: acenaphthenquinone; 9-Flu: 9-fluorenone; Xant: xanthone; PNQQ: perinaphthanione; AQ: anthraquinone; 9-antal: anthraldehyde; and Bzon: benzanthrone (Liu et al., 2010).

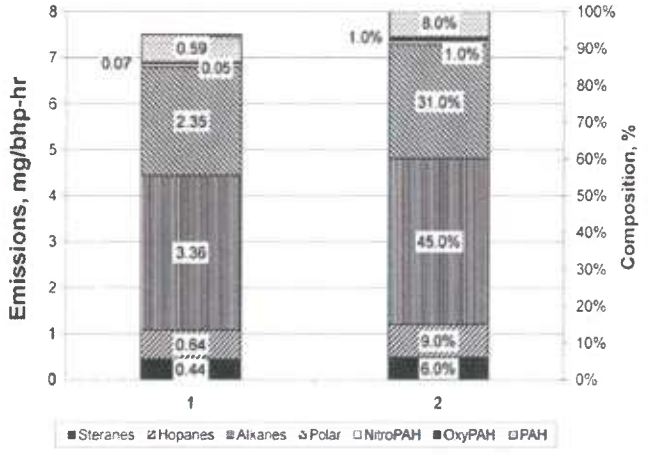


**Fig. 15.** Average particle phase semi-volatile emission rate and composition for all twelve repeats of the 16-h cycles using all four ACES engines (Khalek et al., 2011).

Thus, the exhaust emission compounds of potential concern for producing health effects have been reduced to near-zero levels in NTDE. It is also apparent that the NTDE after-treatment systems are not resulting in the formation of other potential contaminants based on the extensive chemical characterization of NTDE performed to date. If unique chemical species are present in NTDE, they are at extraordinarily low concentrations that would not pose a health hazard. 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 compressed natural gas engines equipped with catalyzed mufflers (Hesterberg et al., 2008).

**Table 11**
Summary of average unregulated emissions for all twelve repeats of the 16-h cycles for all four 2007 ACES engines and for 2004 technology engines used in CRC E55/E59 (Dioxins were compared to 1998 levels) (Khalek et al., 2011).

| | 2004 Engines Avg. ± stdev. (mg/hr) | 2007 Engines[a] Avg. ± stdev. (mg/hp-hr) | 2007 Engines Avg. ± stdev. (mg/hr) | Avg. % reduction relative to 2004 technology engines (%) |
|---|---|---|---|---|
| Single ring aromatics | 405.0 ± 148.5 | 0.76 ± 0.35 | 71.6 ± 32.97 | 82 |
| PAH | 325.0 ± 106.1 | 0.74 ± 0.25 | 69.7 ± 23.55 | 79 |
| Alkanes | 1030.0 ± 240.4 | 1.64 ± 0.83 | 154.5 ± 78.19 | 85 |
| Hopanes/steranes | 8.2 ± 6.9 | 0.0011 ± 0.0013 | 0.1 ± 0.12 | 99 |
| Alcohols and organic acids | 555.0 ± 134.4 | 1.14 ± 0.27 | 107.4 ± 25.4 | 81 |
| Nitro-PAH | 0.3 ± 0.0 | 0.0065 ± 0.0028 | 0.1 ± 0.0 | 81 |
| Carbonyls | 12500.0 ± 3535.5 | 2.68 ± 1.00 | 255.3 ± 95.2 | 98 |
| Inorganic ions | 320.0 ± 155.6 | 0.98 ± 0.40 | 92.3 ± 37.7 | 71 |
| Metals and elements | 400.0 ± 141.4 | 0.071 ± 0.032 | 6.7 ± 3.0 | 98 |
| OC | 1180.0 ± 70.7 | 0.56 ± 0.50 | 52.8 ± 47.1 | 96 |
| EC | 3445.0 ± 1110.2 | 0.24 ± 0.05 | 22.6 ± 4.7 | 99 |
| Dioxins/furans | N/A | 6.6E−07 ± 5.5E−07 | 6.2E−05 ± 5.2E−05 | 99[b] |

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

**Table 12**
PAH and nitro-PAH average emissions for all twelve repeats of the 16-h cycles for all four 2007 ACES engines, and for 2000 technology engine running over the FTP transient cycle (Khalek et al., 2011).

| PAH and nitroPAH Compounds | 2000 Technology Engine[a,b] mg/bhp-hr | 2007 Engines[a] mg/bhp-hr | % Reduction |
|---|---|---|---|
| Naphthalene | 0.4829 | 0.0982000 ± 0.0423000 | 80 |
| Acenaphthylene | 0.0524 | 0.0005000 ± 0.0005000 | 98 |
| Acenaphthene | 0.0215 | 0.0004000 ± 0.0001000 | 98 |
| Fluorene | 0.0425 | 0.0015000 ± 0.0009000 | 96 |
| Phenanthrene | 0.0500 | 0.0077000 ± 0.0025000 | 85 |
| Anthracene | 0.0121 | 0.0003000 ± 0.0001000 | 97 |
| Fluoranthene | 0.0041 | 0.0006000 ± 0.0006000 | 85 |
| Pyrene | 0.0101 | 0.0005000 ± 0.000400 | 95 |
| Benzo(*a*)anthracene | 0.0004 | <0.0000001 | >99 |
| Chrysene | 0.0004 | <0.0000001 | >99 |
| Benzo(*b*)fluoranthene | <0.0003 | <0.0000001 | >99 |
| Benzo(*k*)fluoranthene | <0.0003 | <0.0000001 | >99 |
| Benzo(*e*)pyrene | <0.0003 | <0.0000001 | >99 |
| Benzo(*a*)pyrene | <0.0003 | <0.0000001 | >99 |
| Perylene | <0.0003 | <0.0000001 | >99 |
| Indeno(123-cd)pyrene | <0.0003 | <0.0000001 | >99 |
| Dibenz(*a,h*)anthracene | <0.0003 | <0.0000001 | >99 |
| Benzo(*g,h,i*)perylene | <0.0003 | <0.0000001 | >99 |
| 2-Nitrofluorene | 0.0000650 | 0.00000360 ± 0.00000410 | 94 |
| 9-Nitroanthracene | 0.0007817 | 0.0000148 ± 0.0000213 | 98 |
| 2-Nitroanthracene | 0.0000067 | 0.00000040 ± 0.00000090 | 94 |
| 9-Nitrophenanthrene | 0.0001945 | 0.00002110 ± 0.00002090 | 89 |
| 4-Nitropyrene | 0.0000216 | <0.00000001 | >99 |
| 1-Nitropyrene | 0.0006318 | 0.00001970 ± 0.00002430 | 97 |
| 7-Nitrobenz(*a*)anthracene | 0.0000152 | 0.00000020 ± 0.00000020 | 99 |
| 6-Nitrochrysene | 0.0000023 | <0.00000001 | >99 |
| 6-Nitrobenzo(*a*)pyrene | 0.0000038 | <0.00000001 | >99 |

[a] The significant figures signify the detection limit in mg/bhp-hr.
[b] Standard deviation data were not provided by reference 15.

On the other hand, when compared against NTDE, CNG-fueled engines have been found to produce an order of magnitude more carbonyls (especially formaldehyde), and two orders of magnitude more ethylene and propylene emissions (Lanni et al., 2003). In particular, when compared against the exhaust from CNG-fueled engines, NTDE has significantly lower emissions of 1,3-butadiene (i.e. non-detect levels), benzene, toluene, and carbonyls (especially formaldehyde); similarly low emissions of PAHs; and significantly lower specific mutagenic activity, and mutagen emissions (Kado et al., 2005).

In summary, it is our opinion that NTDE does not contain significant amounts of any unregulated or regulated pollutants that might be of concern from a public health perspective.

### 9.6. NTDE particulate mass is fundamentally different than TDE particulate mass

A core assumption regarding TDE in the earlier evaluation (IARC, 1989) was that diesel exhaust contains a number of toxicologically relevant compounds such as benzene, toluene, xylene and PAHs, and that these PAH compounds were primarily absorbed onto particles. Significantly, much of the information regarding the genotoxicity of TDE was obtained using diesel exhaust particles or organic solvent extracts of diesel exhaust particles.

As detailed above, the nature and composition of diesel exhaust particles in NTDE have changed dramatically and fundamentally from the TDE (emitted from 1970s and 1980s-era diesel engines)

evaluated earlier by IARC (1989). The EC core has been virtually eliminated from NTDE. Instead, the very low concentration nanoparticle emissions in NTDE have a sulfate-rich composition primarily associated with the nucleation of sulfates downstream from the after-treatment systems. This type of sulfate-rich composition differs from the hydrocarbon-rich composition associated with the nuclei mode particles in TDE (Tobias et al., 2001). The relative absence of insoluble elemental carbon, and the presence instead of a larger portion of sulfates, should result in the nanoparticles in NTDE being relatively biosoluble compared to the EC rich particles in TDE. Given this biosolubility and the very low concentrations of NTDE particle mass, it is very unlikely that NTDE could result in any respiratory tract accumulation of particle mass. Furthermore, especially when considered in light of the near-zero concentrations of the organic compounds found in NTDE (if found at all), the earlier *in vitro* findings relating to TDE particles and their extracts are not germane to NTDE.

### 9.7. Lower nanoparticles emissions from NTDE

Concern was expressed as early as the 1980s that more nanoparticles particles could be formed as a result of then-emerging new diesel engine technologies, which could pose a potential health hazard. It is now known that this hypothesized hazard does not exist. Kittelson et al. (2006a,b) using a novel on-road experimental setup demonstrated the impact of exhaust after-treatment systems in reducing nanoparticle emissions from diesel engines. The ACES Phase 1 study similarly revealed that the average total number of particles in NTDE (from engines operating on the FTP transient cycle) was 99% lower than from a 2004 technology engine (and 89% lower when operating on a cycle that triggers regeneration events) (Fig. 16) (Khalek et al., 2011).

An additional perspective on the influence of the catalyzed diesel particulate filter (C-DPF) on the particle emissions is illustrated in Fig. 17 (Khalek et al., 2011). In this figure, the average size distribution of particles is shown for a 2004 engine operating without a C-DPF and a 2007 engine (compliant with EPA emission standards) with a C-DPF device. The geometric number mean diameter (GNMD) observed for the 2004 engine without a C-DPF was 46 nm. For the 2007 engine, size distribution data are plotted for 19 cycles when regeneration was occurring and 29 cycles without regeneration. The C-DPF impacts on particle number during both the cycles with and without regeneration. The net effect which is not shown will, of course, be a reflection of the portion of the total operating

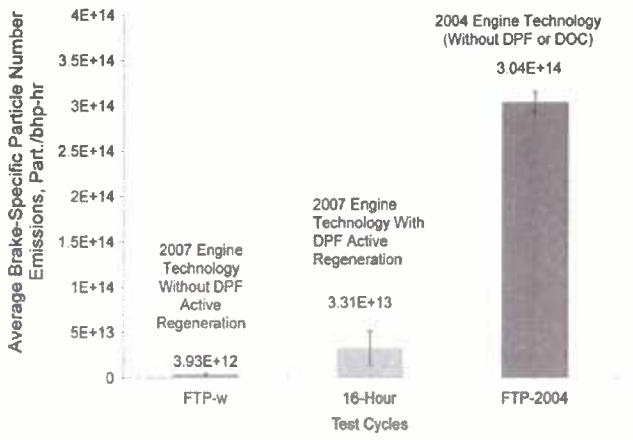


Fig. 16. Average particle number emissions comparison between 2007 ACES engines with and without catalyzed Diesel Particulate Filter (DPF) regeneration and 2004 technology engine without DPF or diesel oxidation catalyst (DOC) (Khalek et al., 2011). Note the log scale.

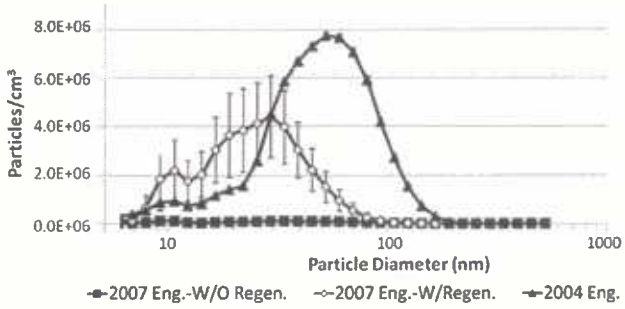


Fig. 17. Average size distribution comparison between four 2007 ACES engines during 19 4-h segments with regeneration using a catalyzed-diesel particulate filter and 29 4-h segments without regeneration and a 2004-technology engine operating without an oxidation catalyst or catalyzed diesel particulate filter (adapted from Khalek et al., 2011).

time that involves regeneration events. For the 2007 engine, the GNMD was reduced to 25 nm during regeneration and the number of particles emitted reduced compared to the 2004 engine without a C-DPF. With the 2007 engine, the GNMD was 40 nm for the very low number of particles emitted during the cycles when regeneration was not occurring. Khalek et al. (2011) also noted that the particle distribution measurements were made in the exposure chamber (without animals present) for the 2007 engines. In contrast, the measurements for the 2004 engine were taken in the constant volume sampler which would involve fresher exhaust. They speculate that the particle number emissions, especially of nuclei-mode volatile particle, for the 2004 engine would have been higher if the measurements had been made in an exposure chamber further downstream from the engine. They also note that the particle numbers would have been higher for the 2004 engine if it had been operating with a higher sulfur content fuel typical of the pre-2007 time period. Thus, it is apparent that the number of particles contained in NTDE has been dramatically reduced – even more so when compared with TDE (as opposed to a 2004 model year engine) – and, thus, should not raise any unique health concerns.

In fact, the nanoparticle number concentration emissions contained in NTDE are well below typical urban ambient air concentrations, and amount to a 10,000-fold reduction when compared against older diesel engines not equipped with DPFs (Barone et al., 2010). Other studies have confirmed that the particle numbers contained in NTDE have been lowered to below ambient background levels (Kittelson et al., 2006a,b). In fact, particle number emissions from NTDE on average, are about two orders of magnitude lower than TDE (Holmén and Ayala, 2002; Holmén and Qu, 2004).

Further, under higher load conditions, the particle count from NTDE is essentially undetectable when compared against ambient background particle counts. Still other studies have confirmed that the particle number emissions contained in NTDE are more than three orders of magnitude lower than TDE, and 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 (Liu et al., 2007) (Fig. 18). It is apparent that the significant reduction of sulfur content in diesel fuel resulting from the adoption of the ULSD fuel standards (<15 ppm) has played a role in reducing fine particle emissions as well as allowing the use of catalytic exhaust after-treatment systems. Indeed, there are reports from Denmark (Wahlin et al., 2001) and England (Jones et al., 2012) that introduction of very low sulfur content diesel fuel in those countries resulted in

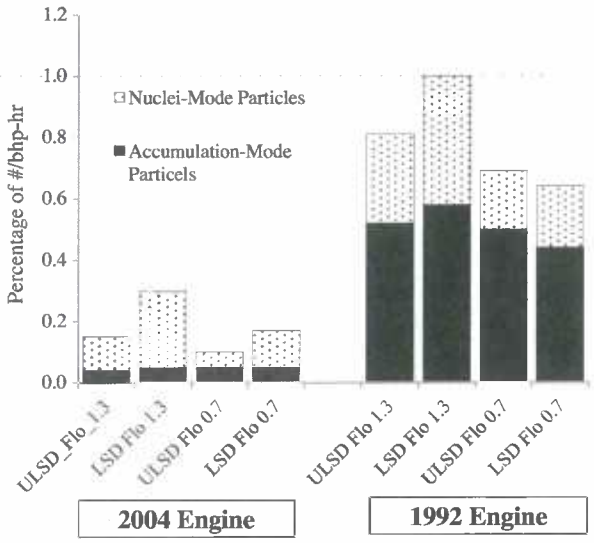


**Fig. 18.** Normalized total Particulate Matter number emissions during entire Federal Test Procedure cycles for a 1992 TDE and a 2004 engine equipped with an Exhaust Gas Recirculation system operating on either ultra-low sulfur <15 ppm) and low sulfur (308 ppm) fuel, with flow rates of 0.7 or 1.3 $m^3$/S (Liu et al., 2007).

substantial reductions in ambient air particle number concentrations soon after the low sulfur content fuel was introduced. Thus, the reduction in ambient particle number was a reflection of the change in fuel in the absence of any changes in the diesel engines.

Herner et al. (2011) have investigated the role of both sulfur storage and exhaust temperature as determinants of the occurrence of nucleation mode particles. Their findings were reviewed by Hesterberg et al. (2012b) who also noted the extent to which the trace concentrations of sulfate-rich particles should not be of concern either due to direct toxicity or from the standpoint of accumulating in the respiratory tract.

In summary, contrary to the concern that new diesel technologies (including DPFs) could augment the formation of nanoparticles, advanced DPFs operating on ULSD are highly efficient in suppressing the PM nucleation mode, and exhibit up to a 1000-fold reduction (or even more) in nucleation mode particles when compared with TDE (Biswas et al., 2008). Consequently, in this very important aspect, NTDE, resulting from the combustion of ULSD, is again fundamentally different from what was assumed to be the case for TDE. This provides additional support for the conclusion that any evaluation of TDE should not automatically apply to NTDE.

## 10. Experimental studies evaluating potential health effects of NTDE

Many reports on the health effects of diesel exhaust have been published in recent years (Hesterberg et al., 2005, 2006, 2012b). A detailed review of those reports indicates that essentially all of those reports involve the study of TDE. It is not surprising that few studies have been conducted with engines producing NTDE since they have only recently become available on a wide-spread basis. Another factor discouraging any studies on NTDE is the extremely clean nature of the NTDE. Even a cursory review by a biomedical investigator of the literature on NTDE characteristics would suggest that NTDE has a very low likelihood of producing any adverse effects in the typical toxicity assays. To be candid, there are limited incentives for scientists to undertake studies unless they are likely to demonstrate adverse effects. This emphasizes the importance of the ACES program with government and private industry support that was created specifically to evaluate potential health effects of protracted, low dilution (high concentration) NTDE exposures, including carcinogenic responses.

As discussed earlier, the initial ACES Phase 3B effort included studies on mice exposed for up to 3 months and rats exposed for at least 24 months and, most likely for 30 months. The McDonald et al. (2012) HEI report describes findings in the mouse studies and for rats exposed for 12 months. That report should be available prior to the IARC June 2012 meeting.

Table 7 was compiled to help place the concentrations of key constituents in the recently initiated ACES chronic inhalation exposure studies (McDonald et al., 2012) in perspective relative to previous studies with TDE (Mauderly et al., 1987), Carbon Black (Nikula et al., 1995) and $NO_2$ alone (Mauderly et al., 1989, 1990). All of those chronic inhalation exposure studies were conducted at the LRRI in Albuquerque, NM in the same basic facilities that are being used for the ACES study. The Mauderly et al. (1987) study with TDE was one of the earliest studies demonstrating that chronic exposure of rats to low dilutions of whole diesel exhaust, with high concentrations of particles, resulted in an increased prevalence of lung tumors. The Mauderly et al. (1987) study was unique in several ways. First, the Mauderly et al. (1987) study involved 30 months of exposure and observation to maximize the potential for detecting an excess of tumors. This is very different than typical cancer bioassays, including those conducted for the NTP, which typically are only 24 months in duration (NTP, 2011b). Second, beyond evaluating the potential carcinogenic effects of TDE, parallel studies were conducted to evaluate many other endpoints (McClellan et al., 1982, 1986; McClellan, 1987). This included concurrent research on the deposition and retention of the diesel soot in the lungs (Wolff et al., 1987, 1989). This research demonstrated impairment of clearance and an accumulation of soot in the lungs of the rats at the highest exposure concentrations, accumulation substantially in excess of that predicted from the kinetics at lower exposure concentrations. That finding, as well as other evidence as reviewed in HEI (1995, 1999), Hesterberg et al. (2005), Mauderly and McCunney (1996), Mauderly (1997), and Wolff et al. (1987, 1989), suggested that the increased prevalence of lung tumors observed in rats with protracted exposure to high concentrations of TDE was likely a result of an "overload" phenomena associated with the elemental carbon core of the particles and independent of any effect of hydrocarbon compounds such as the PAHs.

To further test the particle overload hypothesis, the Nikula et al. (1995) study was conducted with F344 rats exposed to carbon black, essentially pure elemental carbon particles devoid of hydrocarbons. As predicted, an increased prevalence of lung tumors was observed. Similar results were found by Heinrich et al. (1995) in studies with carbon black exposures at high concentrations using Wistar rats. It may be noted (Table 12) that the exposure intensity (in $\mu g/m^3$ hr/week) in the Nikula et al. (1995) study at the two exposure concentrations studied bracketed that of the Mauderly et al. (1987) study with TDE.

An additional study (Mauderly et al., 1989, 1990) involved exposure to $NO_2$ alone, a major oxidant gaseous constituent in both TDE and NTDE. The exposure concentration studied, 9.5 ppm, was substantially higher than was present in the TDE exposure of Mauderly et al. (1987). As discussed earlier, histopathologic changes were observed in the lungs of the rats exposed only to a high concentration of $NO_2$. As also noted earlier, the $NO_2$ exposure intensity of 66.5 ppm-hr/day was considered by the ACES Oversight Committee to be a "Maximum Tolerated Dose," based on effects in the respiratory tract, and used as a basis for selecting the lowest dilution used in the ACES animal study.

In the ACES rat study now in progress, at the lowest dilutions and, thus, the highest concentration of exhaust constituents (i.e.

the Maximum Tolerated Dose based on $NO_2$), it was anticipated that respiratory tract effects would be observed from the nares to the conducting airway as expected from exposure to high concentrations of an oxidant gas such as $NO_2$. The effects should be quite similar to those previously reported by Mauderly et al. (1989, 1990) for 12 or 24 months of exposure to $NO_2$ alone. Indeed, the minimal/limited respiratory tract lesions reported by McDonald (2012), Doyle-Eisele et al. (2012) and McDonald et al. (2012) are remarkably similar to those reported by Mauderly et al. (1989, 1990). It will be useful at an early date to carefully review and compare the histopathological slides of the respiratory tract of rats from the earlier Mauderly et al. (1989, 1990) study and those from the current ACES study. It is important to recall that the $NO_2$ study of Mauderly et al. (1989, 1990) continued through 24 months of exposure, the duration of most cancer bioassays. They did not observe an excess of lung tumors related to the protracted high concentration $NO_2$ exposure.

The findings reported on the NTDE exposures for up to 12 months in the McDonald et al. (2012) report should be carefully reviewed by the IARC Working Group. In that review, it will be important to interpret the respiratory tract lesions expected and observed as resulting from the exposure to high concentrations of $NO_2$ and not attribute the lesions inappropriately to the trace levels of particulate matter in the NTDE. It will be important to also recognize that the ACES rat bioassay results of greatest interest will be the prevalence of lung tumors in rats exposed to diluted whole exhaust compared to sham-exposed controls, data that will not become available until late 2012 (Mauderly, 2010).

## 11. IARC 2012 review of diesel exhaust

The review by IARC of the cancer hazard classification of diesel engine exhaust on June 5–12, 2012 will be the first review of the emissions of diesel engines since the review conducted in 1988 and reported the following year (IARC, 1989). As reviewed in this paper, the last quarter century has been one of evolutionary and then in the last decade revolutionary changes in diesel technology with associated remarkable changes and reductions in engine emissions, including the virtual elimination of elemental carbon particles and associated hydrocarbons. We strongly recommend that the 2012 IARC review, as well as any subsequent reviews of the health hazards of diesel exhaust by international, national, state or local agencies, consider these remarkable changes in the emissions from new technology diesel engines in the course of each assessment. In other portions of this paper we have focused on the large body of scientific information that has been published during the last decade on the physical and chemical characteristics of NTDE compared to TDE. We now move to a broader discussion of the scientific information to be considered in the June 2012 IARC review of the carcinogenic hazards.

Since the 1988 IARC review, a large number of papers have been published on the health effects of diesel exhaust emissions, but essentially all have been concerned with TDE. A review of all of that literature is beyond the scope of this paper. However, it is appropriate to briefly relate some key aspects of the post-1988 literature that should be considered in the 2012 IARC review. It is anticipated that the 2012 review, in the tradition of IARC, will consider scientific information in four areas (recall Section 4): (a) exposure data, (b) studies of cancer in humans, (c) studies of cancer in laboratory animals, and (d) mechanistic and other relevant data as a basis for preparing a (e) summary and (f) evaluation and rationale section.

The section on "exposure data" is especially important in the forthcoming review because of the revolutionary advances made in diesel technology to purposefully reduce and change the composition of the very small quantities of emissions that are still characterized as particulate material. As discussed earlier, this situation is dramatically different than for a specific chemical whose physical properties never change. As we have emphasized in this paper, it will be important for the exposure data review to carefully distinguish between TDE, including advances in knowledge since 1988, and NTDE. These separate reviews in the exposure data section will provide the basis for their separate consideration in the summary and evaluation and rationale sections of the IARC monograph.

In the section of the diesel exhaust monograph reviewing "studies in humans," it will be important to note at the outset that the section covering carcinogenic findings will only consider TDE. Since new diesel technology and improved fuels have only recently been introduced, epidemiological studies of the carcinogenic hazard of NTDE have not been conducted. Indeed, the very low concentrations of potentially hazardous chemicals in NTDE relative to the concentrations of those or similar chemicals from other sources in the workplace and ambient environment suggest that it may not be feasible to conduct epidemiological studies of NTDE even when the new technology has largely displaced the old traditional diesel technology, due to a lack of any unique markers of the low-level NTDE exposures.

Since the 1988 IARC review, some additional epidemiological studies have been conducted and published on TDE and will be central to the 2012 re-evaluation of diesel exhaust. Ward et al. (2010) noted the role of epidemiological evidence in potentially upgrading the IARC classification of diesel exhaust and some 19 other agents. Multiple reviewers (Mauderly and Garshick, 2009; HEI, 1995, 1999, 2002; Hesterberg et al., 2006, 2012b; Gamble, 2010; Gamble et al., 2012) have reviewed and commented on the strengths and weaknesses of the various epidemiological studies. The HEI report made specific note of the absence of a well-accepted marker of exposure to diesel exhaust, what we now call TDE.

The most comprehensive recent review of the epidemiological literature was conducted by Gamble (2010). His review focused on 13 studies. It considered the proportion of cases with more than 20 years since initial DE exposure; strength of association; biological gradients; roles of chance, bias, and confounding; and consistency. Five studies had adequate latency, six had a minority of workers with >20 years' latency, and in two studies most workers had inadequate latency. This pattern suggested too few studies were relevant for evaluating the association between diesel exhaust exposure and lung cancer. The 16 highest exposure categories that were evaluated revealed 7 with probable associations (relative risk [RR] > 1.5), 7 with improbable or no association (RRs < 1.2), and 2 with possible associations (RRs 1.2–1.5). Gamble interpreted this random pattern with many weak RRs as not supporting the DE-lung cancer hypothesis. Ten of 34 exposure–response (E–R) analyses showed positive trends and 24 had indeterminate or negative trends. Gamble concluded that this small number of positive biological gradients did not support causality. Weights of evidence suggested 70% of the studies were indeterminate, whereas 30% were positive or negative, indicating a lack of consistency. He concluded that the epidemiological studies did not provide an adequate test of the hypothesis that diesel exhaust exposure (TDE) and lung cancer were causally associated, and he emphasized the need for additional studies with longer follow-up and quantitative exposure–response analyses.

It is important to note that the Gamble (2010) review included re-evaluations of epidemiological studies that had a prominent role in the 1988 IARC review. In particular, the Garshick et al. (1987, 1988) papers were based on a data set that was subsequently extended and re-evaluated by Crump (1999, 2001). The IARC Working Group in 1988 had exercised caution in interpreting the original reports of Garshick et al. (1987, 1988) as a basis for the

summary conclusion of "limited evidence of carcinogenicity in humans." The subsequent re-evaluation by Crump et al. (1991), Crump (1997, 1999, 2001) indicates that the cautious approach of the 1988 IARC Working Group was well justified. Significantly, the analyses conducted by Crump were commissioned and made possible by the US Environmental Protection Agency.

Very recently, four additional papers have been published on the hypothesized association between exposure to diesel exhaust and lung cancer and have been reviewed by Gamble et al. (2012). Two of the papers (Villeneuve et al., 2011; Olsson et al., 2012) were population-based studies that reported significant exposure–response trends between cumulative diesel exhaust exposure and lung cancer existed that were unlikely to be entirely explained by bias or confounding. Gamble et al. (2012), however, concluded that the Villeneuve et al. (2011) and Olsson et al. (2012) papers do not provide a basis for definitive conclusions on the diesel exhaust-lung cancer association because of their use of qualitative exposure estimates, exposure misclassification issues, inconsistent exposure–response trends and selection bias related to low participation rates.

Two recent papers, whose publication has been anticipated for some time, reported results from the Diesel Exhaust in Miners Study (DEMS). This study was initiated jointly by the National Institute of Occupational Safety and Health and the National Cancer Institute in the mid-1990s. DEMS include 12,315 miners from 8 non-metal mines (3 potash, 3 trona, 1 low silica limestone and 1 salt (halite mine) in the United States. Mortality was followed through December 31, 1997 and substantial effort was directed to retrospectively assessing exposure to Respirable Elemental Carbon (REC), the primary exposure indicator used in the studies. Attfield et al. (2012) reported that "Initial (i.e. a priori defined) analyses from the complete cohort did not reveal a clear relationship of lung cancer mortality with DE exposures." The priori analyses were conducted in accord with the original published protocol (NIOSH, 1997). Nonetheless, the Attfield et al. (2012) paper then goes onto describe posterior analyses which they interpret as demonstrating an association between diesel exhaust exposure and lung cancer risk. Silverman et al. (2012) report findings from a nested case-control study utilizing 198 lung cancer deaths and 562 incident density-sampled controlled subjects. They report statistically significant increasing trends in lung cancer risk with increasing cumulative REC and average REC intensity.

An anticipated strength of the DEMS analyses was to be the careful attention given to developing a retrospective exposure assessment for the cohort to derive quantitative (not surrogate or qualitative) estimates of REC exposure. The results of those analyses have been reported in five papers (Coble et al., 2010; Stewart et al., 2010, 2012; Vermeulen et al., 2010a,b). Unfortunately, only 85 measurements of REC were available pre-1998. All the other REC values used in the analyses reported by Attfield et al. (2012) and Silverman et al. (2012) were based on extrapolations of REC from surrogate CO measurements that were either made post-1975 or that were derived from pre-1976 estimates of the horse-power of diesel equipment and mine ventilation rates. The estimated CO levels ultimately served as the surrogate basis for the stimated levels of REC. The pre-1976 estimates of REC (based solely on estimates of CO levels) are especially critical because the use of a 15-year lag in the DEMS epidemiological analyses means that the DEMS results are entirely dependent upon REC estimates for 1982 and earlier years, recognizing that the latest deaths included in the Attfield et al. (2012) and Silverman et al. (2012) studies would have occurred in 1997.

The validity of the estimated REC exposures has been questioned (Borak et al., 2011). Clark et al. (1999), McKain et al. (2012) and Yanowitz et al. (2000) have reported there is no clear correlation between diesel engine emissions, among different diesel engines of particulate matter (which would include REC) and CO, or between HP and CO emissions, among different diesel engines. Thus, the fundamental assumptions that under-gird the DEMS estimates of REC exposure appear to be flawed. These issues were raised by Borak et al. (2011) after the initial DEMS exposure assessment papers were published and before the Attfield et al. (2012) and Silverman et al. (2012) papers were completed and published. More recently, Crump and Van Landinghan (2012) has reported on a re-analysis of a portion of the DEMS exposure data and has emphasized the significant concerns that result from not carrying major uncertainties in the REC exposure assessment forward in the conduct and reporting of the results of any epidemiological analyses of the DEMS cohort. The recent review by Gamble et al. (2012) critiques both the Attfield et al. (2012) and Silverman et al. (2012) papers.

At this juncture, it is important to recall the experience with the initial papers of Garshick et al. (1987, 1988) that reported a positive, monotone dose (more correctly stated as exposure–response trend) in lung cancer mortality with increasing duration of exposure. After careful independent re-analysis of the original raw data set and further follow-up after the IARC review, it was found that the original finding was not valid. Indeed, Crump et al. (1991), Crump (1997, 2001) concluded there was no consistent exposure–response trend with any quantitative measure of diesel exposure. In view of the potential importance of the reports of Attfield et al. (2012) and Silverman et al. (2012) in the IARC cancer hazard evaluation as well as those that will be conducted by other bodies, it is important that the NIOSH-NCI data (exposure assessments and vital statistics) be independently re-evaluated at the earliest possible time to validate the results of the original analyses and, as warranted, be assessed through more extensive analysis. It is uncertain if such analyses using the total NIOSH/NCI data set can be accomplished prior to the June 2012 IARC review.

The evaluation of "animal studies" of diesel exhaust conducted at four laboratories (in the United States, Germany, Switzerland and Japan) was central to the earlier IARC evaluation of diesel exhaust. Importance of the animal evidence in the 1988 IARC review was heightened by the Working Group's conclusion that the epidemiological findings only provided "limited evidence of carcinogenicity." All of the laboratory animal studies were conducted at about the same time in the 1980s. However, not all of the analyses had been completed and published at the time of the 1988 review. Additional papers from those early studies were published after the 1988 review and will deserve careful attention in the 2012 review. Those papers have been considered in reviews by HEI (1995, 1999), Hesterberg et al. (2005, 2006, 2012b), Mauderly and Garshick (2009), McClellan (1996), Mauderly (2000), and US EPA (2002).

It is anticipated that a major issue to be discussed at the 2012 review will be the role of lung overload as a mode of action in producing the excess of lung tumors observed in rats exposed for extended times to high concentrations of diesel exhaust particulates and the relevance of these findings for evaluating human cancer hazard. The monograph (IARC, 1989) made note of the changes in the lungs of rats exposed to the highest concentrations of diesel exhaust, including altered clearance when exposures were above about 300 mg-hr/week. However, it was not until after the 1988 review that it was generally recognized that prolonged exposure of rats to high concentrations of several kinds of poorly soluble particles (not just diesel exhaust particles) impaired clearance mechanisms, produced lung burdens of particles in excess of that projected from lower exposure levels, produced chronic lung pathology and, most significantly, resulted in an excess of lung tumors (Greim et al., 2001; ILSI, 2000; McClellan, 1990, 1996; Mauderly, 1997, 2000; Mauderly and McCunney, 1996; US EPA, 2002; Watson and Valberg, 1996; Wolff et al., 1987, 1989).

In recent years, the issue of evaluating the hazards of a wide range of poorly soluble particulate material has received additional scientific attention resulting in a number of publications concerning the extrapolation of laboratory animal findings on poorly soluble inhaled particulate material to humans. For example, Pauluhn (2011) has recently offered a unifying approach for evaluating the toxicity of poorly soluble submicron particulate matter which would include the hallmark DEP found in TDE. The outcome of the discussions on the role of particle overload in rats leading to an excess of lung tumors will have implications for deciding on the weight of evidence to be assigned to the finding of excess lung tumors in rats exposed for long periods of time at high concentrations in the overall evaluation of the cancer hazard of TDE. Whatever the outcome of the discussion, it is important to recognize that NTDE is essentially devoid of the hallmark DEP found in TDE.

In the section on "animal studies" for NTDE, it is important that the 2012 Monograph provide a clear description of the ACES chronic bioassay in rats being conducted with NTDE. In short, this description will serve as a promissory note of results yet to be obtained that will be valuable in any future hazard evaluation of NTDE. Recall that a key objective of the ACES program was to test the "null" hypothesis that emissions from diesel engines compliant with the EPA's 2007 emission standards "will not cause an increase in tumor formation – at the highest concentration of exhaust that can be used."

It is to be anticipated that the section on "mechanistic and other relevant data" for TDE will consider the overload mode of action discussed above and the significance of the DEP associated hydrocarbons in evaluating human cancer hazards. It is our view that the excess lung tumors observed in rats chronically exposed to high concentrations of diesel exhaust is a species-specific effect occurring as a result of the overload phenomena. It is not necessary to invoke a role for particle-associated hydrocarbons in explaining these findings in rats. The absence of an excess of lung cancer in mice and Syrian hamsters chronically exposed to high concentrations of diesel exhaust raises questions as to whether the hydrocarbon fraction of diesel exhaust has been demonstrated to cause cancer. For example, the Mauderly et al. (1996) report of an absence of excess lung tumors in mice exposed concurrently with rats that exhibited lung tumors related to the overload phenomena (Mauderly et al., 1987; Wolff et al., 1987) serves as a dramatic illustration of the role of the overload phenomena and species differences in response.

Consistent with the recommendations we have offered earlier, it is our view that the "summary" and "evaluation and rationale" sections of the 2012 IARC review should provide for separate evaluation of TDE and NTDE. In our opinion, the scientific information available on NTDE supports placing NTDE in Group 3, not classifiable as to its carcinogenicity in humans. When the results of the ACES chronic bioassay in rats exposed to the Maximum Tolerated Dose (more correctly concentration and time) becomes available, the cancer hazard classification of NTDE should be re-evaluated.

## 12. Summary

The information reviewed above comparing NTDE to TDE has shown that in the case of technology-specific emissions (such as diesel exhaust), technological advances can have a profound impact on reducing and changing the composition of emissions. This situation is in sharp contrast to that for a particular chemical agent that has physical properties, including those that determine its hazard potential, which never change.

Major revolutionary advances have been made in diesel technology, especially during the last decade, which have impacted on exhaust emissions. Those advances which are integrated as a system include: (a) engine improvements including the use of exhaust gas recirculation; (b) use of ultra-low sulfur diesel fuel; (c) exhaust after-treatment including oxidative catalysts and wall-flow particulate matter traps; and (d) electronic sensing and computerized control systems. The new systems are extraordinarily effective in substantially reducing and changing particulate matter exhaust as compared to TDE emissions. The key changes are: lower particulate mass emissions, different chemical composition, lower particle number emissions, altered composition of the semi-volatile fraction, and lower concentrations of unregulated pollutants. Thus, the NTDE emissions are substantially different, both quantitatively and qualitatively, than TDE emissions. Moreover, the NTDE emissions are now similar to or lower than those of modern CNG or modern gasoline–fueled engines.

The extensive characterization of NTDE has clearly established that the emissions are substantially lower than the applicable, very stringent regulatory emission standards. Moreover, the detailed chemical characterization gives confidence that the emissions do not contain any unique constituents that might pose a hazard to human health. The new technology heavy-duty engines with ultra-low particulate emissions were introduced into the market for on-road use in 2007 as required by US regulations, and have been well received by customers. Starting in 2010, the engines marketed in the USA continue to have ultra-low particulate mass emissions and, in addition, even lower $NO_x$ emissions than the 2007 model engines. In future years, the number of NTDE units will increase and the number of TDE units will decrease in the on-road fleet. Moreover, a similar shift will follow with off-road diesel-power equipment.

To further validate the lack of health hazard of NTDE, exhaustive investigations are now underway in which mice and rats are being exposed to graded concentrations of whole NTDE. The highest concentrations being studied are a dilution of only 40:1 of engine-out emissions, a dilution selected to limit potential effects of the $NO_2$. However, the high concentration $NO_2$ component at the highest exposure level was expected and has produced minimal/limited modest histopathological changes in the respiratory tract. The bioassay with rats exposed for 30 months (16 h/day, 5 days/week) is similar in design to the earlier studies with TDE in which an excess of lung tumors was observed at the highest particulate mass concentrations (the lowest dilutions of whole TDE). Thus, the results of the NTDE and TDE cancer bioassays can be directly compared when the NTDE bioassay is completed and reported in 2013. Moreover, it is clear that the results of the NTDE bioassay will provide a direct evaluation of the ACES core (null) hypothesis that the NTDE exposure "will not cause an increase in tumor formation or substantial toxic health effects in rats and mice at the highest concentration of exhaust that can be used – compared to animals exposed to "clean air," although some biological effects may occur."

Based on the remarkable differences in concentration and composition of NTDE compared to TDE, it is our recommendation that NTDE should be evaluated and classified separately from TDE by the IARC Working Group in June 2012.

## 13. Conclusions

The use of diesel engines as reliable and efficient sources of power to move goods and people and meet other critical needs of society has steadily grown over the past century. During the past half century, concerns arose over the impact of diesel engine exhaust on visibility and human health and more recently on climate change. Those concerns were soon reflected in increasingly more stringent regulations to limit engine emissions. The need for progressively lower emission standards was reinforced by increasingly stringent National Ambient Air Quality Standards for Particulate Matter, Ozone and Nitrogen Dioxides.

In response to the stringent regulations, the manufacturers of diesel engines and refiners of diesel fuel made evolutionary and, more recently, revolutionary advances in diesel technology including improved engines, exhaust after-treatment and use of improved, ultra-low sulfur fuels. This new technology is being rapidly introduced into the market to replace traditional diesel engines and fuels. The particulate matter concentration in NTDE is remarkably lower than in TDE and the composition of NTDE is distinctly different than that of TDE. The TDE particles illustrated in Fig. 1, with their core of elemental carbon and substantial amount of associated hydrocarbons, are simply not present in NTDE. It is clear that there have been paradigm-shifting advances in the control of diesel exhaust emissions in response to progressively more stringent regulations.

The earlier IARC (1989) review classified whole diesel exhaust, which we characterize as TDE, as a "probable human carcinogen, Group 2A." The same IARC Working Group classified whole gasoline exhaust, which we characterize as traditional gasoline exhaust, as a "possible human carcinogen, Group 2B." IARC in June 2012 will again review the carcinogenic hazard classification of diesel exhaust and gasoline exhaust. Since the previous IARC review, substantial new information has been published on epidemiological observations relating to workers exposed to TDE and on the mechanisms by which protracted exposure to high concentrations of TDE and other poorly soluble particles produces lung tumors in rats. That new information will need to be critically evaluated by the IARC working group as it considers appropriate carcinogenic hazard classifications for whole diesel exhaust. It is our view that whatever classification is given, it should be specifically identified as being applicable to TDE. We recommend, in recognition that NTDE is fundamentally different than TDE, that IARC evaluate and classify NTDE separately from TDE. Likewise, it is appropriate for IARC to recognize that sufficient information is now available for gasoline exhaust to separately evaluate TGE and MGE. This is the approach shown schematically in Table 6. This approach would be similar to the approach taken by IARC (2002) in an earlier review and classification of newly developed biosoluble glass wool fibers as "not classifiable as to human carcinogenicity, Group 3." It is our recommendation, based on current scientific information, that it would be appropriate to classify NTDE as "Group 3, not classifiable as to human carcinogenicity." Classifying NTDE in Group 3 will serve to distinguish the new technology diesel engine and fuel from the old traditional diesel technology that produced TDE. Most importantly, this distinction will encourage the deployment of ultra-clean diesel technology around the world with a resulting profoundly positive impact in improving ambient air quality and public health.

## Conflict of interest statement

The authors have had a long association with private sector firms and organizations striving to develop ultra-clean diesel technology. Roger O. McClellan has served on numerous advisory committees to the US EPA and other government and private organizations on air quality issues. He was first alerted to issues concerning the potential health effects of diesel exhaust emissions from traditional diesel technology while serving on an EPA Advisory Committee in the 1970s. In the late 1970s, he was responsible for providing leadership for initiating the Lovelace organization's pioneering studies of diesel exhaust. From that time to the present time, he has served in an advisory role to the Health Effects Institute, the Engine Manufacturers Association and private firms concerned with diesel technology and its potential health impact. In addition, he has served in an Advisory Role to the US Environmental Protection Agency on setting of air quality standards, including service as Chair of the US Environmental Protection Agency Clean Air Scientific Advisory Committee (CASAC) and service on CASAC Panels for the revision of National Ambient Air Quality Standards for all the criteria pollutants. He served from 1985 to 1987 as a Member of the Advisory Committee on Standards and Regulations for Diesel Powered Equipment in Underground Coal Mines, Mine Safety and Health Administration, Department of Labor. He served as a member of the Working Group that prepared the IARC (1989) Monograph on Diesel and Gasoline Exhaust and Some Nitroarenes. Thomas W. Hesterberg has been employed by Navistar International since 2002 and has responsibility for coordinating that firm's product stewardship program of which a major component is the development of improved diesel technology. John C. Wall has been employed by Cummins, Inc. since 1986 and has a leadership role in that firm's programs to develop improved diesel technology. Both Cummins, Inc. and Navistar International are major international producers and marketers of diesel engines.

The three authors have sole responsibility for the final manuscript. The analyses, interpretations and recommendations in the manuscript reflect their professional expertise and judgments and do not necessarily reflect the views of their employers, the Engine Manufacturers Association (EMA) or other EMA member companies.

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## References

Ahlvik, P., 2002. Environmental and health impacts from modern cars. A comparison between two petrol and two diesel cars with varying emission control technology. A report for the Swedish National Road Administration, Vehicle Standards Division, Börlange, Sweden, Ecotraffic R&D3 AB, Vägverket, Publikation.

Albert, R.E., Lewtas, J., Nesnow, S., Thorslund, T.W., Anderson, E., 1983. Comparative potency method for cancer risk assessment: application to diesel particulate emissions. Risk Anal. 3 (2), 101–117.

Attfield, M., Schleiff, P., Stewart, P. et al., 2012. Effects of diesel exhaust among nonmetal miners: a cohort mortality study with emphasis on lung cancer. J. Natl. Cancer Inst., 104, http://dx.doi.org/10.1093/jnci/djs035.

Ayala, A., Kado, N.Y., Okamoto, R.A., Holmen, B.A., Kuzmicky, P.A., Kobayashi, R., Stiglitz, K.E., 2002. Diesel and CNG heavy-duty transit bus emissions over multiple driving schedules: Regulated pollutants and project overview, SAE Paper No. 2002-01-1722, Society of Automotive Engineers, Warrendale, PA.

Ayala, A., Gebel, M.E., Okamoto, R.A., Rieger, P.L., Kado, N.Y., Cotter, C., Verma, N., 2003. Oxidation catalyst effect on CNG transit bus emissions, SAE Paper No. 2003-01-1900, Society of Automotive Engineers, Warrendale, PA.

Ayres, J.G., Harrison, R.M., Maynard, R., McClellan, R.O., Nichols, G.L., 2010. Environmental medicine. In: Jon G. Ayres, Roy M. Harrison, Robert Maynard,

Gordon L. Nichols (Eds.), Textbook of Environmental Medicine, first ed., Hodder Education, London, UK, pp. 3–21 (Chapter 1).
Baan, R., Gross, Y., Straif, K., et al., 2009. A review of human carcinogens – Part F: chemical agents and related occupations. Lancet Oncol. 10 (12), 1143–1144.
Barone, T., Storey, J., Domingo, N., 2010. An analysis of field-aged diesel particulate filter performance. J. Air Waste Manag. Assoc. 60, 968–976.
Bauner, D., Laestadius, S., Iida, N., 2009. Evolving technological systems for diesel engine emission control: balancing GHG and local emissions. Clean Tech. Environ. Policy 11, 339–365.
Bemis, J.C., Torous, D.K., Dertinger, S.D., 2012. Part 2. Assessment of genotoxicity after exposure to diesel exhaust from US 2007-compliant diesel engines: Report on 1- and 3-month exposures in the ACES bioassay. In: Advanced Collaborative Emissions Study (ACES) Subchronic Exposure Results: Biologic Responses in Rats and Mice and Assessment of Genotoxicity. Research Report 166. Health Effects Institute, Boston, MA (Available at: <http://pubs.healtheffects.org/view.php?id=377>).
Bernstein, D.M., 2007. Synthetic vitreous fibers: a review toxicology, epidemiology and regulations. Crit. Rev. Toxicol. 37 (10), 839–886.
Biswas, S., Hu, S., Verma, V., Herner, J.D., Robertson, W.H., Ayala, A., Sioutas, C., 2008. Physical properties of particulate matter (PM) from late model heavy-duty diesel vehicles operating with advanced PM and $NO_x$ emission control technologies. Atmos. Environ. 42, 5622–5634.
Biswas, S., Verma, V., Schauer, J.J., Sioputas, C., 2009. Chemical speciation of PM emissions from heavy-duty vehicles equipped with diesel particulate filter (DPF) and selective catalytic reduction (SCR) retrofits. Atmos. Environ. 43, 1917–1925.
Boorman, G.A., Catalano, P.J., Jacobson, B.J., Kaden, D.A., Mellilck, P.W., Nauss, K.M, Ryan, L.M., 1995. Consequences of prolonged inhalation of ozone on F344 rats: collaborative studies. Part VI. Background and study design. Health Effects Institute, Cambridge, MA, Report No. 065-V1.
Borak, J., Bunn, W.B., Chase, G.R., et al., 2011. Comments on the diesel exhaust in miners study. Ann. Occup. Hyg. 55, 339–342.
Bosteels, D., May, J., Karlsson, H., de Serves, C., 2006. 'Regulated' and 'Non-regulated' emissions from modern european passenger cars. SAE International, SAE Paper No. 2006-01-15 16, Warrendale, PA.
Bouvard, V., Baan, R., Straif, K., et al., 2009. A review of human carcinogens – Part B: biological agents. Lancet Oncol. 10 (4), 321–322.
Brightwell, J., Fouillet, X., Cassano-Zoppi, A.L., Bernstein, D., Crawley, F., Duchosal, F., Gatz, R., Perczel, S., Pfeifer, H., 1989. Tumours of the respiratory tract in rats and hamsters following chronic inhalation of engine exhaust emissions. J. Appl. Toxicol. 9 (1), 23–31.
CAA (Clean Air Act), 1970. The Clean Air Act Amendments of 1970-P.L. 91-04 (December 31, 1970), Plus technical amendments made by P.L. 92-157 (November 18, 1971).
CAA (Clean Air Act), 1990. The Clean Air Act Amendments to 1990, Public Law No. 101-549; 104 STAT 2399.
CARB (California Air Resources Board), 1998a. Resolution 98-3 5 on Particulate Emissions from Diesel Engines, Agenda Item No. 98-8-1 (August 27, 1998).
CARB (California Air Resources Board), 1998b. Report to the Air Resources Board on the Proposed Identification of Diesel Exhaust as a Toxic Air Contaminant, Exposure Assessment (Part A), Health Risk Assessment for Diesel Exhaust, Office of Environmental Health Hazard Assessment. California Environmental Protection Agency.
CARB (California Air Resources Board), 1998c. Health Risk Assessment for Diesel Exhaust; Proposed Identification of Diesel Exhaust as a Toxic Air Contaminant (Part B). Health Risk Assessment for Diesel Exhaust. Office of Environmental Health Hazard Assessment. California Environmental Protection Agency, Sacramento, CA.
CARB (California Air Resources Board) Scientific Review Panel, 1998d. Scientific Review Panel Findings for the Proposed Identification of Diesel Exhaust as a Toxic Air Contaminant Report, adopted April 22, 1998. Air Resources Board, California Environmental Protection Agency, May 27, 1998. Available at: <http://www.arb.ca.gov/srp/findings/4-ww-98.pdf> (accessed 29.1.2012).
Catalano, P.J., Chang, L.-Y.L., Harkema, J.R., Kaden, D.A., Lat, J.A., Mellick, P.W., Parks, W.C., Pinkerton, K.E., Radhakrishnamurthy, B., Ryan, L.M., Szarek, J.L., 1995. Consequences of Prolonged Inhalation of Ozone on F344 Rats: Collaborative Studies Part XI: Integrative Summary. Health Effects Institute, Cambridge, MA, Report No. 065-XI.
Charlton, S., Dollmeyer, T., Grana, T., 2010. Meeting the US heavy-duty EPA 2010 Standards and providing increased value for the customer. SAE Int. J. Commer. Veh. 3 (1), 101–110.
Cheung, K.L., Polidori, A., Nziachristos, L., Tzamkiozis, T., Samaras, Z., Cassee, F.R., Gerlofs, M., Sioutas, C., 2009. Chemical characteristics and oxidative potential of particulate matter emissions from gasoline, diesel and biodiesel cars. Environ. Sci. Technol. 43, 6334–6340.
Clark, N.N., Jarrett, R.P., Atkinson, C.M., 1999. Field measurement of particulate matter emissions, carbon monoxide, and exhaust opacity from heavy-duty diesel vehicles. J. Air Waste Manag. Assoc. 49, 75–84.
Clark, N.N., Zhen, F., Bedick, Gautam, M., Wayne, W., Thompson, G., Lyons, D., 2007. Creation of the 16-hour engine test schedule from the heavy- heavy-duty diesel engine test schedule. CRC Report: ACES-1-a. Coordinating Research Council, Alpharetta, GA. Available at <http://www.crcac.org/publications/emissions/index.html> (accessed 10.1.2011).
Coble, J.B., Stewart, P.A., Vermeulen, R., et al., 2010. The diesel exhaust in miners study. Part II: exposure monitoring surveys and development of exposure groups. Ann. Occup. Hyg. 54 (7), 747–761.
Colucci, J.M., 2004. Fuel quality – an essential element in vehicle emission control. ICEF 2004-982. In: Proceedings of ICEF 04: ASME Internal Combustion Engine Division 2004 Fall Conference, Long Beach, CA, USA, October 24–27, 2004, pgs. 1–16.
CRC (Coordinating Research Council), 2012. About CRC. Available at: <http://www.crcao.com/bout/index.html> (accessed 29.1.2012).
Crump, K.S., Lambert, T., Chen, C., 1991. Assessment of risk from exposure to diesel engine emissions. US EPA Contract 68-02-4601; Appendix B in US EPA, Health Assessment Document for Diesel Emissions, vol. 2, EPA-600/8-90/0578b.
Crump, K.S., 1997. Comments on March 27, 1997, California Office of Environmental Health Hazard Assessment Draft Document: Health Risk Assessment for Diesel Exhaust. Unpublished Comments provided to OEHHA.
Crump, K., 1999. Lung cancer mortality and diesel exhaust: reanalysis of a retrospective cohort study of US railroad workers". Inhal. Toxicol. 11, 101–107.
Crump, K., 2001. Modeling lung cancer risk from diesel exhaust: suitability of the railroad worker cohort for quantitative risk assessment. Risk Anal. 21 (1), 19–23.
Crump, K., Van Landingham, C., 2012. Evaluation of an exposure assessment used in epidemiological studies of diesel exhaust and lung cancer in underground mines. Crit. Rev. Toxicol., in press. http://dx.doi.org/10.3109/10408444.2012.689755.
Dollmeyer, T.A., Vittorio, D.A., Grana, T.A., Katzenmeyer, J.R., Charlton, S.J., 2007. Meeting the US 2007 heavy-duty diesel emission standards – designing for the customer. SAE International, 18 pp.
Doyle-Eisele, M., Holmes, T., Gigliotti, A., Seagrave, J., Miller, R., Seikop, S., Mauderly, J., McDonald, J., 2012. ACES Phase 3: 4- and 13-week results from rats and mice exposed to 2007-compliant diesel emissions. Toxicologist, Abstract #2643.
El Ghissassi, F., Baan, R., Straif, K., et al., 2009. A review of human carcinogens – Part D: radiation. Lancet Oncol. 10 (8), 751–752.
EU, 1997. Commission Directive 97/69/EC of December 5, 1997. European Union. Official Journal of the European Communities 343/19.
Evans, M.J., 1984. Oxidant gases. Environ. Health Perspect. 55, 85–95.
Gamble, J., 2010. Lung cancer and diesel exhaust: a critical review of the occupational epidemiology literature. Crit. Rev. Toxicol. 40, 189–244.
Gamble, J.F., Nicolich, M.J., Boffetta, P., 2012. Lung cancer and diesel exhaust: an updated critical review of the occupational epidemiological literature. Crit. Rev. Toxicol., in press. http://dx.doi.org/10.3109/10408444.2012.690725.
Garshick, E., Schenker, M.B., Muñoz, A., Segal, M., Smith, T.J., Woskie, S.R., Hammond, K.S., Speizer, F.E., 1987. A case-control study of lung cancer and diesel exhaust exposure in railroad workers. Am. Rev. Respir. Dis. 135, 1242–1248.
Garshick, E., Schenker, M.B., Muñoz, A., Segal, M., Smith, T.J., Woskie, S.R., Hammond, S.K., Speizer, F.E., 1988. A retrospective cohort study of lung cancer and diesel exhaust exposure in railroad workers. Am. Rev. Respir. Dis. 137, 820–825.
Gautam, M., Kappanna, H., John, B., Wayne, W.S., Carder, D., Osinuga, A., Kreeb, B., Paris, H., Graham, L., Tadrous, T., Brown, K., 2005. Reduction and characterization of exhaust emissions from a catalyzed trap-equipped natural gas fueled transit bus. In: Proceedings of the 15th CRC On-Road Vehicle Emissions Workshop, San Diego, CA, April 4–7, 2005.
Grahame, T.J., Schlesinger, R.B., 2005. Evaluating the health risk from secondary sulfates in eastern North American regional ambient air particulate matter. Inhal. Toxicol. 17 (1), 15–27.
Greim, H., Borm, P., Schins, R., Donaldson, K., Driscoll, K., Hartwig, A., Kuempel, E., Oberdörster, G., Speit, G., 2001. Toxicity of fibers and particles. Report of the workshop held in Munich, Germany, October 26–27, 2000. Inhal. Toxicol. 13, 737–754.
Grose, M., Sakurai, H., Savstrom, J., Solzenburg, M.R., Watts Jr., W.F., Morgan, C.G., Murray, I.P., Twigg, M.V., Kittelson, D.B., McMurry, P.H., 2006. Chemical and physical properties of ultrafine diesel exhaust particles sampled downstream of a catalytic trap. Environ. Sci. Technol. 40, 5502–5507.
Grosse, Y., Baan, R., Straif, K., et al., 2009. A review of human carcinogens – Part A: pharmaceuticals. Lancet Oncol. 10 (1), 13–14.
Hallberg, L.M., Ward, J.B., Hernandez, C., Ameredes, B.T., Wickliffe, J.K., 2012. Part 3. Assessment of genotoxicity and oxidative stress after exposure to diesel exhaust from US 2007-compliant diesel engines: Report on 1- and 3-month exposures in the ACES bioassay. In: Advanced Collaborative Emissions Study (ACES) Subchronic Exposure Results: Biologic Responses in Rats and Mice and Assessment of Genotoxicity. Research Report 166. Health Effects Institute, Boston, MA (Available at: <http://pubs.healtheffects.org/view.php?id=377>).
Harkema, J.R., Mauderly, J.L., 1994. Consequences of prolonged inhalation of ozone on F344 rats: collaborative studies. Part V: effects on pulmonary function. Health Effects Institute, Cambridge, MA, Report No. 065-V.
HEI (Health Effects Institute), 1995. Diesel Exhaust: Critical Analysis of Emission Exposure and Health Effects. Special Report.
HEI (Health Effects Institute), 1999. Diesel Emissions and Lung Cancer, Epidemiology and Quantitative Risk Assessment, Special Report.
HEI (Health Effects Institute), 2002. Research Directions to Improve Estimates of Human Exposure and Risk from Diesel Exhaust. HEI Special Report #2002-01-01 (Available at: <http://pubs.healtheffects.org/view.php?id=377>).
HEI (Health Effects Institute), 2012a. Home Page <http://www.healtheffects.org> (accessed 29.1.2012).
HEI (Health Effects Institute), 2012b. Advanced Collaborative Emissions Study (ACES) Subchronic Exposure Results: Biologic Responses in Rats and Mice and Assessment of Genotoxicity. Research Report 166. Health Effects Institute, Boston, MA (Available at: <http://pubs.healtheffects.org/view.php?id=377>).

Heinrich, U., Peters, L., Mohr, U., Bellman, B., Fuhst, R., Ketkar, M.B., König, H., Pott, E., 1986. Investigation of subacute and chronic effects of gasoline engine exhaust on rodents (Ger), (FAT Series No. 55), Frankfurt/Maine, Forschungsvereingteng Automobiltechik, e.V.

Heinrich, U., Fuhst, R., Rittinghausen, S., Creutzenberg, O., Bellman, B., Koch, W., Levsen, K., 1995. Chronic inhalation exposure of Wistar rats and two different strains of mice to diesel engine exhaust, carbon black and titanium dioxide. Inhal. Toxicol. 7, 533–556.

Herner, J.D., Hu, S., Robertson, W.H., Huai, T., Collins, J.F., Dwyer, H., Ayala, A., 2009. Effect of advanced aftertreatment for PM and $NO_x$ control on heavy-duty diesel truck emission. Environ. Sci. Technol. 43 (15), 5928–5933.

Herner, J.D., Hu, S., Robertson, W.H., Huai, T., Chang, M.-C.O., Rieger, P., Ayala, A., 2011. Effect of advanced aftertreatment for PM and $NO_x$ reduction on heavy-duty diesel engine ultrafine particle emissions. Environ. Sci. Technol. 45 (24), 2413–2419.

Hesterberg, T.W., Bunn, W.B., McClellan, R.O., Hart, G.A., Lapin, C.A., 2005. Carcinogenicity studies of diesel engine exhausts in laboratory animals: a review of past studies and a discussion of future research needs. Crit. Rev. Toxicol. 35, 379–411.

Hesterberg, T.W., Bunn, W.B., Chase, G.R., Valberg, P.A., Slavin, T.J., Lapin, C.A., Hart, G.A., 2006. A critical assessment of studies on the carcinogenic potential of diesel exhaust. Crit. Rev. Toxicol. 36, 727–776.

Hesterberg, T.W., Lapin, C.A., Bunn, W.B., 2008. A comparison of emissions from vehicles fueled with diesel or compressed natural gas. Environ. Sci. Technol. 42 (17), 6437–6445.

Hesterberg, T.W., Long, C.M., Sax, S.N., Lapin, C.A., McClellan, R.O., Bunn, W.B., Valberg, P.A., 2011. Particulate matter in New Technology Diesel Exhaust (NTDE) is quantitatively and qualitatively very different from that found in traditional diesel exhaust (TDE). J. Air Waste Manag. Assoc. 61, 894–913.

Hesterberg, T.W., Anderson, R., Bernstein, D.M., Bunn, W.B., Chase, G.A., Marsh, G.M., Jankousky, A.L., McClellan, R.O., 2012a. Product stewardship and science: safe manufacture and use of fiber glass. Reg. Toxicol. Pharmacol. 62, 257–277.

Hesterberg, T.W., Long, C.M., Bunn, W.B., Lapin, C.A., McClellan, R.O., Valberg, P.A., 2012b. Research and regulation of diesel exhaust emissions and health effects: a historical overview focused on lung cancer risk. Inhal. Toxicol., in press.

Holmén, B.A., Ayala, A., 2002. Ultrafine PM emissions from natural gas, oxidation-catalyst diesel, and particle-trap diesel heavy-duty transit buses. Environ. Sci. Technol. 36 (23), 5041–5050.

Holmén, B.A., Qu, Y., 2004. Uncertainty in particle number modal analysis during transient operation of compressed natural gas, diesel, and trap-equipped diesel transit buses. Environ. Sci. Technol. 38 (8), 2413–2423.

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

IARC (International Agency for Research on Cancer) Monograph, vol. 46, 1989. Diesel and Gasoline Engine Exhausts and Some Nitroarenes: World Health Organization, International Agency for Research on Cancer, Lyon, France.

IARC (International Agency for Research on Cancer), 1991. A Concensus Report of an IARC Monographs Working Group on the Use of Mechanisms of Carcinogenesis in Risk Identification (IARC Internal Report 91/002), Lyon, France (Available at: <http://monographs.iarc.fr/>).

IARC (International Agency for Research on Cancer), 2002. Man-Made Vitreous Fibres. IARC Monographs on the Evaluation of Carcinogenic Risk to Humans, vol. 81, International Agency for Research on Cancer, Lyon, France (Available at: <http://monographs.iarc.fr/>).

IARC (International Agency for Research on Cancer), 2005. Report of an Advisory Group to Recommend Updates to the Preamble to the IARC Monographs (IARC Internal Report No. 05/001) (Available at: <http://monographs.iarc.fr/>).

IARC (International Agency for Research on Cancer), 2006. Report of an Advisory Group to Review the Amended Preamble to the IARC Monographs (IARC Internal Report No. 06/001), Lyon, France. Available at: <http://monographs.iarc.fr/EN6/Preamble/CurrentPreamble.pdf> (accessed 19.2.2012).

IARC (International Agency for Research on Cancer), 2011a. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 100A (2011). A Review of Human Carcinogenss, Part A: Pharmaceuticals, Lyon, France. Available at: <http://monographs.iarc.fr/ENG/Classification/index.php> (accessed 2.12.2012).

IARC (International Agency for Research on Cancer), 2011b IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 100B (2011). A Review of Human Carcinogens, Part B: Biological Agents, Lyon, France. Available at: <http://monographs.iarc.fr/ENG/Classification/index.php> (accessed 2.12.2012).

IARC (International Agency for Research on Cancer), 2011c. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 100C (2011). A Review of Human Carcinogens, Part C: Arsenic, Metals, Fibres, and Dusts, Lyon, France. Available at: <http://monographs.iarc.fr/ENG/Classification/index.php> (accessed 2.12.2012).

IARC (International Agency for Research on Cancer), 2011d. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 100D (2011). A Review of Human Carinogens, Part D: Radiation (accessed 28.1.2012), Lyon, France. Available at: <http://monographs.iarc.fr/ENG/Classification/index.php> (accessed 12.2.2012).

IARC (International Agency for Research on Cancer), 2012a. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 100E. A Review of Human Carcinogens, Personal Habits and Indoor Combustion, Lyon, France. Available at: <http://monographs.iarc.fr/ENG/Classification/index.php> (accessed 12.2.2012).

IARC (International Agency for Research on Cancer), 2012b. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 100F. Chemical Agents and Related Occupations. Announcement of June 5–12, 2012 Meeting, Lyon, France. Available at: <http://monographs.iarc.fr/ENG/Classification/index.php> (accessed 12.2.2012).

IPCS (International Program on Chemical Safety), 1996. Environmental Health Criteria 171, Diesel Fuel and Exhaust Emissions.

ILSI (International Life Sciences Institute), 2000. The relevance of the rat lung response to particle overload for human risk assessment: a workshop consensus report. ILSI Risk Science Institute workshop participants. Inhal. Toxicol. 12(1–2), 1–17.

Johnson, T.V., 2010. Diesel Emissions in Review. SAE International, 2010-01-0301, Published April 12, 2010.

Johnson, T.V., 2011. Diesel Emissions in Review. SAE International, 2011-01-0304, Published April 12, 2011.

Jones, A.M., Harrison, R.M., Barratt, B., Fuller, G., 2012. A large reduction in airborne particle number concentrations at the time of the introduction of "sulfur free" diesel and the London low emission zone. Atmosph. Environ. 50, 129–138.

Kado, N.Y., Okamoto, R.A., et al., 2005. Emissions of toxic pollutants from compressed natural gas and low sulfur diesel-fueled heavy-duty transit buses over multiple driving cycles. Environ. Sci. Technol. 39 (19), 7638–7649.

Khalek, I.A., Bougher, T.L., Merritt, P.M., 2009. Phase 1 of the Advanced Collaborative Emissions Study. CRC Report: ACES Phase 1. Coordinating Research Council, Alpharetta, Ga. Available at: <http://www.crcao.org/publications/emissions/index.html> (accessed 10.1.2011).

Khalek, I.A., Boughner, T.L., Merritt, P.M., Zielinska, B., 2011. Regulated and unregulated emissions from highway heavy-duty diesel engines complying with US Environmental Protection Agency 2007 Emissions Standards. J. Air Waste Manag. Assoc. 61, 427–442.

King-Herbert, A., Thayer, K., 2006. NTP workshop: animal models for the NTP rodent cancer bioassay: stocks and strains-should we switch? Toxicol. Pathol. 34 (6), 802–805.

King-Herberg, A.P., Sills, R.C., Bucher, J.R., 2010. Commentary update on animal models for NTP studies. Toxicol. Pathol. 38 (1), 180–181.

Kittelson, D.B., 1998. Engines and nanoparticles: a review. J. Aerosol. Sci. 29 (5/6), 575–588.

Kittelson, D.B., Watts, W.F., Johnson, J.P., Rowntree, C., Payne, M., Goodier, S., Warrens, C., Preston, H., Zink, U., Ortiz, M., et al., 2006a. On-road evaluation of two diesel exhaust aftertreatment devices. Aerosol. Sci. 37, 1140–1151.

Kittelson, D.B., Watts, W.F., Johnson, J.P., Rowntree, C.J., Goodier, S.P., Payne, M.J., Preston, W.H., Warrens, C.P., Ortiz, M., Zink, U., Goersmann, C., Twigg, M.V., Walker, A.P., 2006b. Driving down on-highway particulate emissions, SAE Paper No. 2006-01-0916.

Lanni, T., Frank, B.P., Rosenblatt, D., Lowell, D., 2003. Performance and emissions evaluation of compressed natural gas and clean diesel buses at New York City's Metropolitan Transit Authority. Society of Automotive Engineers Technical Paper Series, Paper No. 2003-01-0300, Warrendale, PA.

LeTavec, C., Uihlein, J., Hallstrom, K., Vertin, K., Chandler, K., Chatterjee, S., Coburn, T., Wayne, S., Clark, N., Gautam, M., Thompson, G., Lyons, D., 2002. Year-long evaluation of trucks and buses equipped with passive diesel particulate fitters, SAE Paper No. 2002-01-0433, Society of Automotive Engineers, Warrendale, PA.

Lev-On, M., LeTavec, C. et al., 2002. Chemical speciation of exhaust emissions from trucks and buses fueled on ultra-low sulfur diesel and CNG, Society of Automotive Engineers Technical Paper Series, SAE Paper No. 2002-01-0432, Warrendale, PA.

Lewtas, J., Nesnow, S., Albert, R.E., 1983. A comparative potency method for cancer risk assessment: clarification of the rationale, theoretical basis, and application to diesel particulate emissions. Risk Anal. 3 (2), 133–137.

Liu, Z.G., Vasys, V.N., Kittelson, D.B., 2007. Nuclei-mode particulate emissions and their response to fuel sulfur content and primary dilution during transient operations of old and modern diesel engines. Environ. Sci. Technol. 41, 6479–6483.

Liu, Z.G., Berg, D.R., Schauer, J.J., 2008a. Comparative analysis on the effects of diesel particulate filter and selective catalytic reduction systems on a wide spectrum of chemical species emissions. Environ. Sci. Technol. 42 (16), 6080–6085.

Liu, Z.G., Berg, D.R., Schauer, J.J., 2008b. Detailed effects of diesel particulate filter on the reduction of chemical species emissions. SAE Int. J. Fuels Lubr. 1 (1), 184–191.

Liu, Z.G., Berg, D., Swor, T., Schauer, J., 2009a. Comparison of strategies for the measurement of mass emissions from diesel engines emitting ultra-low levels of particulate matter. Aerosol. Sci. Technol. 43 (11), 1142–1152.

Liu, Z.G., Berg, D., Swor, T., Schauer, J., 2009b. A Study on the Emissions of Chemical Species from Heavy-duty Diesel Engines and the Effects of Modern Aftertreatment Technology. SAE Technical Paper No. 2009-01-1084.

Liu, Z.G., Berg, D.R., Vasys, V.N., Dettmann, M.E., Zielinska, B., Schauer, J.J., 2010. Analysis of C1, C2, and C10–C33 particle-phase and semi-volatile organic compound emissions from heavy-duty diesel engines. Atmos. Environ. 44, 1108–1115.

Mauderly, J.L., Jones, R.K., Griffith, W.C., Henderson, R.F., McClellan, R.O., 1987. Diesel exhaust is a pulmonary carcinogen in rats exposed chronically by inhalation. Fundam. Appl. Toxicol. 9, 208–221.

Mauderly, J.L., Bice, D.E., Cheng, Y.S., Gillett, N.A., Henderson, R.F., Pickrell, J.A., Wolff, R.K., 1989. Influence of Experimental Pulmonary Emphysema on Toxicological Effects from Inhaled Nitrogen Dioxide and Diesel Exhaust. Research Report 30, Health Effects Institute, Cambridge, MA.

Mauderly, J.L., Cheng, Y.S., Gillett, N.A., Griffith, W.C., Henderson, R.F., Pickrell, J.A., Wolff, R.K., 1990. Influence of pre-existing pulmonary emphysema on susceptibility of rats to chronic inhalation exposure to nitrogen dioxide. Inhal. Toxicol. 2, 129–150.

Mauderly, J.L., Banas, D.A., Griffith, W.C., Hahn, F.F., Henderson, R.F., McClellan, R.O., 1996. Diesel exhaust is not a pulmonary carcinogen in CD-1 mice exposed under conditions carcinogenic to F344 rats. Fundam. Appl. Toxicol. 30, 233–242.

Mauderly, J.L., McCunney, R.J. (Eds.), 1996b. Particle Overload in the Rat Lung and Lung Cancer: Implications for Human Risk Assessment. Taylor and Francis, Washington, DC.

Mauderly, J.L., 1997. Relevance of particle-induced rat lung tumors for assessing lung carcinogenic hazard and human lung cancer risk. Environ. Health Perspect. 105 (Suppl. 5), 1337–1346.

Mauderly, J.L., 2000. Diesel exhaust. In: Lippmann M. (Ed.), Environmental Toxicants: Human Exposure and Their Health Effects, second ed., Wiley, New York, pp. 193–241 (Chapter 7).

Mauderly, J.L., Garshick, E., 2009. Diesel exhaust. In: Lippmann M. (Ed.), Environmental Toxicants, Wiley, New York, pp. 551–631 (Chapter 16).

Mauderly, J.L., 2010. Current status of the toxicology of diesel engine exhaust – and the ACES Project. Zbl Arbeitsmed 60, pp. 412–417. Available at: <http://www.zentralblatt-online.dc>.

Mauderly, J.L., McDonald, J.D., 2012. Advanced Collaborative Emissions Study (ACES) Phase 3A: Characterization of US 2007 – Compliant Diesel Engine and Exposure System Operation: Communication 17. Health Effects Institute, Boston, MA (Available at: <http://pubs.healtheffects.org/view.php?id=377>).

McClellan, R.O., Brooks, A.L., Cuddihy, R.G., Jones, R.K., Mauderly, J.L., Wolff, R.K., 1982. Inhalation toxicology of diesel exhaust particles. In: Lewtas, J. (Ed.), Toxicological Effects of Emissions from Diesel Engines, Elsevier North Holland, Inc., New York, pp. 99–120.

McClellan, R.O., Bice, D.E., Cuddihy, R.G., Gillett, N.A., Henderson, R.F., Jones, R.K., Mauderly, J.L., Pickrell, J.A., Shami, S.G., Wolff, R.K., 1986. Health Effects of Diesel Exhaust. In: Lee, S.D., Schneider, T., Grant, L.D., Verkerk, P.J. (Eds.), Aerosols. Lewis Publishers, Chelsea, MI, pp. 597–615.

McClellan, R.O., 1987. Health effects of exposure to diesel exhaust particles. Ann. Rev. Pharmacol. Toxicol. 27, 279–300.

McClellan, R.O., 1990. Particle overload in the lung: approaches to improving our knowledge. J. Aerosol. Med. 3, S197–S207.

McClellan, R.O., 1996. Lung cancer in rats from prolonged exposure to high concentrations of particles: Implications for human risk assessment. Inhal. Toxicol. 8 (Suppl.), 193–226.

McClellan, R.O., 2011. Role of Science and Judgment in Setting National Ambient Air Quality Standards: How Low is Low Enough? Air Quality, Atmosphere and Health Journal (published on-line, June 1, 2011).

McConnell, E.E., 1996. Maximum tolerated doses in particulate inhalation studies: a pathologist's point of view. Inhal. Toxicol. 8 (Suppl.), 111–123.

McCormick, R.L., Graboski, M.S., Alleman, T., Herring, A.M., Nelson, P., 1999. In-use emissions from natural gas fueled heavy-duty vehicles, SAE Paper No. 1999-01-1507. Society of Automotive Engineers, Warrendale, PA.

McDonald, J.D., 2012. Biological response to inhaled 2007 compliant diesel emissions. Presentation to the California Air Resources Board, Sacramento, CA, February 28, 2012.

McDonald, J.D., Doyle-Eisele, M., Gigliotti, A., Miller, R.A., Seilkop, S., Mauderly, J.L., Seagrave, J., Chow, J., Zielinska, B., 2012. Part 1. Biological response in rats and mice to subchronic inhalation of diesel exhaust from US 2007-compliant engines: Report on 1-, 3-, and 12-month exposures in the ACES bioassay. In: Advanced Collaborative Emissions Study (ACES) Subchronic Exposure Results: Biologic Responses in Rats and Mice and Assessment of Genotoxicity. Research Report 166, Health Effects Institute, Boston, MA (Available at: <http://pubs.healtheffects.org/view.php?id=377>).

McKain, D.L., Wayne, S., Clark, N., 2012. Relationship between carbon monoxide and particulate matter levels across a range of engine technologies. SAE Technical Paper Series 2012-01-1346, Published 2012_04_16.

Mollenhauer, K., Tschoeke, H., 2010. Quote from Rudolph Diesel in Preface. In: Mollenhauer, K., Tschoeke, H. (Eds.), Handbook of Diesel Engines, pp. v–vi.

NIOSH, 1988. Carcinogenic Effects of Exposure to Diesel Exhaust, Current Intelligence Bulletin 50, DHHS (NIOSH) Publication No. 88–116. August 19, 1988.

NIOSH/NCI, 1997. A Cohort Mortality Study with a Nested Case-Control Study of Lung Cancer and Diesel Exhaust Among Non-Metal Miners. US Department of Health and Human Resources, Washington, DC.

NTP (National Toxicology Program), 1994. Toxicology and carcinogenesis studies of ozone (CAS No. 10028–15-6) and Ozone/NNK (CAS No. 10028-15-6/64091-91-4) in F344/N Rats and B6C3F1 mice. National Toxicology Program Technical Report Series No. 440, October 1994.

NTP (National Toxicology Program), 2000. Report on Carcinogens, Contains Listing for Diesel Exhaust Particles, 9th ed., US Department of Health and Human Services, Research Triangle Park, NC, USA (Available at: <http://ntp.niehs.nih.gov/go/8187>) (accessed 13.2.2012).

NTP (National Toxicology Program), 2011a. 12th Report on Carcinogens. Certain Glass Wool Fibers (Inhalable). US Department of Health and Human Services, Research Triangle Park, NC, USA (Available at: <http://ntp.niehs.nih.gov/ntp/roc/twelfth/roc12.pdf>).

NTP (National Toxicology Program), 2011b. Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP), National Toxicology Program, Research Triangle Park, NC.

NTP (National Toxicology Program), 2012. Request for Public Comments on Nominations and Call for Additional Nominations to the Report on Carcinogens. Announcement of review of "diesel exhaust particulates" for 13 Report on Carcinogens Fed. Reg., vol. 77, 2728–2729, January 19, 2012.

Nikula, K.J., Snipes, M.B., Barr, E.B., Griffith, W.C., Henderson, R.F., Mauderly, J.L., 1995. Comparative pulmonary toxicities and carcinogenicities of chronically inhaled diesel exhaust and carbon black in F344 rats. Fundam. Appl. Toxicol. 25, 80–94.

Nixon, President Richard Milhous, 1970. Reorganization Plan #3 Creating the US Environmental Protection Agency (initiated 12/2/1970).

Northeast Advanced Vehicle Consortium, M.J. Bradley & Associates, Inc., West Virginia University, 2000. Hybrid-electric drive heavy-duty vehicle testing project: Final emissions report, NAVC1098-PG009837, Northeast Advanced Vehicle Consortium (NAVC) and Defense Advanced Research Projects Agency (DARPA), Boston, MA.

Norton, P., Frailey, M., Clark, N., Lyons, D., Gautam, M., Addy, J., Beck, N., 1999. Chassis dynamometer emission measurements from trucks and buses using dual-fuel natural gas engines, SAE Paper No. 1999-01-3525, Society of Automotive Engineers, Warrendale, PA.

OEHHA (Office of Environmental Health Hazard Assessment, California Environmental Protection Agency), 2011. Notice of Modification of the Listing of Glasswool Fibers (Airborne Particles of Respirable Size) to Glass Wool Fibers (Inhalable and Biopersistent). California Registry Notice. Register 2011, vol. No. 46–2, p. 1878.

Olsson, A.C., Gustavsson, Kromhout, H., Peters, S., Vermeulen, R., Brüske, I., Pesch, B., Slemlatycki, J., Pintos, J., Brüning, T., Cassidy, A., Wichmann, H.-E., Consonni, D., Landi, M.T., Caporaso, N., Plat, N., Merietti, F., Mirabelli, D., Richiardi, L., Jöckel, K.-H., Ahrens, W., Pohlabeln, H., Lissowska, J., Szeszenia-Dabrowska, N., Zaridze, D., Stücker, I., Benharnou, S., Bencko, V., Foretova, L., Janout, V., Rudnai, P., Fabianova, E., Dumitru, R.S., Gross, I.M., Kendzia, B., Forastiere, F., Beno-de-Mesquita, B., Brennan, P., Boffetta, P., Straif, K., 2012. Exposure to diesel motor exhaust and lung cancer risk in a pooled analysis from case-control studies in Europe and Canada. Am. J. Respir. Crit. Care Med. 183(7), 941–948.

Pakbin, P., Ning, Z., Schauer, J.J., Sioutas, C., 2009. Characterization of particle bound organic carbon from diesel vehicles equipped with advanced emission control technologies. Environ. Sci. Technol. 43, 4679–4686.

Pauluhn, J., 2011. Poorly soluble particulates: searching for a unifying denominator of nanoparticles and fine particles for DNEL estimations. Toxicology 279, 176–188.

Plopper, C.G., Chow, C.K., Dungworth, D.L., Brummer, M., Nemeth, T.J., 1978. Effects of low levels of ozone on rats lungs. II. Morphological responses during recovery and re-exposure. Exp. Mol. Pathol. 29, 400–411.

Plopper, C.G., Chow, C.K., Dungworth, D.L., Tyler, W.S., 1979. Pulmonary alterations in rats exposed to 0.2 and 0.1 ppm ozone: a correlated morphological and biochemical study. Arch. Environ. Health 34, 390–395.

Reiss, R., Anderson, E.L., Cross, C.E., Hidy, G., Hoel, D., McClellan, R., Moolgavkar, S., 2007. Evidence of health impacts of sulfate-and nitrate-containing particles in ambient air. Inhal. Toxicol. 19, 419–449.

Rijkeboer, R.C., Hendriksen, P., Hollemans, B., van der Weide, J., 1994. Potential Impact of Four Different Car Fuels on the Dutch Environment. SAE Paper No. 941914, Society of Automotive Engineers, Warrendale, PA.

Robinson, A., Donahue, N., Shirivastava, M., Weitkamp, E., Sage, A., Greishop, A., Lane, T., Pierce, J., Pandis, S., 2007. Rethinking organic aerosols: semivolatile emissions and photochemical aging. Science 3 (15), 1259–1262.

Schauer, J.J., Christensen, C.G., Kittelson, D.B., Johnson, J.P., Watts, W.F., 2008. Impact of ambient temperatures and driving conditions on the chemical composition of particulate matter emissions from non-smoking gasoline-powered motor vehicles. Aerosol. Sci. Technol. 42, 210–223.

Schlesinger, R.B., Cassee, F., 2003. Atmospheric secondary inorganic particulate matter: the toxicological perspective as a basis for health effects risk assessment". Inhal. Toxicol. 15, 197–235.

Schlesinger, R.B., 2007. The health impact of common inorganic components of fine particulate matter ($PM_{2.5}$) in ambient air: a critical review. Inhal. Toxicol. 19, 811–832.

Secretan, B., Straif, K., Baan, R., et al., 2009. A review of human carcinogens – Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. Lancet. Oncol. 10 (11), 1033–1034.

Silverman, D.T., Samanic, C.M., Lubin, J.H. et al., 2012. The diesel exhaust in miners study: a nested case-control study of lung cancer and diesel exhaust. J. Natl. Cancer Inst., 104, 2012, http://dx.doi.org/10.1093/jnci/djs034.

Stewart, P.A., Coble, J.B., Vermeulen, R., et al., 2010. The diesel exhaust in miners study: I. Overview of the exposure assessment process. Ann. Occup. Hyg. 54 (7), 728–746.

Stewart, P.A., Coble, J.B., Vermeulen, R. et al. 2012. The diesel exhaust in miners study: V. Evaluation of the exposure assessment methods. Ann. Occup. Hyg., pp. 1–12 (Open Access Article) http://dx.doi.org/10.1093/annhyg/mes020.

Straif, K., Benbrahim-Tallna, l., Baan, R., et al., 2009. A review of human carcinogens – Part C: metals, arsenic, dusts and fibres. Lancet Oncol. 10 (5), 453–454.

Tobias, H.J., Beving, D.E., Ziemann, P.J., 2001. Chemical analysis of diesel engine nanoparticles using a nano-DMA/thermal desorption particle beam mass spectrometer. Environ. Sci. Technol. 35, 2233–2243.

Tomatis, L., Aitio, A., Wilborn, J., Shuker, L., 1989. Human carcinogens so far identified. Jpn. J. Cancer Res. 80, 795–807.

Tschoeke, H., Graf, A., Stein, J., Krüger, M., Schaller, J., Breuer, N., Engeljehringer, K., Schinler, W., 2010. Diesel engine exhaust emissions. In: Mollenhauer, K., Tschoeke, H. (Eds.), Handbook of Diesel Engines, Springer-Verlag, Berlin, Heidelberg, TSBN 978-3-540-89082-9, pp. 417–486.

Twigg, M.V., 2005. Controlling automotive exhaust emissions: successes and underlying science. Phil. Trans. R. Soc. A 363, 1013–1033. http://dx.doi.org/10.1098/rsta.2005.1547.

US Environmental Protection Agency, 1996. Air quality criteria for ozone and related photochemical oxidants, Research Triangle Park, NC. Office of Research

and Development Report Nos. EPA/600/AP-93/004aF-cE3v. Available from NTIS, Springfield, VA. PB96-185582, PB96-185590, and PB96-185608, and at <http://www.epa.gov/ttn/naaqs/standards/pm/s_pm_cr_cd.html> (accessed April 2012).

US Environmental Protection Agency, 2002. Health Assessment Document for Diesel Engine Exhaust, EPA/600/8-90/057F, US Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Washington, DC.

US Environmental Protection Agency, 2006. Air quality criteria for ozone and related photochemical oxidants (Final), US Environmental Protection Agency, Washington, DC, EPA/600/R-05/004aF-cF.

US Environmental Protection Agency, 2012a. Technical Transfer National Ambient Air Quality Standards (NAAQS). Particulate Matter (PM) Standards, Table of Historical PM NAAQS. Available at: <http://www.epa.gov/ttn/naaqs/standards/pm/s_pm.history.html> (accessed 15.2.2012).

US Environmental Protection Agency, 2012b. Technical Transfer National Ambient Air Quality Standards (NAAQS). Ozone ($O_3$) Standards, Table of Historical Ozone Standards. Available at: <http://www.epa.gov/ttn/naaqs/standards/ozone/s_03_index.html> (accessed 15.2.2012).

Vainio, H., Magee, P., McGregor, D., McMichael, A. (Eds.), 1992. Mechanisms of Carcinogenesis in Risk Identification, IARC Working Group Meeting, Lyon, France, June 11–18, 2001. IARC Science, Publication 1161-608.

Vainio, H., Wilbourn, J.D., Sasco, A.J., et al., 1995. Identification of human carcinogenic risks in IARC monographs. Bull. Cancer 82, 339–348.

Vermeulen, R., Coble, J.B., Yereb, D., Lubin, J.H., Blair, A., Portengen, L., Stewart, P.A., Attfield, M., Silverman, D.T., 2010a. The diesel exhaust in miners study: III. Interrelations between respirable elemental carbon and gaseous and particulate components of diesel exhaust derived from area sampling in underground non-metal mining facilities. Ann. Occup. Hyg. 54 (7), 762–773.

Vermeulen, R., Coble, J.B., Lubin, J.H., Portengen, L., Blair, A., Stewart, P.A., Attfield, M.D., Silverman, D.T., 2010b. The diesel exhaust in miners study: IV. Estimating historical exposures to diesel exhaust in underground non-metal mining facilities. Ann. Occup. Hyg. 54 (7), 774–788.

Villeneuve, P., Prent, M.-E., et al., 2011. Occupational exposure to diesel and gasoline emissions and lung cancer in Canadian men. Environ. Res. 111, 727–735.

Wahlin, P., Palmgren, F., Van Dingenenen, R., Raes, F., 2001. Pronounced decrease of ambient particle number emissions from diesel traffic in Denmark after reduction of the sulfur content in diesel fuel. Atmosphere. Environ. 35, 3549–3552.

Wang, W.G., Clark, N.N., Lyons, D.W., Yang, R.M., Gautam, M., Bata, R.M., Loth, J.L., 1997. Emissions comparisons from alternative fuel buses and diesel buses with a chassis dynamometer testing facility. Environ. Sci. Technol. 35, 3132–3137.

Wang, H., Jacob, D.J., Le Sager, P., Streets, D.G., Park, R.J., Gilliland, A.B., van Donkelaar, A., 2009. Surface ozone background in the US: Canadian and Mexican pollution influences. Atmospheric Environ. 43, 1310–1319.

Ward, E.M., Schulte, P.A., Straif, K., Hopf, N.B., Caldwell, J.C., Carreon, T., DeMarini, D.M., et al., 2010. Research recommendations for selected IARC-classified agents. Environ. Health Perspect. 118, 1355–1362.

Watson, A.Y., Valberg, P.A., 1996. Particle-induced lung tumors in rats: evidence for species specificity in mechanisms. Inhal. Toxicol. 8 (Suppl.), 227–257.

Wilbourn, J., Haroun, L., Heseltine, E., et al., 1986. Response of experimental animals to human carcinogens based upon the IARC monographs programme. Carcinogenesis 7, 1853–1863.

Wolff, R.K., Henderson, R.F., Snipes, M.B., Griffith, W.C., Mauderly, J.L., Cuddihy, R.G., McClellan, R.O., 1987. Alterations in particle accumulation and clearance in lungs of rats chronically exposed to diesel exhaust. Fundam. Appl. Toxicol. 9, 154–166.

Wolff, R.K., Griffith, W.C., Cuddihy, R.G., Snipes, M.B., Henderson, R.F., Mauderly, J.L., McClellan, R.O., 1989. Modeling accumulations of particles in lung during chronic inhalation exposures that lead to impaired clearance. Health Phys. 57, 61–68.

Yanowitz, J., McCormick, R.L., Graboski, M.S., 2000. In-use emissions from heavy-duty vehicle emissions. Environ. Sci. Technol. 34, 729–740.

Zhang, L., Jacob, D.J., Downey, N.V., Wood, D.A., Blewitt, D., Carouge, C.C., van Donkelaar, A., Dylan, B.A., Jones, Murray, L.T., Wang, Y., 2011. Improved estimate of the policy-relevant background ozone in the United States using the GEOS-Chem global model with $1/2° \times 2/3°$ horizontal resolution over North America. Atmos. Environ. 45, 6769–6776.