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**Multi-Centre Health Effect Studies on Inhaled Combustion Derived (nano)particles in Rats and Humans**

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Epidemiological studies have repeatedly linked short term as well as chronic exposure to particulate matter (PM) with shortening of life expectancy. It has also been shown that living near a freeway has adverse effects on lung development of otherwise healthy children, and this is directly linked to PM exposure. In addition, several in vivo studies suggest that emissions from highways result in inflammation of the lung and cardiovascular changes. Concern for potential adverse health effects of PM has prompted policy makers to try and elucidate the sources of emissions that are responsible for these observed adverse effects. Combustion generated (nano)particles, also known as ultrafine particulates, seem to play a major role in the development of adverse health effects. Diesel exhaust comprises a significant fraction of near road ambient PM and ultrafine particles are a substantial part of diesel soot. These ultrafine particles are of major concern because they will penetrate deep into the lung, are likely to escape normal defense mechanisms, and may enter the systemic circulation. In addition, nanoparticles may also be translocated to the brain through the olfactory nerve pathway. There is increasing scientific support for theories proposing a unifying model for effects of ambient PM, where oxidative and nitrosative stress may be a primary pathway leading to respiratory and systemic inflammatory responses.

We have performed several controlled inhalation studies with diesel exhaust in volunteers and experimental animals. Many different biological endpoints such as measures for oxidative stress, inflammation and tissue damage in the cardiopulmonary system have been included to determine whether or not PM can cause adverse health effects. This paper will summarize major outcomes of studies in rats. The PM treatments were as following: 1) subchronic exposure (4 week exposure to 150 µg/m<sup>3</sup>), 2) acute exposure (2 hours 1.9 mg/m<sup>3</sup>), 3) acute exposure (2 hours ± 300 µg/m<sup>3</sup>), and 4) acute exposure (2 hours 4.91 mg/m<sup>3</sup>). In addition, we have exposed healthy and compromised volunteers for 1-2 hours to 300 µg/m<sup>3</sup> of diesel exhaust (with and without a particle filter), as well as to carbon nanoparticles, to study effects on vascular, blood and brain function. The effects of exposure on the pulmonary and vascular system, such as endothelial function, endogenous fibrinolysis, and blood coagulation, were assessed. The results show that at levels encountered in an urban environment, inhalation of diesel exhaust impaired vascular function in volunteers, whereas this effect was fully absent in healthy rats. High exposure to diesel engine exhaust, however, resulted in an oxidative stress reaction possibly preceding inflammation. We detected a decrease in pro-inflammatory cytokine levels in the brain of the subchronically exposed animals. Since baseline levels of these cytokines are thought to play a house-keeping role, this decline in levels may cause neuronal stress. The studies presented in this paper suggest that exposure to nanoparticles can mediate changes in the vasculature and CNS of both healthy volunteers and an animal model. To what extent these changes may contribute to chronic neurodegenerative or vascular diseases is at present unknown.