Endothelial response to oxidative stress: the link between particles and cardiovascular diseases?

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Recent research on ultrafine ambient air pollution particles and nanomaterials raised many questions about their (potential) biological responses. The basic principles established for particles seem to apply to all types of particulate materials whether nanoparticles or larger nanostructured entities (Figure 1). In the most simple case, (nano)materials overload the target organ: even completely inert materials can disturb the function of an organ if there are excessive quantities deposited. Second, particle can be the carrier of toxic substances. This applies again to all particles with the addition that nanoparticles were reported to easily transfer biological barriers implying that they can carry the toxic substances through membranes [1] into cells and, by translocation [2] to other organs even though only very small quantities do translocate. Thus, this opens the way to novel effects in cells or distant organs.

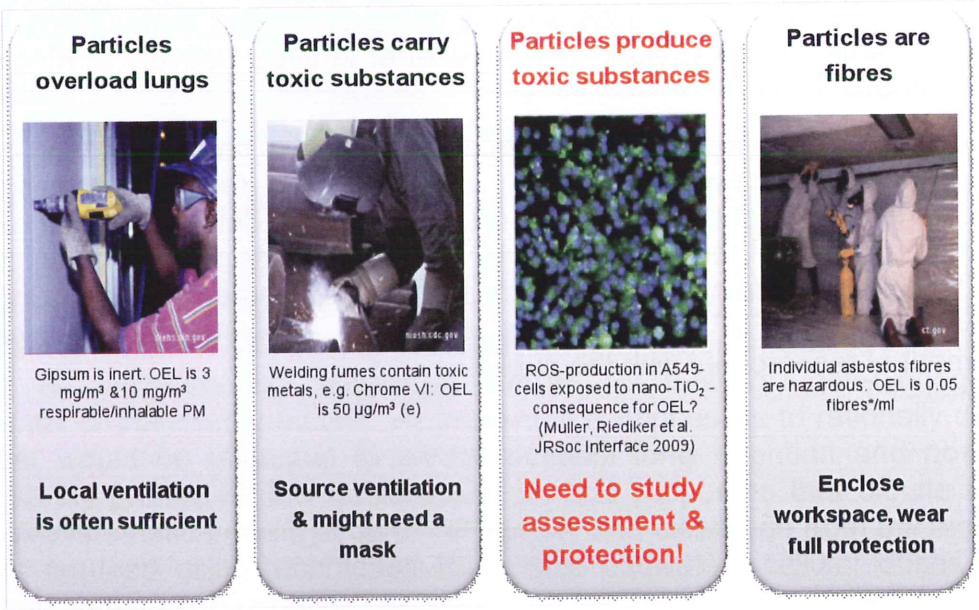

Figure 1: Established paradigms in particle toxicology. The paradigm that particles can produce toxic substances is relatively new. This is a lesson learnt mostly from ambient air pollution research. It is the topic of this presentation.

The morphology of material can play a critical role in the hazardousness of biopersistent materials, which is well known for asbestos fibres. Initial research suggests that multi-walled carbon nanotubes provoke a similar response as asbestos fibres provided they are sufficiently long [3].

The concept of toxic substances being produced by the particles (as opposed to a mere activation by metabolic processes) comes from epidemiological studies of airborne particulate matter. Ambient air pollution is associated to adverse health effects such as cancer, cardiovascular and pulmonary diseases [4]. The production of Reactive Oxygen Species (ROS) and the generation of oxidative stress is believed to be one of the key mechanisms. Oxidative stress is an imbalance between oxidants and antioxidants. In the presence of particulate matter, the natural antioxidant

defenses may be overwhelmed. A model [5] to explain how this is possible is shown in Figure 2.

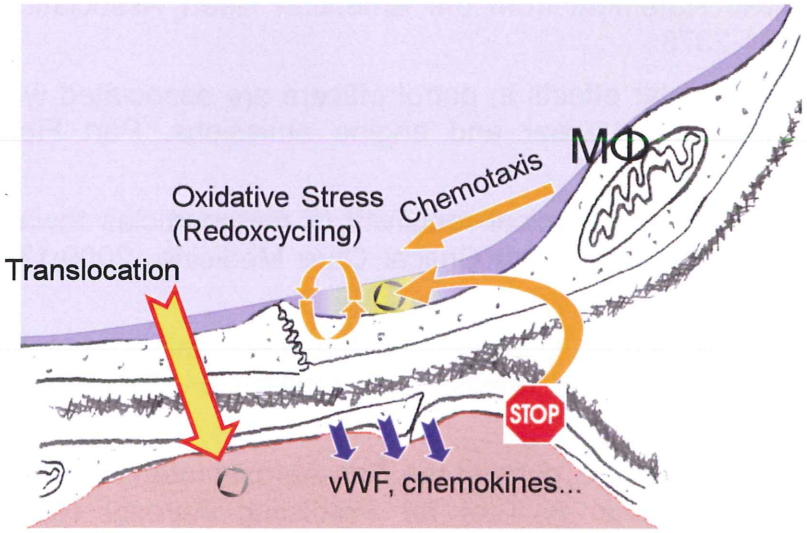

Figure 2: Proposed model how particles deposited on the lung surface generate oxidative stress that causes direct damage and initiates an endothelial cell response that is pro-thrombotic, pro-inflammatory and can release substances that can interfere with the cardiac rhythm.

It proposes that oxidative stress can build up quickly in the thin liquid layer of the alveolar region surrounding the deposition site of the particle by the production of ROS on the particle surface but also the adsorption of antioxidants on particles [6]. This is a site with a high oxygen concentration and antioxidants can quickly be overwhelmed. The presence of the ROS leads to epithelial cell damage and to the release of pro-thrombotic and pro-inflammatory mediators from the adjacent endothelial cells [5]. Some of these factors, such as endothelin can also influence the heart rate [7]. This stress also can lead to DNA-damage in the surrounding cells and subsequent DNA-repair [8]. Ambient air pollution particles and also nanoparticles are small and can easily reach all parts of the lungs. Consequently, the above-described cellular responses to oxidative stress can occur over large parts of the surface of the lungs, resulting in a response that is visible and relevant on a systemic level.

In conclusion, the existing paradigms of particle toxicology can be used to explain many of the toxic effects of particulate materials of all sizes. It is still so unclear what consequences can result from translocation of nanoparticles into cells and to novel target organs, to what extent one has to consider morphological effects of nanomaterials on large biological molecules such as DNA and proteins, and what potential interactions can occur with the immunological system. The answer to these questions will most likely require close multidisciplinary collaborations.

References:

1. Geiser M., et al., Ultrafine particles cross cellular membranes by nonphagocytic mechanisms in lungs and in cultured cells. Environ Health Perspect 2005, 113:1555-1560.
2. Kreyling W.G., et al., Translocation of ultrafine insoluble iridium particles from lung epithelium to extrapulmonary organs is size dependent but very low. J Toxicol Environ Health A 2002, 65:1513-1530.
3. Duffin R., et al., Proinflammogenic effects of low-toxicity and metal

nanoparticles in vivo and in vitro: highlighting the role of particle surface area and surface reactivity. Inhal Toxicol 2007, 19: 849-856.

4. Brook R.D., et al., Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. Circulation 2010, 121:2331-2378.
5. Riediker M., et al., Cardiovascular effects in patrol officers are associated with fine particulate matter from brake wear and engine emissions. Part Fibre Toxicol 2004, 1:2.
6. Sauvain J.J., et al., Differentiated chemical reactivity of nanoparticles toward DTT. American Journal of Respiratory and Critical Care Medicine, 2009:179, A5258
7. Isaka M., et al., Endothelin receptors, localized in sympathetic nerve terminals of the heart, modulate norepinephrine release and reperfusion arrhythmias. Basic Res Cardiol 2007, 102:154-162.
8. Setyan A., et al., Probing Functional Groups at the Gas-Aerosol Interface Using Heterogeneous Titration Reactions: A Tool for Predicting Aerosol Health Effects? Chemphyschem 2010.

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He leads several research projects in the field of particles and health. His focus is on micro- and nano-sized particles from traffic and industrial processes, the particle's intrinsic reactive oxidative stress potential and surface functional groups; and how these characteristics affect cardiovascular and pulmonary health. His group contributed already numerous articles to journals targeting researchers (peer-review) and occupational health experts ("grey" literature).

Michael Riediker chairs NanoImpactNet, which is a European Commission funded Network on the Health and Environmental Impact of Nanomaterials comprising over 900 researchers from 30 countries mostly from Europe but also from Asia, America and Africa, and which reaches out to over 1000 European stakeholders. He also chairs the Commission for Occupational Safety and Health Sciences of Suissepro (Swiss Association of Safety and Health Practitioner Organizations) and the WHO-network activity on occupational risks of nanomaterials (AA3). He is chapter-editor of the upcoming 5th edition of the ILO Encyclopaedia of Occupational Health (chapter nanotechnology); co-chair of the implementation committee for the GoodNanoGuide; member of the editorial board of two toxicological journals ("Nanotoxicology" and "Particle and Fibre Toxicology"), and editor of the European NanoSafetyCluster compendium. His is also member of several expert groups consulting the Swiss and French government and of several ISO working groups (TC229).

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