Written Testimony Before U.S. EPA's Clean Air Scientific Advisory Committee Review of the Integrated Science Assessment for Particulate Matter (December 2008 First External Review Draft)

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on behalf of the Utility Air Regulatory Group (UARG)

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Gradient Corporation was asked by the Utility Air Regulatory Group (UARG) to review and prepare an independent analysis of the December 2008 first external review draft of the U.S. EPA "Integrated Science Assessment for Particulate Matter" (hereafter referred to as the "Draft PM ISA"). In comments submitted to the EPA Docket, we summarized the findings of our analysis and addressed what we see as large discordances that remain among the three principal lines of health effects evidence for PM, namely observational epidemiology, experimental toxicology (*i.e.*, human clinical and laboratory animal studies), and biological-mechanism-of-action studies. These discordances are illustrated in Figures 1 and 2 below that show that **PM concentrations 1 to 3 orders of magnitude higher than ambient levels are required to elicit biological responses in experimental toxicology studies**.

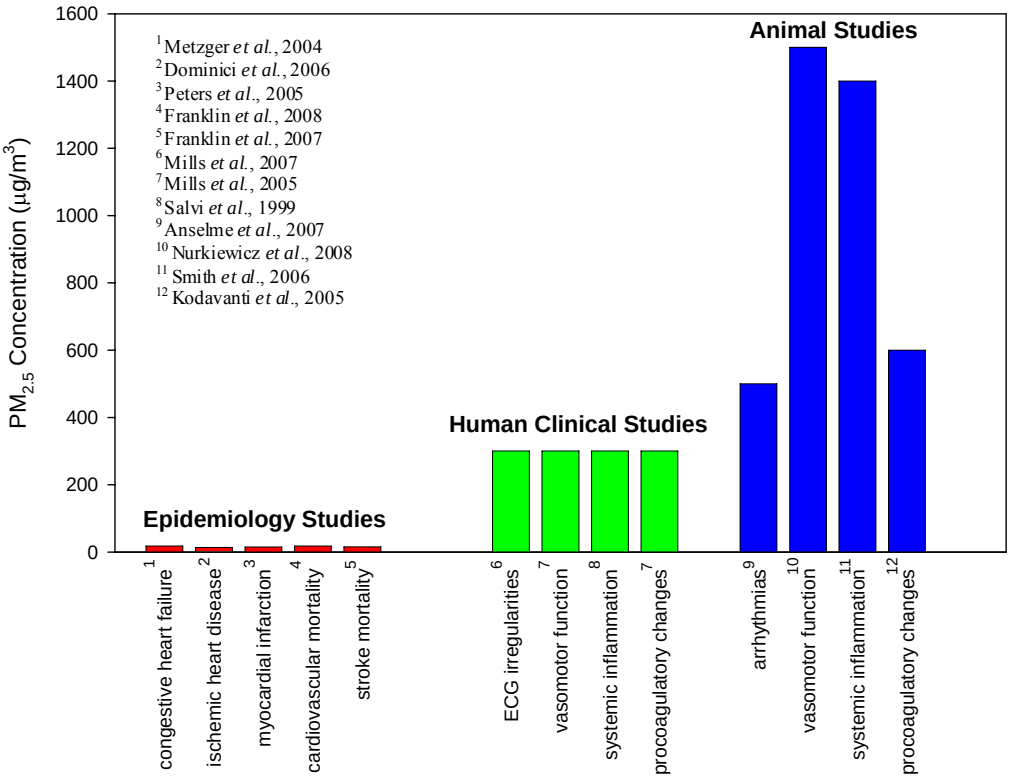

Figure 1. Representative Studies of $PM_{2.5}$-associated Cardiovascular Effects by Study Type.

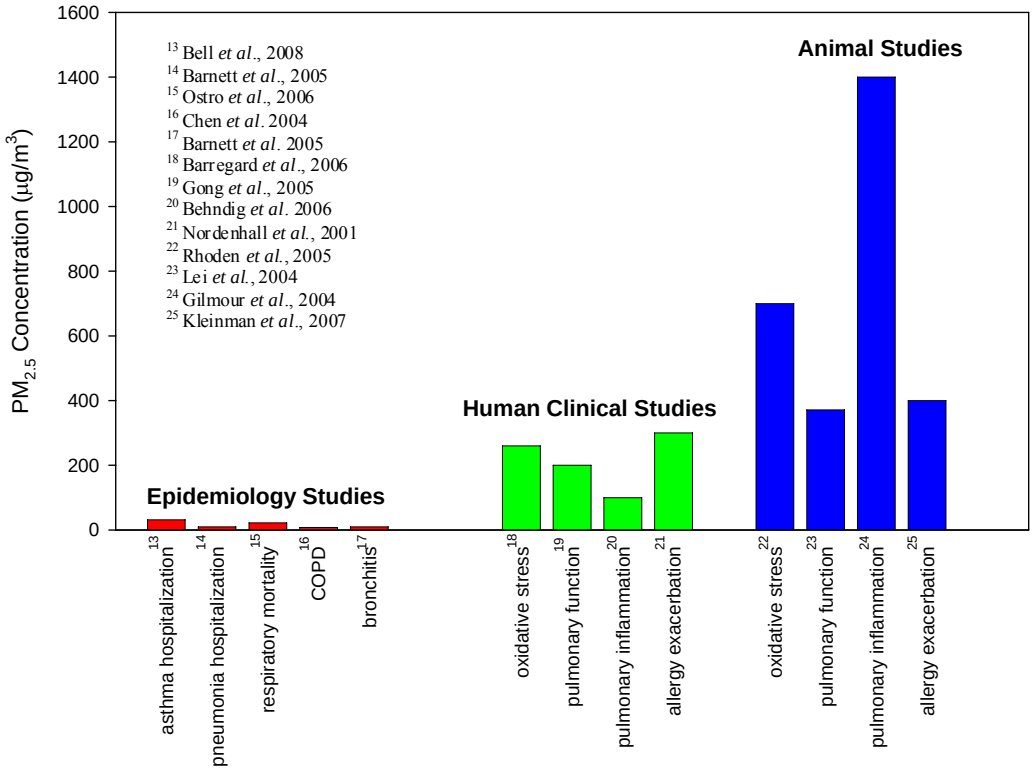

Figure 2. Representative Studies of $PM_{2.5}$-associated Respiratory Effects by Study Type.

There is also a large discrepancy in the degree of severity of the health effects linked with PM exposure in each type of study. While experimental studies use highly sensitive techniques to detect what are generally transient, clinically mild health responses, such as small changes in lung function or subtle irregularities in ECG parameters, epidemiological studies report associations between small day-to-day fluctuations in $PM_{2.5}$ levels and mortality and other serious health effects (*e.g.*, emergency department visits, hospitalizations). While it is certainly true that human clinical studies are generally limited to small groups of healthy volunteers who may not be representative of larger populations (note that members of diseased populations, including asthmatics, individuals with COPD, and patients with coronary heart disease, are increasingly being studied), can it be, as would be predicted by ambient PM epidemiological studies, that there are large numbers of people in the general population who are 10 to 1,000-fold more sensitive to PM than human volunteers?

Occupational epidemiology shows that worker populations in "dusty trades" who have been routinely exposed over long durations to high levels of airborne PM do not have significantly increased standardized mortality rates (SMR). For example, studies of worker health in the carbon-black, titanium-dioxide, and talc industries do not identify "premature mortality" and "high hospitalization levels" as health issues even with PM exposure levels that range up to and beyond 100-fold higher than ambient PM levels (see Dell *et al*., 2006; Fryzek *et al*., 2003). While it is true that worker populations generally show 10 to 20% lower disease statistics than the general population, can it be that human sensitivity to "generic PM" varies over such a dramatic range (*i.e.*, no adverse effect levels at occupational PM exposures in the hundreds of $\mu g/m^3$, yet lethal outcomes at tens of $\mu g/m^3$ of ambient PM)?

There are other possible explanations for the apparent discrepancies between the ambient-PM observational epidemiologic evidence and the experimental evidence for PM that support placing less weight on the epidemiologic evidence. As acknowledged in the Draft PM ISA, air pollution epidemiological studies are well-known to have a number of large uncertainties, including potential confounders, measurement error, exposure misclassification, and model uncertainty. For example, mortality and morbidity can be statistically correlated not only with PM, but also with the other criteria air pollutants (*e.g.*, carbon monoxide, ozone, nitrogen dioxide, and sulfur dioxide), as well as with non-criteria pollutants (see Krewski *et al*., 2000; Stieb *et al*., 2002; Hagen *et al*., 2000; Oftedal *et al*., 2003). In addition to potential confounding by ambient co-pollutants (including both criteria and non-criteria air pollutants), the effects of residual confounding cannot be ruled out for PM epidemiologic associations, particularly given that relative risks (RRs) are generally within a few percent of 1.0 (see Boffetta *et al*., 2008; Fewell *et al*., 2007). For example, a number of studies (*e.g.*, von Klot *et al*., 2008; Babisch *et al*., 2005; Phillips *et al*., 2001) have identified important non-pollutant factors (*e.g.*, stress and activity patterns, noise) that have a strong effect on day-to-day variations in mortality, but generally remain uncontrolled in PM epidemiological studies, despite their potential role as confounders of PM associations. Furthermore, while air pollution epidemiologic studies typically attempt to address potential confounding from meteorological parameters, recent studies have shown the difficulties in removing the potential effects of even these "controlled" variables from the air pollution associations (*e.g.*, HEI, 2003; Keatinge *et al*., 2006).

Until alternative explanations for the PM associations have been critically examined and ruled out, the ambient-PM epidemiology should not be given greater weight than the other lines of health effects evidence, as is done by US EPA in the Draft PM ISA. Additional support for this approach can be found in the considerable number of inconsistent, mixed, and unexplained, contrary findings that remain in the ambient-PM epidemiology. For example, analyses reported for the American Cancer Society (ACS) prospective cohort study have yielded a number of results that undermine making a causal interpretation for the PM associations, including the Pope *et al*. (2002) findings indicating immunity from PM-associated mortality with increasing educational level and the Pope *et al*. (2004) finding indicating a statistically significant protective effect of long-term $PM_{2.5}$ exposures on diseases of the respiratory system. In addition, recent, large multi-city epidemiological studies have observed substantial geographical and seasonal heterogeneity that remains largely unexplained- *e.g.*, the findings from the Bell *et al*. (2008) analyses of the Medicare Air Pollution Study (MCAPs) data indicating the greatest $PM_{2.5}$ effects for cardiovascular disease hospitalizations in the winter *vs*. findings from other multicity studies of $PM_{2.5}$ or PM_{10} that have reported larger effect estimates for seasons other than winter (*e.g.*, summer in Peng *et al*., 2005; spring and summer in Franklin *et al*., 2007). Furthermore, some epidemiology studies (*e.g.*, Moolgavkar *et al*., 2003; Abramahowicz *et al*., 2003) report PM "effect factors" that are larger at lower concentration levels than at higher levels, which goes contrary to the fundamental toxicological principle, "the dose makes the poison."

In summary, there remain large uncertainties and limitations in the ambient PM epidemiology, in particular regarding the causal linkage between PM constituents or sources and health outcomes, which have not been substantially reduced since the last PM NAAQS review. Before a causal interpretation for PM effects can be relied upon, careful and critical work must be done on evaluating, and ruling out, if appropriate, alternative pathways of causation. Importantly, the toxicologic basis for the epidemiologic associations at low ambient concentrations remains hypothetical and unproven. Human clinical studies and laboratory animal studies- *i.e.*, the lines of evidence which epidemiology requires for support- fail to corroborate, for example, the idea that ambient PM concentrations can lead to hospitalization or death. **For more detailed analysis of the discrepancies among the various lines of health effects evidence cited in the Draft PM ISA, please see our written comments submitted to EPA Docket No. EPA-HQ-ORD-2007-0517 as an attachment to comments by UARG. Based on our analysis, we conclude that there remain clear discrepancies between the different lines of health evidence that must either be resolved prior to making causal determinations or be factored in as a large uncertainty in the determinations.**

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