

February 24, 2012

Dr. Ruth Lunn
Director, Office of the Report of Carcinogens
DNTP, NIEHS
P.O. Box 12233, MD K2-14
Research Triangle Park, NC 27709

RE: Public Comments on Nominations, National Toxicology Program Report
on Carcinogens: Diesel Emission Particles

Dear Dr. Lunn:

On behalf of the Health Effects Institute (HEI), I write in response to the recent request for public comments (Federal Register January 19, 2012, page 2728-2729). Our comments are focused on diesel exhaust particles, one of the substances identified in the abovementioned notice.

HEI is an independent, non-profit research organization that provides high-quality, impartial, and relevant science on the health effects of air pollution. HEI conducts, reviews and evaluates new research; reviews the literature in specific areas to assess the state of and gaps in knowledge; and, re-analyzes key studies on important health questions. HEI is governed by an independent Board of Directors and prominent and independent scientific committees: a Research Committee which selects and oversees all work, and a Review Committee, which rigorously peer reviews comprehensive reports of each project. The Board of Directors also periodically appoints special expert panels to review an entire body of scientific literature and/or to oversee reanalyses of key studies.

Typically, HEI receives half of its core funds from the US Environmental Protection Agency and half from the worldwide motor vehicle industry. Other public and private organizations periodically support special projects or certain research programs. However, HEI's sponsors do not have any role in management and operations of HEI or in its scientific decisions or judgments on investigator selection, project oversight, or peer review of reports. Also, HEI confines its work to science and does not make or lobby for policy recommendations.

During the last two decades, HEI has published more than 50 reports from the research we have sponsored on the effects of diesel exhaust and its components as well as more than 10 special reports and communications, including comprehensive reviews of diesel toxicology and epidemiology. This has included a number of relevant publications on diesel and cancer. I am

glad to enclose a CD which contains reports from all of these studies. Upon request, we will be glad to provide you with print copies of these reports; additionally, most of these reports are also accessible at no cost at our website, www.healtheffects.org. We believe that these documents will help NTP in evaluating the health effects of diesel emission particles.

HEI Findings on Older Diesel Engine Exhaust

HEI's work has included a number of seminal investigations into toxicology, epidemiology, and exposure markers of diesel exhaust and its potential effects on cancer. We highlight key findings of that work below (all HEI and ACES reports referenced can be found on the enclosed CD).

Toxicology

HEI has funded dozens of toxicology studies of the potential effects of diesel exhaust and its components from older diesel engines. The most comprehensive and prominent of these was a lifetime exposure of mice and rats to older diesel engine exhaust and to carbon black (Mauderly 1994). That study, as with other similar studies, found a dose-dependent increase in tumors in the rats exposed to diesel exhaust but not in the mice. However, the study found an almost identical increase in tumors in the rats exposed to carbon black. The HEI Review Committee and the HEI Diesel Working Group Expert Panel (HEI 1995) concluded that this evidence suggested that tumor formation was likely not due to diesel exhaust, but was most likely due to "particle lung overload" from both types of particles. Companion genotoxicity testing was not able to detect elevated effects related to dose (Belinsky 1995, Randerath 1995).

Epidemiology

HEI has also engaged in extensive review of the occupational literature on exposure to diesel exhaust. The HEI Diesel Working Group reported that the epidemiologic data were "consistent in showing weak associations" between diesel 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 exposed." (HEI 1995) There was not a similar increase in risk for bladder cancer. The Panel noted that although those 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 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. That Panel concluded that the two major studies – 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). Although several of the feasibility studies held limited promise for additional work, 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 an 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.

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 had explored a number of potential chemical and atmospheric markers of diesel exhaust but concluded that even the most widely available and potential 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)

Health Effects of New Technology Diesel Engines

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. Since this is a relatively young technology, very little information is available on either the emissions or the health effects of emissions from such engines. Currently, HEI is in the midst of the most comprehensive emissions and health effects study yet undertaken of the newest generation of diesel technology. This program – the Advanced Collaborative Emissions Study (ACES) – focuses on emissions from modern diesel engines now in the market and 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 -- available as a report by HEI's contractor for this work, the Coordinating Research Council (CRC 2009) and in a paper in the Journal of the American Waste Management Association (Khalek et al. 2011) -- demonstrated that the PM control technology substantially reduces emissions of PM, organics, and gases, and also significantly changes the character of the emissions from particles dominated by carbon to ones dominated by sulfates. The substantial changes in both the quantity of emissions and their characteristics suggest that modern diesel exhaust from these engines is significantly different from older engines. Therefore, health studies of older diesel engines may not be relevant to these new, very different emissions.

- Phase 2: ACES will soon characterize the emissions from 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. We anticipate testing three such engines manufactured by different companies during the next several months. The results of this study are expected to be published in early 2013.

- Phase 3: Finally, to begin 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 from completion of this 24-30 month lifetime study. The endpoints being examined in this study include lung histopathology, inflammation and function, genotoxicity, tumor development, and many others. Phase 3 is producing the reports listed below;
 - Phase 3A: this represents preparatory work with the dynamometer-engine-emissions dilution-animal chamber system to achieve optimal and pre-determined conditions for animal exposures (Mauderly 2012).

 - Phase 3B – 1: We now have extensive results from early time points in this study (1 and 3 months in both mice and rats, and some 12 months results in rats). The reports from these studies have now been peer-reviewed and accepted for publication, in accordance with the standard HEI process. These reports are now in-press and will be available in mid- to late-April, 2012. We will forward these reports to NTP immediately upon publication. To summarize the results very briefly: the interim results provide no evidence of genotoxicity at this stage of the study, and only some mild re-modeling of the rat lungs (which are most likely due to the levels of NO2 in the exhaust, since it is the predominant component of the exposure atmosphere, in the almost-total absence of particles from these new engines).

 - Phase 3B – 2: This report will present the detailed results of the 24-30 month exposures. The exposures will be completed during mid- to late-2012, depending on whether the study is terminated at 24 months or extended to 30 months. Please note that *the comprehensive carcinogenicity results at the end of this lifetime study using*

contemporary engines – the first to completed since the 1980s- 1990s studies by HEI and others which used much older technologies – will not be available until mid- to late-2013.

We are not aware of the detailed schedule NTP will use to review the various substances listed in the Federal Register notice. We will ensure that as much as possible of our studies are available to NTP in a timely fashion. We would hope that, as the NTP weighs the evidence on diesel emission particles for its Report on Carcinogens, it would consider two important issues in addition to the broader HEI and other findings on older diesel exhaust:

- (1) That the significantly different emissions from new diesel engines – in terms of mass, number and size of PM and their chemical composition – along with the paucity of health data for those emissions, may call for separating evaluation of new exhaust from older diesel engine exhaust; and,
- (2) We would respectfully suggest that the most comprehensive consideration of cancer risk from this new technology diesel exhaust would be enhanced substantially by the availability of the only long term health study currently underway – the HEI ACES Phase 3B study – which will be available in 15-18 months from now.

Thank you for this opportunity to comment. And please let us know if we can be of any further assistance to NTP.

Sincerely,
[Redacted]

Dan Greenbaum
President
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Enclosure: HEI Studies CD

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