Human Clinical Studies with Diesel Exhaust Particulate: Implications for the Potential Human Health Hazards of Nanoparticles

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Introduction

In recent years, numerous in vitro and in vivo toxicity studies have provided evidence of the biological activity of various types of nanoparticles albeit at high doses and typically for unrealistic exposure scenarios. These studies have been interpreted as providing evidence that the novel properties, and particularly the small size and large surface area, of nanoparticles modulate their toxicity relative to micron-sized and larger bulk materials of the same composition. Although there are, at present, few human data addressing the potential health hazards posed by nanoparticles under realistic exposure scenarios, there is an abundance of human data for another source of nanoparticle (NP) exposure, notably for the NPs found in the context of exposure to diesel engine exhaust. Diesel nanoparticles, including individual nuclei mode particles and carbonaceous agglomerates, are well known to dominate particle number concentrations in diesel exhaust particulate (DEP). However, it is important to note that DE is a highly complex mixture that also contains fine- and coarse-mode particles as well as a variety of gaseous components of toxicological relevance (e.g., nitrogen oxides, carbon monoxide, aldehydes). Thus, DE human clinical studies do not address NPs in isolation, but the results can help provide an upper-bound limit on possible NP toxic effects. We propose that DEP NPs have utility as a tool for investigating the fundamental question of whether nano-sized particles necessarily have enhanced toxicity to humans due to their small size, as has been widely hypothesized. We thus examined the existing database of human clinical studies of whole diesel exhaust (DE) to identify insights relevant to potential NP human health hazards.

Background on nanoparticle emissions from diesel engines

On a number- concentration basis, DEP is predominantly composed of nano-sized particles in the 5 to 50 nm range and contribute more than 90% of the total particle number in diesel exhaust (see Slide 6). In contrast, DEP mass concentration is generally dominated by accumulation-mode particles in the 0.1 to 0.3 μm range, with DEP NP contributing only between 1% to 20% of total particle mass. DEP nanoparticles consist of a mixture of agglomerated solid carbonaceous and ash particles including volatile organic and sulfur compounds. DE nuclei mode particles have typical sizes of 5 to 20 nm, consisting mainly of volatile materials, plus soluble organic material and sulfates, and lesser amounts of solid carbon and metal compounds. A substantial portion of DE accumulation mode particles consist largely of agglomerated solid carbonaceous material (i.e., soot) and adsorbed hydrocarbons, sulfuric acid, and water, with subunits having diameters in the nano-region. DEP is generally found in the form of complex chains and agglomerates, consisting of tens to thousands of carbon-centered primary particles, with typical mean diameters in the range of 60 to 100 nm (see Slide 5).

Characterization of DEP nanoparticle exposures during human volunteer whole DE studies

Human clinical studies of whole DE have typically exposed human volunteers to highly elevated concentrations of DEP mass, DEP NPs, and DE gaseous constituents. Typical DEP mass concentrations have ranged from 100 to 300 μg/m3, which are one to two orders of magnitude higher than either short-term or long-term average, ambient DEP exposure levels (see Slides 7 and 8). The levels of gaseous DE constituents measured in these studies are in general substantially higher than for ambient, "cleanair" exposures, exceeding clean-air levels by as much as 110 times. The highest levels of gaseous DE constituents, including mean NO2 and formaldehyde concentrations exceeded 50% of their respective occupational Threshold Limit Values (TLVs). The co-occurrence of elevated exposure levels to DEP plus gaseous DE constituents contributes to remaining uncertainties regarding whether the effects observed in the human clinical studies of whole DE can be interpreted as attributable to DEP, or instead to one or more gaseous components.

The use of elevated exposure concentrations of DEP NPs in DE human clinical studies increases the likelihood that NP-induced toxicity would be observed, even acknowledging the potential role of the gaseous and DEP mass fractions in the observed health responses. Many of the DE human clinical studies have measured total number concentrations in the DE exposure chambers, and total number concentration is assumed to be a good surrogate for NP number concentration, given that DEP numbers are dominated by nano-sized particles. Where measured number concentrations were not provided, we estimated the ratio of particle number to mass using measured DEP mass and number concentration data from other studies of the same engine.

The average particle number concentrations measured in the DE exposure chambers are higher than those reported in several of the limited number of studies that have measured potential workplace exposure levels to ENPs under simulated production and handling scenarios (see Slide 9). The ENP workplaces or laboratories exposure data are more representative of worst-case exposure conditions in ENP manufacturing and handling environments than typical exposure conditions, because measurements were generally made directly at the source, with little or no containment or other engineering controls. In addition the NP exposure levels used in the DE human clinical studies were far above the average particle number concentrations for roadways and occupational environments (e.g., parking garages, bus depots, and bus service garages).

Health effects findings from DE human clinical studies and their implications for potential NP toxicity

A number of recent human clinical studies have investigated the acute health effects of elevated, short-term exposures to whole DE, focusing on lung and systemic inflammatory responses as well as cardiovascular health responses. Overall, these studies, for DEP nanoparticle concentrations that are considerably higher than both ambient DEP nanoparticle and ENP exposures expected for either the general population or worker populations, provide evidence of mild, transient pulmonary responses that are not likely of health adversity in healthy individuals or asthmatics (see Slides 10-12). There is some mixed evidence of subclinical effects on cardiovascular health endpoints from whole DE exposure, with most positive findings coming from the Swedish studies of highly elevated DE exposures (see Slide 13).

Conclusions

Because diesel exhaust (DE) has been the subject of a number of human clinical studies, and because nanoparticles are known to be a major constituent of DEP, we suggest that the DE human clinical data may offer insights into the potential health hazards of other nanoparticles, including ENPs.

Prior to discussing key insights, it is important to highlight again several caveats to relying on the available DE human clinical data for extrapolation to the potential human health hazards of short-term ENP exposures. First, whole DE exposures employed in the human clinical studies have typically involved elevated exposures to not only DEP nanoparticles, but also to larger DEP fine particles (as reflected in the typical DEP mass concentrations of 100 to 300 μg/m3), as well as to an assortment of DE gases, including CO, NO2, NO, and a number of volatile organic compounds (VOCs). Insofar as observed effects from the human clinical studies of whole DE exposures are due to DE constituents other than DEP NPs, these findings may thus provide an upper-bound representation of the potential toxicity of DEP NPs from the tested engine emissions. Moreover, various other NPs may have unique properties that will differ from those of DEP NPs and that may modify their toxicity. Overall, these limitations and uncertainties have implications for the relevance of the DE human clinical data to the potential health hazards posed by either DEP nanoparticles specifically, or other nanoparticles more broadly. Keeping in mind these important caveats, we have identified several key insights from our analysis, including:

1. The DE human clinical studies have not consistently shown acute adverse effects of a serious nature for DEP nanoparticle concentrations that likely well exceed ENP levels in workplaces that adhere to well-established occupational hygiene practices.

2. Generally, these studies provide some evidence that elevated short-term DE exposures may elicit transient, subclinical health responses that include lung and systemic inflammation, thrombogenesis, vascular function, and brain electrical activity.

3. Importantly, similar responses have also been associated with exposures to a variety of other fine and coarse particle types.

4. Overall, these DE human clinical data do not give evidence of a unique toxicity for NPs as compared to other small particles.

These data provide evidence suggesting that not all nano-sized particles are likely to be of high acute toxicity as a result of their small size. In other words, the DE human clinical data do not provide support for any unique toxicities of nano-sized particles compared to other small particles, as might arise from their nano-size per se.

Reference

Thomas W. Hesterberg, Christopher M. Long, Charles A. Lapin, Ali K. Hamade, and Peter A. Valberg. Diesel exhaust particulate (DEP) and nanoparticle exposures: What do DEP human clinical studies tell us about potential human health hazards of nanoparticles? *Inhalation Toxicology*, 2010; 22(8): 679–694.

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Introduction

- We are at the early stages of assessing human health hazards and risks of nanoparticles
- Animal and in vitro studies of nanoparticles have substantial uncertainties and may not be relevant to human health
- Diesel exhaust (DE) has been the subject of many human clinical studies
- Nanoparticles are a major constituent of DE particulate
- DE human clinical data may offer insights for potential health hazards of other nanoparticles

Approach

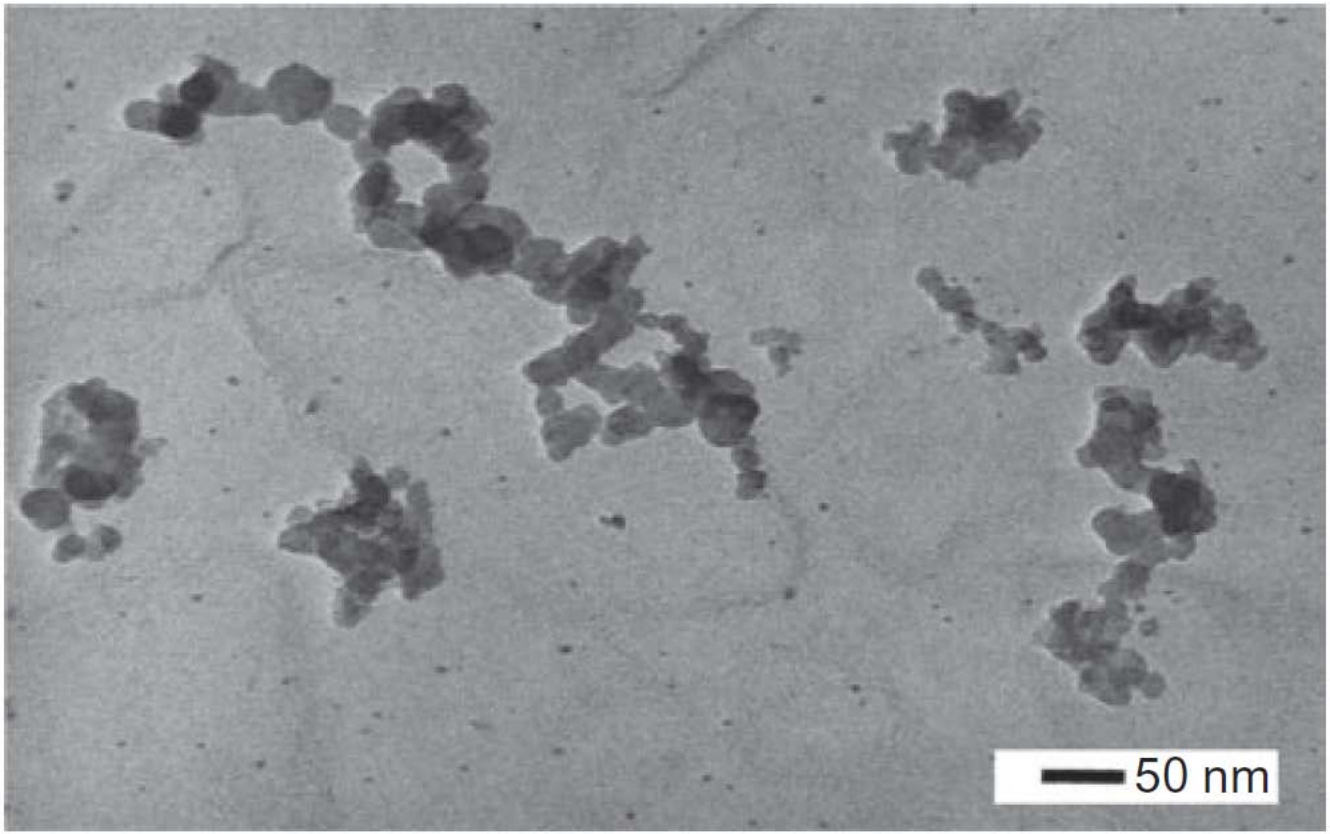
- Reviewed 30 human volunteer studies
- Studies used exposure chambers
  - Allows control and precise measurement of exposure conditions
- Exposed to freshly generated whole diesel exhaust
- Studies performed in UK, Sweden, and USA
- Old technology diesel engines
  - High sulfur fuel
  - No exhaust after treatment which has been required since 2007

(Reference: Hesterberg et al. Inhalation Toxicology 22(8):679-694, 2010)

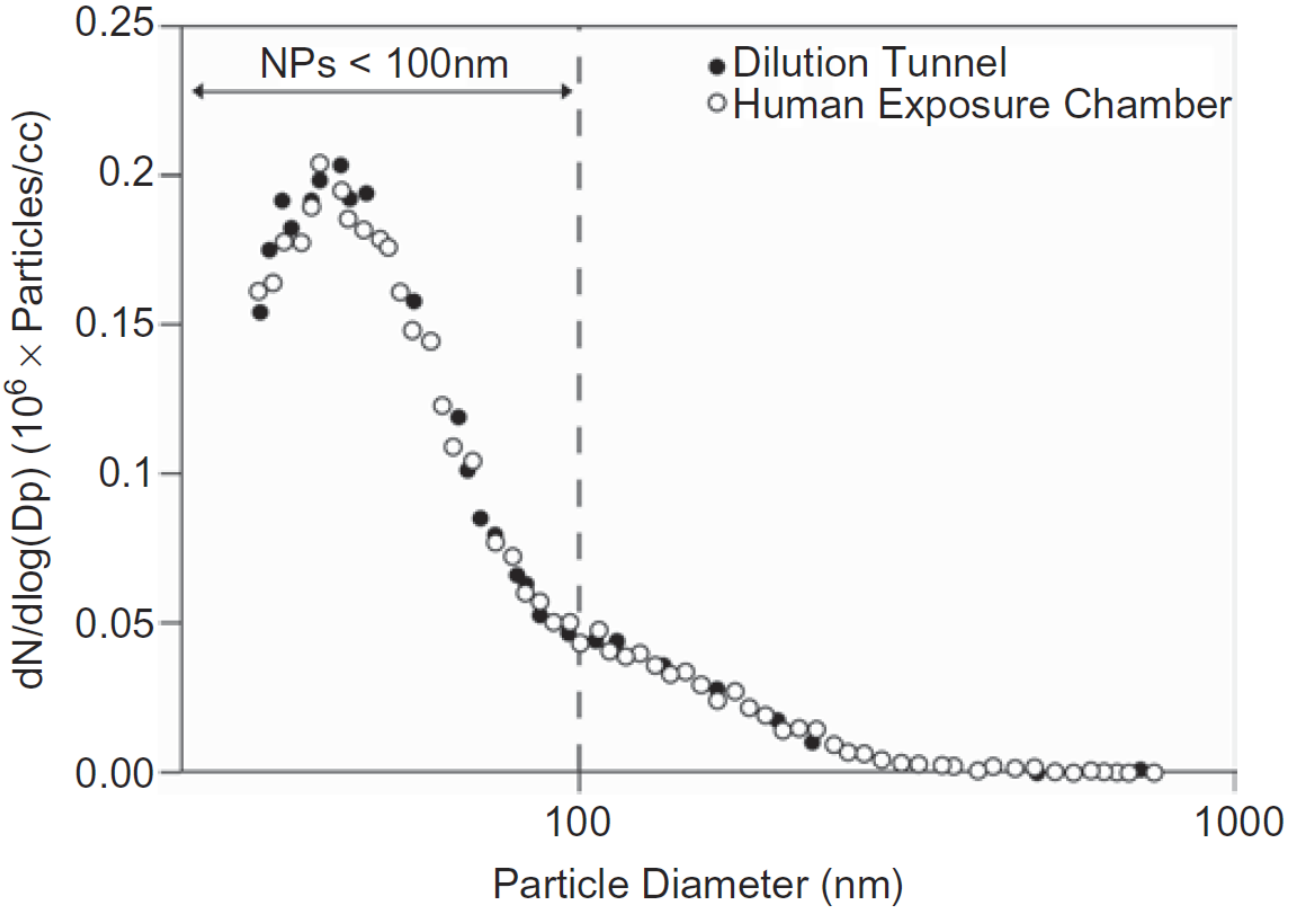
Some Caveats

- Whole diesel exhaust (DE) exposure also contains:
  - Larger-sized particles in the fine range
  - Gases: carbon monoxide, nitrogen dioxide, nitric acid, carbon dioxide
  - Volatile organic compounds
- Other nanoparticles have properties that may be different from diesel nanoparticles which may affect their toxicity
- DE particles may be less toxic than some nanoparticles, but this may be offset by the high exposure levels used in DE clinical studies

Diesel Particulate

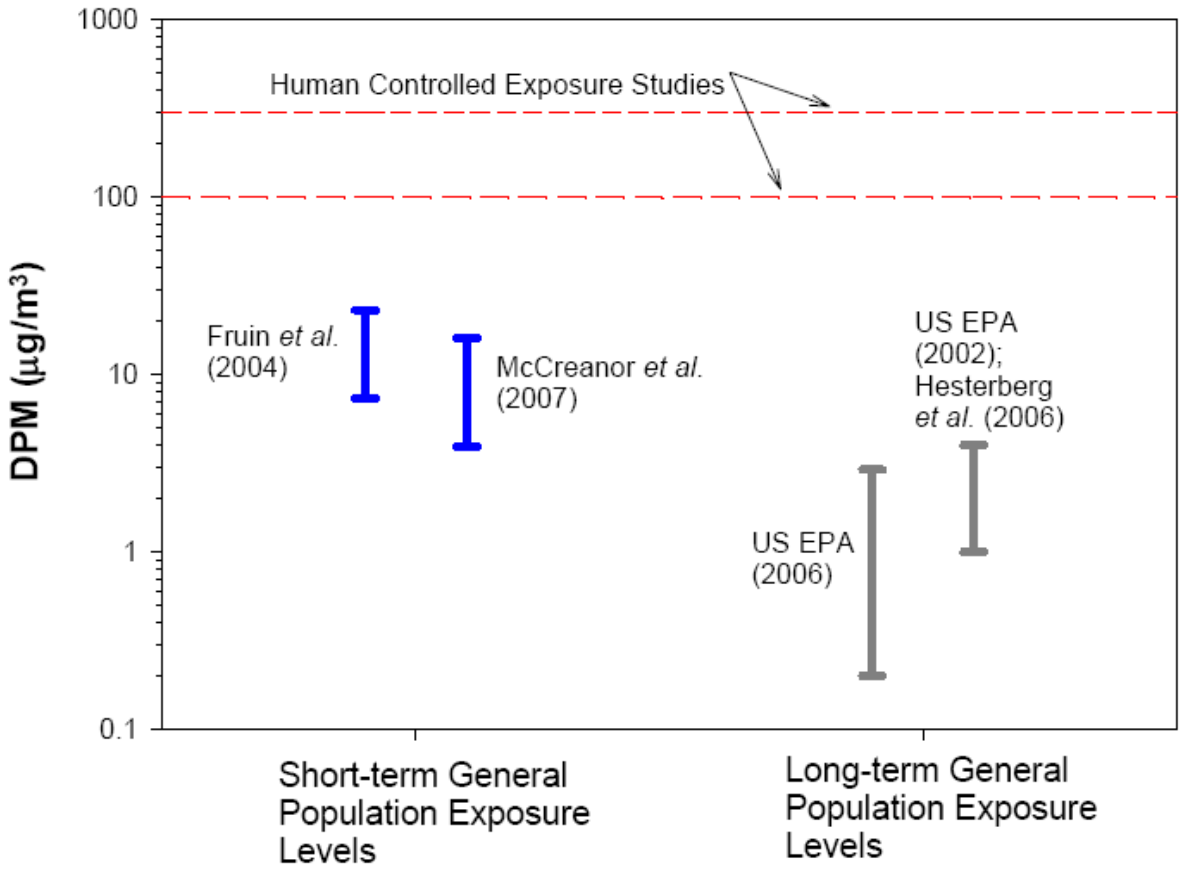


Diesel Particle Size Distribution

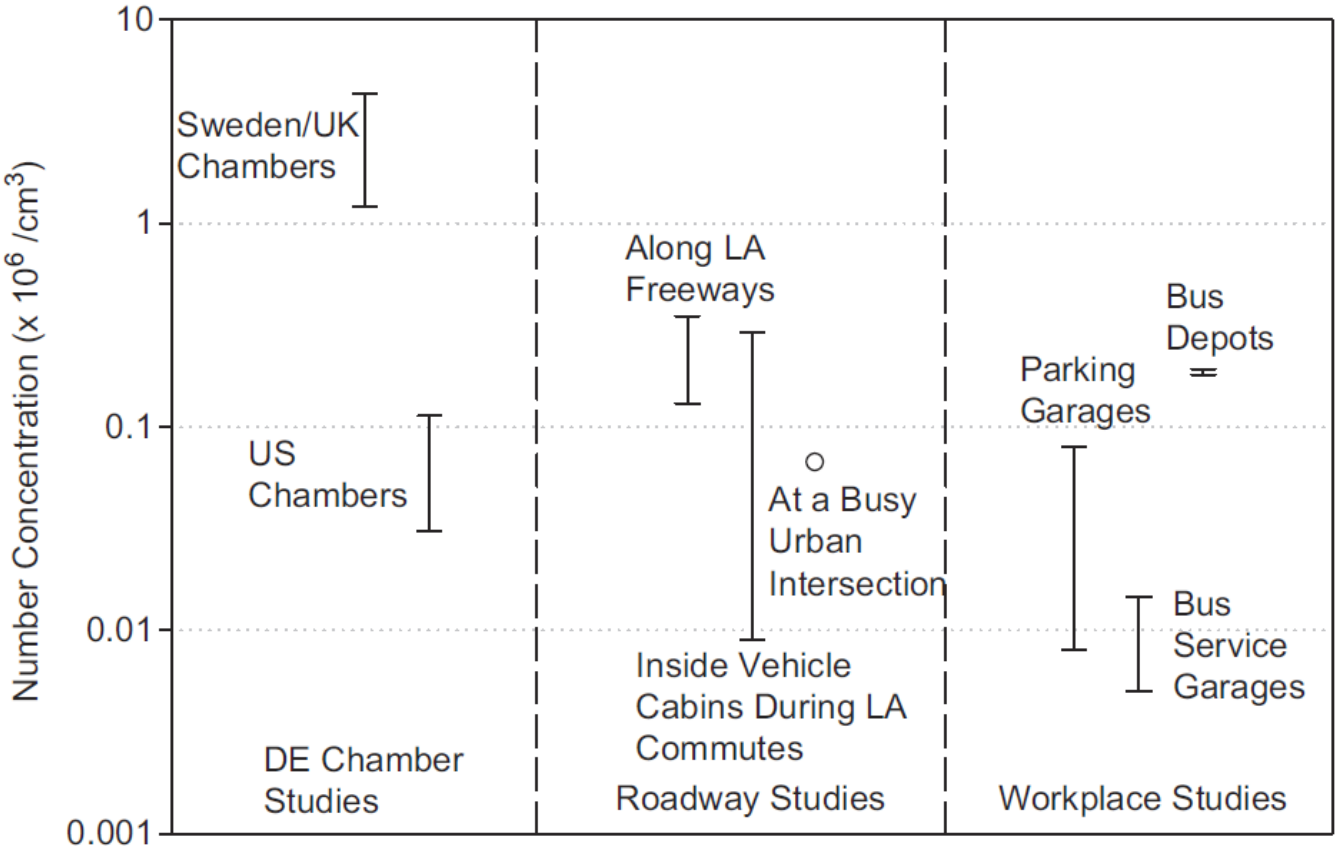


Controlled and Ambient Exposure to Diesel Particulate Matter

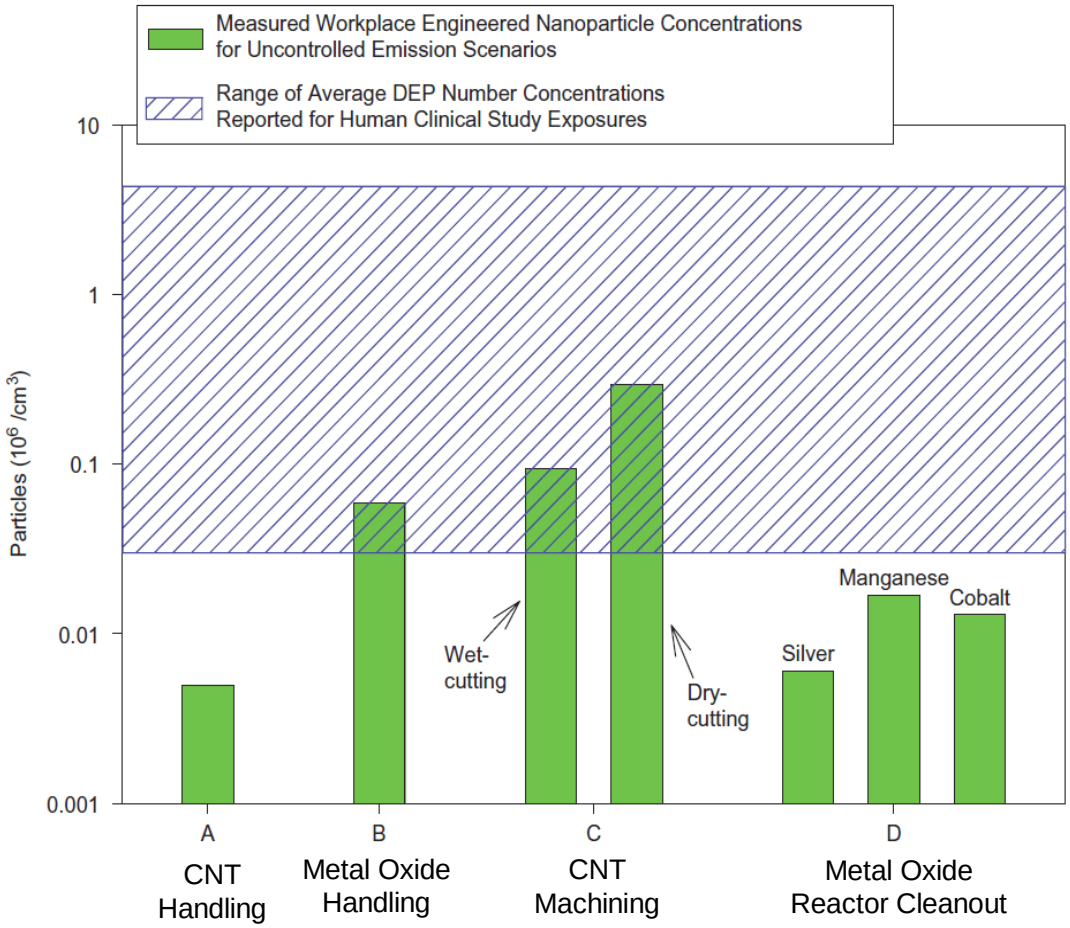
Controlled diesel exposures 5 to 10 times higher than ambient exposures



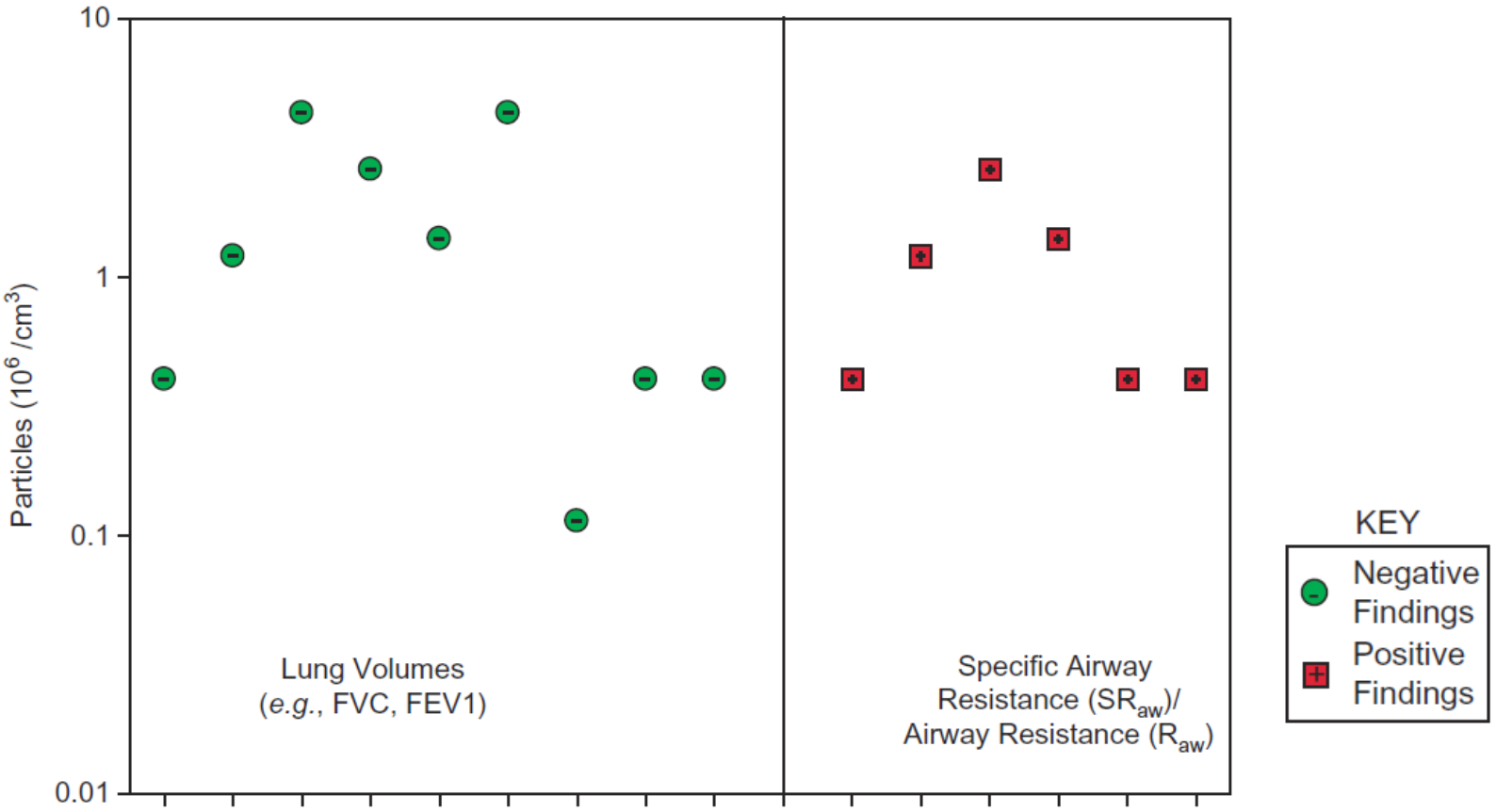
Controlled and Ambient Exposure to Diesel Particles



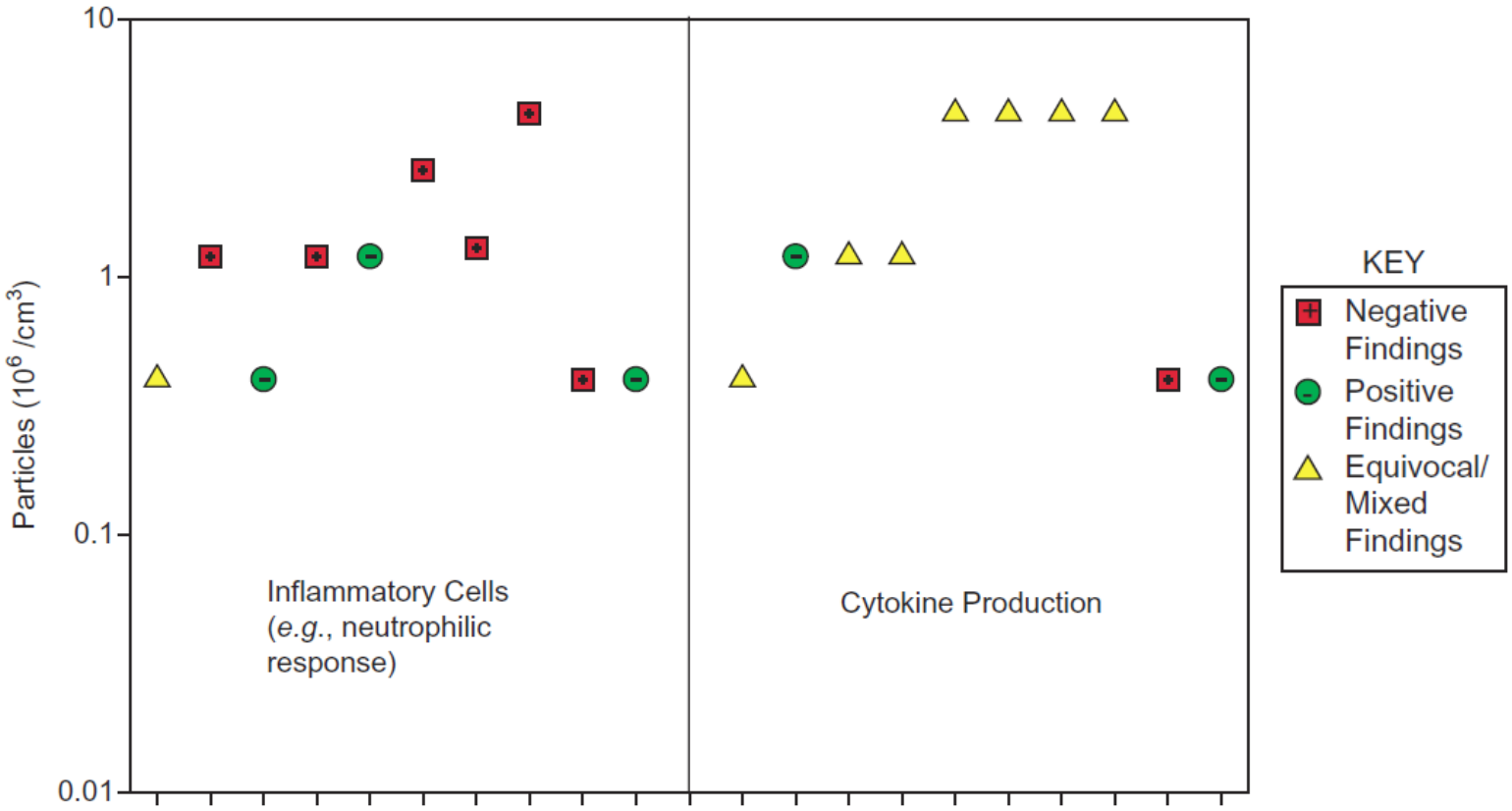
Exposure Comparisons: Workplace Nanoparticles vs. DE Studies



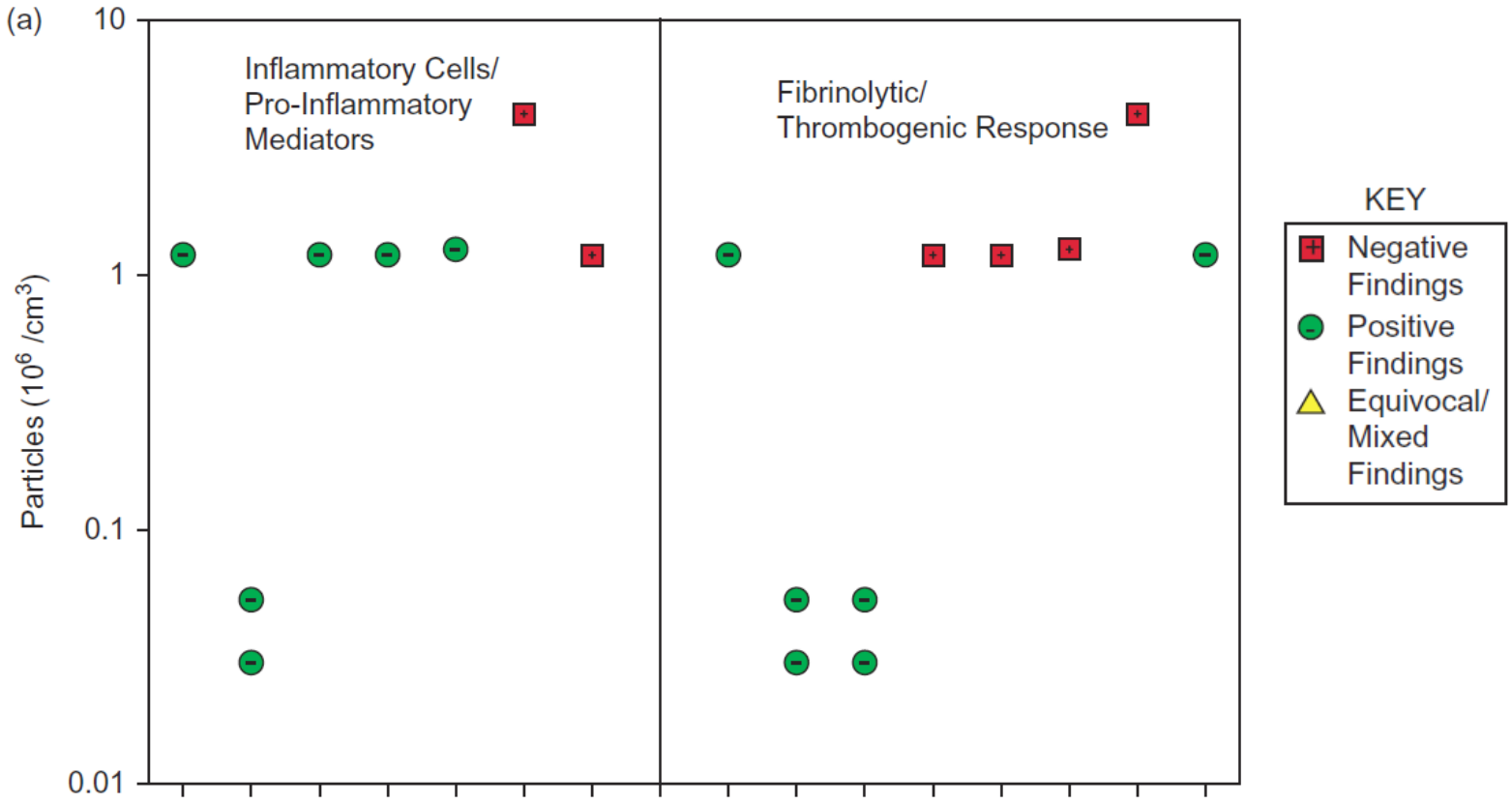
Lung Function



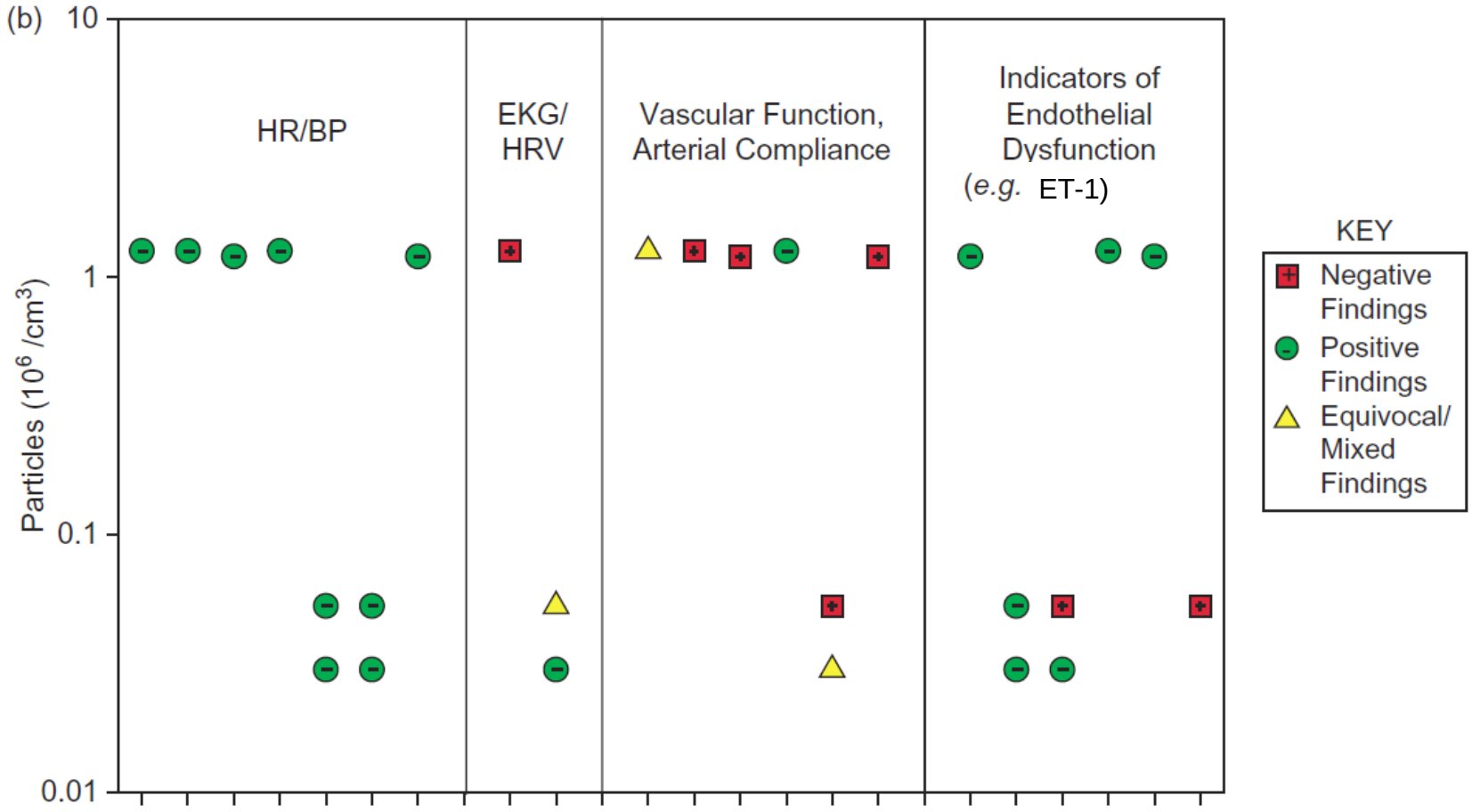
Lung Inflammation



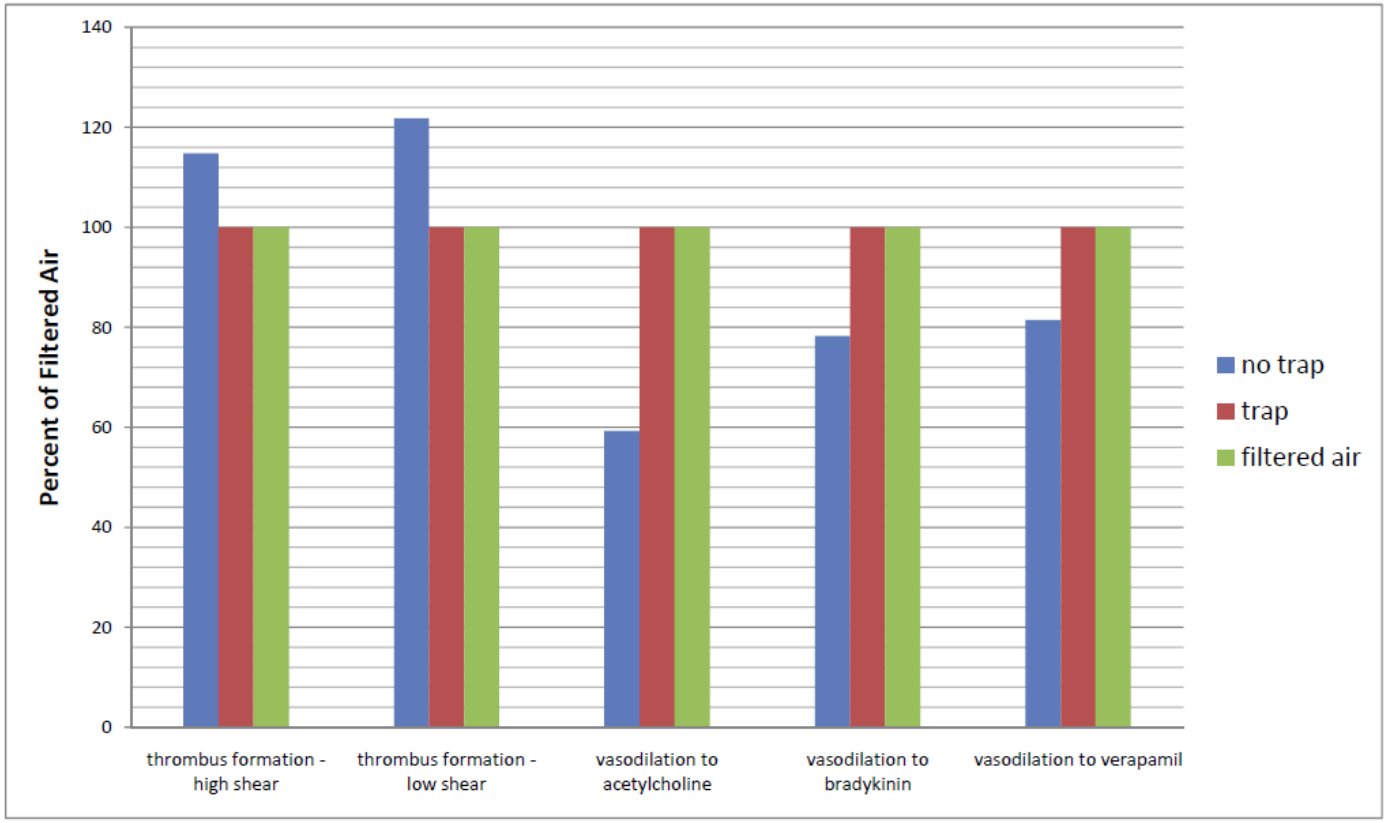
Lung Inflammation and Blood Clotting



Cardiovascular System



Particulate Traps Eliminate DE Effects



(chart developed from data presented in Barath, et al. 2009; Lundback, et al. 2009; Mills, et al. 2009)

Conclusions

- Elevated DE exposure may elicit transient, subclinical health responses including:
  - Lung and systemic inflammation
  - Changes in blood clotting and vascular function
  - Changes in brain electrical activity (EEG)—discussed in publication
- Effects often not seen at lower exposure levels
- Effects are eliminated with particulate traps
- Responses similar to those observed with larger particles
- These studies do not provide evidence of a unique toxicity for nanoparticles compared to other particles