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**Differentiation between Sources of Particle-induced Oxidative Stress:  
Surface Area versus Organic Compounds**

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At present it is commonly hypothesised that the surface toxicity of soot particles originates from adsorbed redox-active components, which cause oxidative stress responses by reactive oxygen species (ROS) that in turn may lead to pulmonary or even systemic inflammation.

In this study we address the question whether the inflammatory response of mice to particle exposure can be predicted by the *in vitro* assessed oxidative potential of these particles. To this end we assessed the oxidative potency of six types of carbonaceous NPs (10 to 50nm in diameter; combustion and spark-discharge generated particles; 1 to 20% OC content) by measuring the consumption of an indicator antioxidant, *ascorbic acid*, in a cell free, physiologically buffered system. There was a good linear correlation between the *in vitro* oxidative potency of the different particles and their specific surface area. Furthermore, comparison of the oxidative *in vitro* effect and the *in vivo* inflammatory response (PMN influx into the lung 24h after intratracheal particle instillation) revealed a good linear correlation for five out of the six NPs investigated here, i.e., particle surface area can be directly related to the *in vitro* and *in vivo* response. The only exception was the SootH sample (high-OC flame soot; OC = 19%), for which the *in vitro* test underestimated its *in vivo* toxicity by a factor of 3. Since this was not observed for the other high OC sample investigated here (diesel exhaust particles (DEP); OC = 20%), the OC content alone could not account for this discrepancy. Hypothesizing that bioavailability of OC plays an important role, we searched for specific genetic expression markers by qPCR and immunoblotting of mouse lung samples to identify those particle types with *bioavailable* toxic organics. Among all candidates of inducible phase I and II detoxication enzymes our expression analysis detected only the cytochrome P450 oxidase Cyp1A1 to be significantly induced by the OC rich particles, namely SootH and weaker by DEP. Since metabolic activation of aromatic hydrocarbons by Cyp1A1 is known to generate intracellular oxidative stress, this suggests that bioavailability of OC may contribute to the *in vivo* inflammatory response of NPs.

In summary, adequate prediction of *in vivo* particle toxicity based on *in vitro* tests requires an *in vitro* test for the oxidative potential related to particle surface area combined with a test for the bioavailability of particle adsorbed bioactive compounds, such as Cyp1A1 expression.