Oxidant generation by particulate matter: from biologically effective dose to a promising, novel metric

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The classic toxicology paradigm between exposure and response provides the justification for accurate measurement of exposure to underpin good epidemiological studies aimed at relating an environmental exposure to an adverse effect. The closer the exposure metric approaches the dose, the more accurate the response function. Toxicologists identify the true harmful entity in the dose as the biologically effective dose (BED)—the entity that drives the adverse effects. Measuring exposure is, however, notoriously difficult, and the relationship between a mass measure (the current convention for assessing environmental exposures) and the BED has not always been clear. In the past decade, the mass of particulate matter measured as PM10 or PM2.5 has proved useful in demonstrating associations between ambient particle levels and a wide range of health outcomes, including mortality and morbidity, among patients with cardiovascular and/or respiratory diseases.^{1,2} In the context of both toxicological and epidemiological research, it is well accepted that the PM10 mass is not ideal but represents a surrogate for the BED. This is self-evident from the fact that much of the PM10 mass consists of low-toxicity components such as ammonium sulphates and nitrates, sea salt (sodium chloride), crustal dust and road dust. By contrast, relatively tiny masses of transition metals and organic species may redox cycle and make a major contribution to the BED.^{3,4} So, although our current and future particulate matter standards are set on mass, we know that it is at best only a rough indicator of the BED, as most of the mass is actually biologically inactive. In fact, studies have shown that the particle number, which is not necessarily related to mass, can be a better descriptor of some health effects.^{5,6} This can be explained by the fact that combustion-derived nanoparticles, the dominant particle type by number in urban air, represents a key component of the particulate matter mix because they contain a

large surface area, transition metals and organics.^{4,7,8} Experimental studies have shown that these three components have a role in the pro-inflammatory effects of particulate matter and model particles in animal and in vitro models.⁴ A common mechanism linking these parameters is their ability to generate oxidative stress in lung cells both by direct generation of reactive oxygen species (ROS) and indirectly through the induction of inflammatory responses in the lung. In fact, ROS production has been suggested as a unifying factor in the biological activity of pathogenic particles^{3,9} and ambient air pollutants in general.¹⁰ It has also been suggested to be the primary mechanism of lung injury caused by PM10 and its components, and a number of research groups have set out to measure ROS production by particulate matter sampled from ambient air and link this to biological effects in vivo and in vitro.^{4,11–15}

One of the first methods used to detect the radical-generating capacity of particles used supercoiled plasmid DNA, which unwinds on nicking by radical damage.¹⁶ Other approaches have used particle-induced depletion of antioxidants to measure the oxidative potential of particles.^{17,18} A method developed by Borm *et al* recovers particulate matter from filters by sonication in water, addition of hydrogen peroxide to the resulting suspensions to produce reducing conditions similar to those that pertain in the lungs and detection of very reactive OH radicals by a specific spin-trap and electron paramagnetic resonance.¹⁹ Although this system is highly artificial, it was recently shown that this method of measuring OH generation is strongly correlated with the depletion of antioxidants such as ascorbate and GSH in a reducing environment,²⁰ and with the induction of oxidative DNA damage in lung epithelial cells in vitro.²¹ Others have used filters as a whole²² or have led sampled air through impingers¹⁸ to detect stable quinones,²² thereby suggesting that these chemicals can catalyse redox cycling in the lung environment.

The (indirect) measurement of oxygen radical generation as the BED of particulate matter has features that make it highly advantageous, as it integrates a number of aspects, including (i) redox activity of bound and soluble transition metals, (ii) the bioavailability of these metals for reaction, (iii) interactions between different metals in the reaction, (iv) redox cycling by complex organic contaminants and (v) oxidative stress delivered by surfaces.

Oxidant activity of particulate matter, measured as described above, was also shown to be relevant in field studies²⁰ where oxidant generation by 716 samples of PM2.5, sampled over a 2-year period in 20 European cities, was measured. There were low correlations between their redox activity and all other characteristics, both within centres (temporal correlation) and across communities (annual mean). Thus, mass measurements do not capture redox activity well. This is also underscored by a volunteer study in which 12 normal individuals were instilled with 100 µg of PM2.5 from either a polluted or a non-polluted city in two different bronchial segments.²³ Although all samples were delivered at equal mass, the oxidant activity of the samples was different, and pulmonary inflammatory response reflected this difference.²³ However, in similar work with coarse particulate matter samples in rats, the inflammatory response did not parallel the oxidant activity.²⁴

In conclusion, oxidant activity has been shown to be a property of particulate matter and its components that reflect crucial biological mechanisms. So far, it has been used largely for detecting activity in limited samples of particulate matter and other pathogenic dusts, and for understanding mechanisms. We advocate that open methodological questions such as the sampling of particles to measure redox activity and spatial variation of particulate matter redox activity be considered in future research. We may build on the few studies that have used it in epidemiological studies linking oxidative activity of particulate matter to health end points and expand this to larger population studies, with a view towards its adoption as a standard exposure metric. We hope that this discussion paper will prompt research into the development of instrumentation leading to rapid-working sensors of the oxidative activity of airborne dust particles, which would prove useful in occupational and environmental settings. We do not believe that this measure should replace the PM10 or PM2.5 metrics at present but we do believe that a complementary metric that more closely approaches the

BED should have intriguing scientific merit in testing the "oxidative stress hypothesis" more specifically, both in the total population as well as in subgroups particularly susceptible to oxidative stress.¹⁰

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REFERENCES

- Brunekreef B**, Holgate ST. Air pollution and health. *Lancet* 2002;**360**:1233–42.
- Pope CA III**, Dockery DW. Epidemiology of particle effects. In: Holgate ST, Samet JM, Koren HS, Maynard RL, eds. *Air pollution and health*. London: Academic Press, 1999:673–705.
- Kelly FJ**. Oxidative stress: its role in air pollution and adverse health effects. *Occup Environ Med* 2003;**60**:612–16.
- Donaldson K**, Tran L, Jimenez L, et al. Combustion-derived nanoparticles: a review of their toxicology following inhalation exposure 1. *Part Fibre Toxicol* 2005;**2**:10.
- Peters A**, Wichmann HE, Tuch T, et al. Respiratory effects are associated with the number of ultrafine particles. *Am J Respir Crit Care Med* 1997;**155**:1376–83.
- Pekkanen J**, Timonen KL, Ruuskanen J, et al. Effects of ultrafine and fine particles in urban air on peak expiratory flow among children with asthmatic symptoms. *Environ Res* 1997;**74**:24–33.
- Donaldson K**, Stone V, Borm PJ, et al. Oxidative stress and calcium signaling in the adverse effects of environmental particles (PM₁₀). *Free Radic Biol Med* 2003;**34**:1369–82.
- Donaldson K**, Jimenez LA, Rahman I, et al. Respiratory health effects of ambient air pollution particles: role of reactive species. In: Vallyathan V, Shi X, Castranova V, eds. *Oxygen/nitrogen radicals: lung injury and disease*. New York: Marcel Dekker, 2004.
- Donaldson K**, Beswick PH, Gilmour PS. Free radical activity associated with the surface of particles: a unifying factor in determining biological activity? *Toxicol Lett* 1996;**88**:293–8.
- Gilliland FD**, McConnell R, Peters J, et al. A theoretical basis for investigating ambient air pollution and children's respiratory health. *Environ Health Perspect* 1999;**107**:403–7.
- Nel A**, Xia T, Madler L, et al. Toxic potential of materials at the nanolevel 2. *Science* 2006;**311**:622–7.
- Aust AE**, Ball JC, Hu AA, et al. Particle characteristics responsible for effects on human lung epithelial cells. *Res Rep Health Eff Inst* 2002;**110**:1–65.
- Dye JA**, Adler KB, Richards JH, et al. Epithelial injury induced by exposure to residual oil fly-ash particles: role of reactive oxygen species? *Am J Respir Cell Mol Biol* 1997;**17**:625–33.
- Ghio AJ**. Biological effects of Utah Valley ambient air particles in humans: a review. *J Aerosol Med* 2004;**17**:157–64.
- Nel AE**, Diaz-Sanchez D, Li N. The role of particulate pollutants in pulmonary inflammation and asthma: evidence for the involvement of organic chemicals and oxidative stress. *Curr Opin Pulm Med* 2001;**7**:20–6.
- Gilmour PS**, Brown DM, Lindsay TG, et al. Adverse health-effects of PM₁₀ particles—involvement of iron in generation of hydroxyl radical. *Occup Environ Med* 1996;**53**:817–22.
- Zielinski H**, Mudway IS, Berube KA, et al. Modelling the interactions of particles with epithelial lining fluid antioxidants. *Am J Physiol* 1999;**277**:L719–26.
- Cho AK**, Sioutas C, Miguel AH, et al. Redox activity of airborne particulate matter at different sites in the Los Angeles Basin. *Environ Res* 2005;**99**:40–7.
- Shi T**, Schins RP, Knaapen AM, et al. Hydroxyl radical generation by electron paramagnetic resonance as a new method to monitor ambient particulate matter composition. *J Environ Monit* 2003;**5**:550–6.
- Kunzli N**, Mudway IS, Gotschi T, et al. Comparison of oxidative properties, light absorbance, total and elemental mass concentration of ambient PM_{2.5} collected at 20 European sites. *Environ Health Perspect* 2006;**114**:684–90.
- Shi T**, Duffin R, Borm PJ, et al. Hydroxyl-radical-dependent DNA damage by ambient particulate matter from contrasting sampling locations. *Environ Res* 2006;**101**:18–24.
- Squadrito GL**, Cueto R, Dellinger B, et al. Quinoid redox cycling as a mechanism for sustained free radical generation by inhaled airborne particulate matter. *Free Radic Biol Med* 2001;**31**:1132–8.
- Schaumann F**, Borm PJ, Heinrich A, et al. Metal-rich ambient particles (particulate matter 2.5) cause airway inflammation in healthy subjects. *Am J Respir Crit Care Med* 2004;**170**:898–903.
- Schins RP**, Lightbody JH, Borm PJ, et al. Inflammatory effects of coarse and fine particulate matter in relation to chemical and biological constituents. *Toxicol Appl Pharmacol* 2004;**195**:1–11.