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May 2, 2012

Dr. Kurt Straif
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RE: HEI Submissions of Peer-Reviewed Science on Diesel Exhaust for Consideration in the IARC Volume 105 Review

Dear Drs. Straif and Benbrahim-Tallaa:

On behalf of the Health Effects Institute (HEI), I am pleased to transmit three important studies of diesel engine emissions and health effects for the consideration of the panelists convening in June 2012 for review of diesel exhaust and other substances. These are in addition to the extensive set of HEI publications which we transmitted to you last fall via a CD and an email from Dr. Rashid Shaikh. These additional submissions constitute both the newest HEI report on this subject as well as reports of two studies which are now available in electronic form. *All of these studies have been subjected to the rigorous independent peer review prior to publication which IARC requires for consideration of the results and has accepted for inclusion of HEI reports in previous Volumes.*

Specifically, I enclose the following reports – and comment on their significance below:

HEI Research Report 166	Advanced Collaborative Emissions Study (ACES) Subchronic Exposure Results: Biologic Responses in Rats and Mice and Assessment of Genotoxicity. 2012.
	Part 1: *Biologic responses in rats and mice to subchronic inhalation of diesel exhaust from U.S. 2007-compliant engines: Report on 1-, 3-, and 12-month exposures in the ACES bioassay.* McDonald JD, et al.
	Part 2: *Assessment of genotoxicity after exposure to diesel exhaust from U.S. 2007-compliant diesel engines: Report on 1- and 3-month exposures in the ACES bioassay.* Bemis JC, et al.
	Part 3: *Assessment of genotoxicity and oxidative stress after exposure to diesel exhaust from U.S. 2007-compliant diesel engines: Report on 1- and 3-month exposures in the ACES bioassay.* Hallberg LM, et al.
HEI Research Report 107	Real-World Particulate Matter and Gaseous Emissions from Motor Vehicles in a Highway Tunnel 2002 Alan W Gertler, et al.
HEI Research Report 68	Pulmonary Toxicity of Inhaled Diesel Exhaust and Carbon Black in Chronically

Exposed Rats.

Part I: *Neoplastic and nonneoplastic lung lesions.* Mauderly JL, et al 1994

Part II: *An Investigation of DNA Damage in the Lungs of Rats Exposed to Diesel Exhaust.* Randerath K, et al. 1995

Part III: *Examination of Possible Target Genes.* Belinsky SA, et al.1995

HEI Research on New Technology Diesel Engine Emissions

Based on a number of studies of the health effects of fine particulate matter, the US EPA in 2001 finalized rules requiring diesel particle filters for diesel vehicles in the United States starting in 2006 (light duty) and 2007 (heavy duty). Similar rules have now also been implemented in all other industrialized countries. As you know from our previous correspondence, HEI is in the midst of the most comprehensive emissions and health effects study yet undertaken of the newest generation of diesel technology – the Advanced Collaborative Emissions Study (ACES) – on emissions from modern diesel engines now in the market. It comprises three main phases:

- Phase I: ACES has already characterized in detail the emissions from U.S. 2007-compliant heavy duty engines manufactured by four different companies, each outfitted with PM control technology, and compared such emissions with those from an older diesel engine. The results of this study have been published and we sent you the reports in the fall, 2011.

- Phase 2: ACES is now beginning to characterize the emissions from three even more advanced engines that are compliant with U.S. 2010-rules and which are outfitted with enhanced NOx control devices along with the particulate filters. The results of this study are expected to be published in early 2013.

- Phase 3: To provide health effects information for these new engines, HEI is sponsoring a rigorous chronic inhalation study in mice (3 months) and rats (lifetime) which are being exposed to emissions from a US 2007-compliant engine with a PM control device; we are within the last several months of completion of the exposure in this lifetime study. The endpoints being examined in this study include lung histopathology, inflammation and respiratory function, genotoxicity, tumor development, and many others. The results of Phase 3 are being published in the reports listed below:

    - Phase 3A: describing preparatory work with the dynamometer-engine-emissions dilution-animal chamber system to achieve optimal and pre-determined conditions for animal exposures (Mauderly 2012; available at the HEI website).

    - Phase 3B – 1: We have now peer-reviewed, published, and are submitting with this letter, extensive results from initial time points in this study (1 and 3 months in both mice and rats, and some 12 months results in rats); as customary for HEI, this report also includes a detailed commentary from the panel that reviewed these results (Health Effects Institute, 2012. Report No. 166; attached)

    - Phase 3B – 2: This report will present the detailed results of the 12 and 24-30 month exposures. The life-time exposures will be completed during late-2012. We expect fully peer-reviewed results of these studies to be available in mid- to late-2013, along with a commentary by our review panel.

HEI Findings on Emissions from New and Older Diesel Engines

Emissions from New Technology Diesel Engines

As noted above, ACES Phase 1 performed extensive characterization of four new technology diesel engines meeting 2007 US emissions requirements for on-road heavy duty engines. The results of this study -- available as a report by HEI's research partner for this work, the Coordinating Research Council (Khalek et al. 2009) and in a paper in the Journal of the American Waste Management Association (Khalek et al. 2011) -- demonstrated that the PM control technologies substantially reduces emissions of PM, organics, and gases, and also significantly changes the chemistry of the emissions from particles dominated by carbon to ones dominated by sulfates. The substantial reductions in the mass and number of PM (Figures 1 and 2) and in the shift in composition from a carbon-dominated composition to a sulfate-dominated composition (Figure 3) suggest that modern diesel exhaust from these engines is significantly different from older engines.

Figure 1. Reductions in Particle Mass from 2004 compared to 2007 diesel technology (Source: Khalek 2011, 2012)

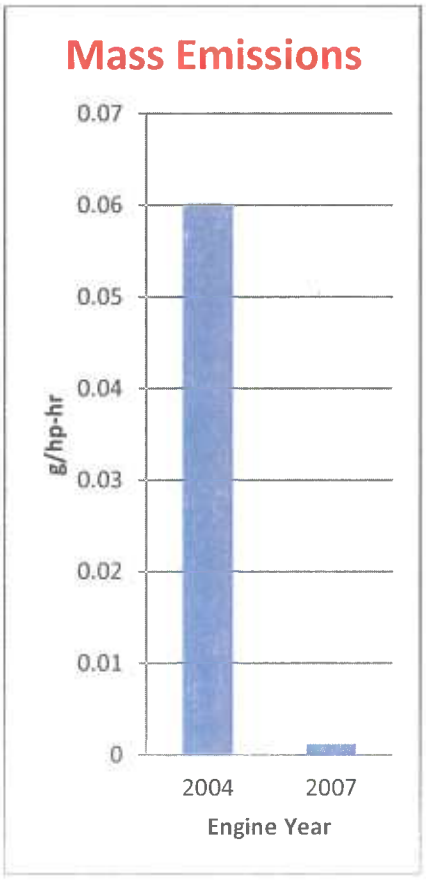


Figure 2. Reductions in Particle Numbers from 2004 compared to 2007 diesel technology (Source: Khalek 2011)

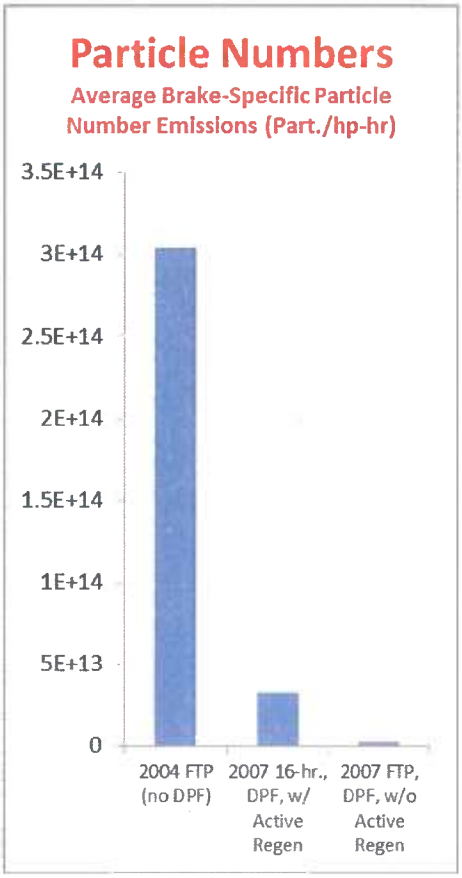
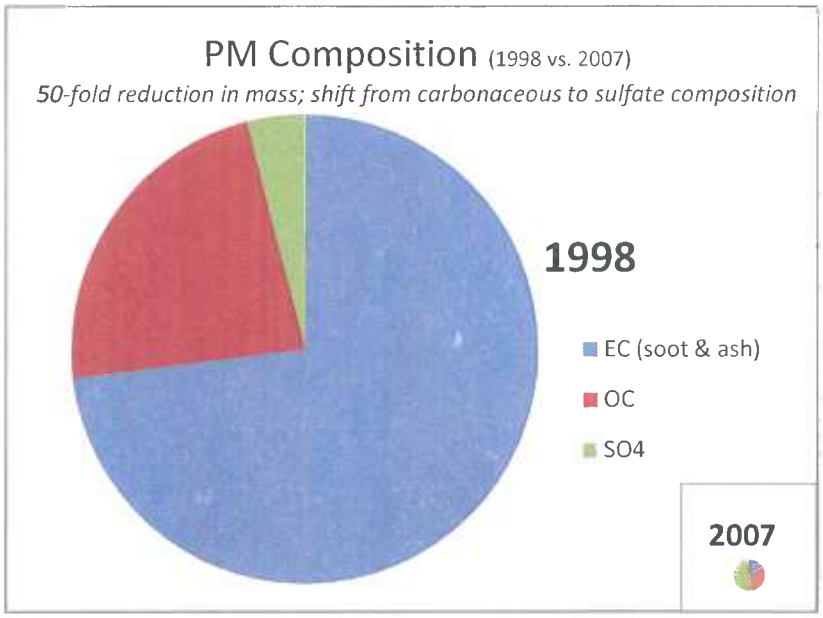


Figure 3. Change in Particulate Matter Composition, comparing 1998 diesel engine (w/o DOC, FTP cycle cold/hot composite) with 2007-compliant engine (ACES 16-hour cycle)



Prior Improvements in Diesel Emissions 1975 – 2000

Although the advent of these newest technology diesel engines has resulted in substantial reductions in emissions, and significant changes in emissions composition, improvements in diesel technology started with the first emissions regulations in the US in the 1980s. To test the extent of the real world changes in emissions that resulted from these earlier rules, HEI supported the most recent of a series of seven real world tests of diesel and other exhausts in the Tuscarora tunnel on the Pennsylvania Turnpike, a motorway in the state of Pennsylvania in the northeast United States (Gertler 2002). That study, the primary results of which are reproduced below (Figure 9 from the report) found substantial reductions. It was intensively and independently peer-reviewed by the HEI Review Committee, which concluded:

> "The study by Gertler and colleagues adds substantially to our knowledge of the emission factors, particle size distribution, and chemical composition of diesel PM and the levels of gaseous emissions produced under a select set of on-road driving conditions. Comparing their results with those of earlier tunnel studies indicates that many components of diesel engine emissions have declined dramatically."

HEI Findings on Toxicological Effects of New and Older Technology Diesel Engines

New Technology Toxicology Results

HEI has recently published its peer-reviewed Research Report 166 *Advanced Collaborative Emissions Study (ACES) Subchronic Exposure Results: Biologic Responses in Rats and Mice and Assessment of Genotoxicity* (HEI 2012; attached). These provide the first systematic examination of health effects in mice and rats of exposure to emissions from new technology diesel engines. In its review and commentary on the results, the HEI Review Panel concluded: "Overall, these results indicate

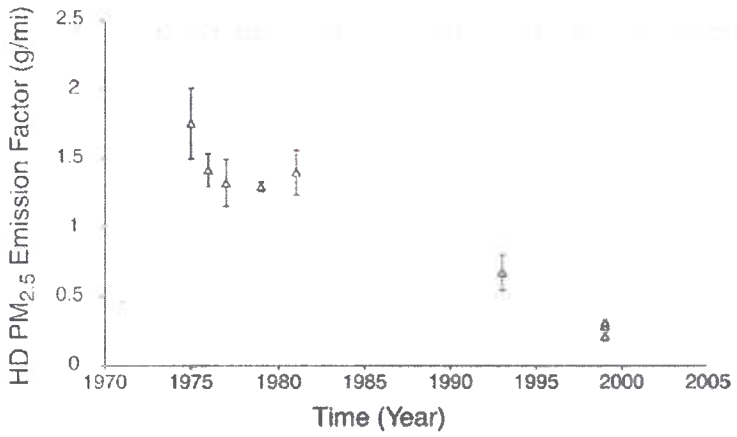


Figure 9. HD emission factor estimates between 1975 and 1999 (present study) derived from tunnel studies. Note that the markers for 1999 include Tuscarora PM_{10}, $PM_{2.5}$, and $PM_{2.5}$ (reconstructed mass).
(Source: Gertler 2002)

that rats exposed to one of three levels of diesel exhaust from a 2007-compliant engine for up to 12 months, for 16 hours per day, 5 days a week, with use of a strenuous [engine] operating cycle that was more realistic than cycles used in previous studies, showed few biologic effects related to diesel exhaust exposure. Even fewer exposure-related biologic effects were found in mice exposed for 3 months to diesel exhaust. In rats, the effects that were observed were limited to the respiratory tract and were mild, and the changes in lungs were consistent with previous findings after long-term exposure to NO_2 — a major component of the exposure atmosphere. No exposure-related genotoxic effects were found in rats or mice after 3 months of exposure."[1]

Older Technology Toxicology Results

HEI has previously funded dozens of toxicology studies of the potential effects of diesel exhaust and its components, including nitroarenes, from older diesel engines. The most comprehensive and prominent of these was a study of lifetime exposure of mice and rats to older diesel engine exhaust and to carbon black (Mauderly, 1994). That study, as with similar studies conducted in Germany and Japan, found a dose-dependent increase in lung tumors in the rats but not in the mice exposed to diesel exhaust. However, the study found an almost identical increase in lung tumors in the rats exposed to the same levels of carbon black (containing the carbon core but none of the adsorbed chemicals of diesel exhaust). The HEI Review Committee and the HEI Diesel Working Group Expert Panel (HEI 1995) concluded that this evidence suggested that lung tumor formation most likely resulted from a "particle overload" mechanism that was common to both types of particles. Companion studies evaluating samples from the Mauderly study did not find genotoxic effects (Belinsky.1995, Randerath.1995).

The Mauderly report also presented effects of the diesel and carbon black exposures on rats at 12 months, and found significantly different and greater effects in the lungs - in particular the presence of particle-laden macrophages (Figures 12 and 13), and a significantly higher level of alveolar epithelial hyperplasia (Figure 19) - than were seen in the ACES 3B study at the same time point.

[1] Note that these NO2 levels are already being substantially further reduced in 2010-compliant engines.

HEI Findings on Epidemiological Effects of Older Diesel Engine Exhaust

The Occupational Epidemiology Evidence

HEI has engaged in extensive review and analysis of the occupational literature on exposure to diesel exhaust and risk of cancer. The HEI Diesel Working Group reported that the epidemiologic data were consistent in showing weak associations between diesel exhaust exposure and lung cancer risk across a number of occupational studies. "The available evidence suggests that long term exposure to diesel exhaust in a variety of occupational circumstances is associated with a 1.2 to 1.5-fold increase in the relative risk of lung cancer compared with workers classified as not exposed." (HEI 1995) There was not a similar increase in risk for bladder cancer. The Panel noted that although studies that attempted to control for smoking behavior still reported this increase in lung cancer risk, the studies were unable to control for other possible confounders, and the analyses were not based on actual measures of exposure to diesel exhaust for the workers.

Based on questions identified in the HEI 1995 Special Report, HEI convened a Diesel Epidemiology Expert Panel to re-analyze the major occupational studies of diesel exposure that were then available and review their utility in risk assessment. The Panel concluded that the two major studies at that time – of trucking industry workers and railroad workers - were likely not suitable for use in quantitative estimation of diesel risk (HEI 1999). They reported further that in the largest of these studies, the railroad workers cohort (Garshick 1988), there was evidence that longer years worked (i.e. greater exposure) was related to a *reduced* risk of lung cancer.

Having identified a number of key research gaps, HEI then sought competitive proposals for feasibility studies of occupational exposure to diesel exhaust, and funded five such studies (HEI 2002). We found that the cohorts analyzed in these feasibility studies held limited promise for additional work. However, one of them – a study in a new trucking industry cohort - sought and received additional funding from the National Cancer Institute and has now been published (Garshick 2008); HEI also funded additional exposure measurements in this study. These investigators found a positive association between lung cancer and exposure to "vehicle exhaust from diesel and other types of vehicles on highways, city streets, and loading docks" although they were not able to isolate the increased lung cancer risk solely to diesel exhaust exposure.

Markers of Diesel Exposure

One of the key questions arising from efforts to characterize exposure to and health effects of diesel exhaust is the challenge of identifying a relatively unique atmospheric marker of diesel emissions that can be used to estimate exposure of the general population and be used as a marker for retrospective estimation of exposure in longer term occupational epidemiology studies. The HEI Diesel Epidemiology Expert Panel (HEI 1999) noted significant limitations in the retrospective exposure assessment in both the trucking industry worker and railroad worker studies they analyzed, which contributed to their conclusion that the studies were not suitable for quantitative dose-response and risk assessment.

In reviewing the results of the HEI-supported diesel exhaust and cancer feasibility studies, including two that focused specifically on characterization of exposure in mines and elsewhere, the HEI Diesel Epidemiology Work Group (Special Report 2002) noted significant challenges with characterizing exposure. They explored a number of potential chemical and atmospheric markers of diesel exhaust but concluded that even the most widely available and potentially relevant emission marker, elemental carbon, had limitations. They concluded: "The Working Group does not recommend proceeding with full studies of the populations considered here, *largely because of concern about the lack of available data from which one could estimate past exposures*" (emphasis added).

Following their report, HEI hosted a large, multi-disciplinary workshop - "Improving Estimates of Diesel and Other Emissions for Epidemiologic Studies" - to even more broadly investigate potential atmospheric and emissions markers of diesel exhaust. That workshop also noted the significant limitations in the existing markers, and recommended a wide range of new research to try to fill the gaps. (HEI 2003)

We are pleased to have the opportunity to submit these findings from HEI scientific investigations and reviews for consideration in the IARC process and look forward to answering any questions that the IARC staff or Panel may have.

Sincerely,

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