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EDITORIAL

From bench to policies: ready for a nanoparticle air quality standard?

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This editorial refers to 'Combustion-derived nanoparticulate induces the adverse vascular effects of diesel exhaust inhalation'†, by N.L. Mills *et al.*, on page 2660

As ambient concentrations of urban particulate matter (PM) increase, more people end up in hospital due to heart attacks, and more people suffer sudden death even prior to getting help from cardiologists.[1] This is one of the many current conclusions from an exponentially growing transdisciplinary research agenda on air quality and health.[2] The annual output of >2000 peer-reviewed publications is now > 10 times larger than 20 years ago.[3] This research is not just a self-serving 'l'art pour l'art' but it comes with a long-standing tradition to apply knowledge to policies.[4] The success stories include the adoption of clean air standards for several markers of ambient air pollution [e.g. PM up to 10 μm (PM10) or 2.5 μm (PM2.5) in diameter, ozone, sulfur dioxide, nitrogen dioxide, and others] and the implementation of strategies to comply with the science-based standards. The underlying objective of clean air policies is the protection or improvement of health and, as can been demonstrated, these policies are indeed effective.[5]

The public health-driven research agenda that underlies clean air policies does not just go from the bench to the bedside but embraces the community. In fact, epidemiological research plays a very strong role in the assessment of air pollution-related health effects.[3] However, like all sciences, epidemiology has its limits. For example, Peters *et al.* convincingly showed with a very elegant epidemiological study design that the risk of suffering a myocardial infarction increases almost 3-fold during the first hour after exposure to traffic.[6] A recent comparison of the established triggers of myocardial infarction in fact ranked exposure to traffic as the most important trigger, with 7.4% of all events attributed to this activity.[7] However, while the study of Peters *et al.* used state-of-the-art methods to estimate the risk, the findings are not easily translated into policy. Does the risk increase due to traffic-related pollutants? Is it caused by particles and, if so, by what constituents or what size fraction? What is the role of the gaseous pollutants?

To answer such specific questions, the community must be carried to the bench. That is the key contribution of a series of studies carried out by the Scottish–Swedish–Dutch collaboration that has now published its newest findings.[8] In contrast to more traditional toxicological studies where experiments are often done with unrealistically high concentrations or artificially manufactured pollutants, Mills *et al.* again used an exposure chamber that mimics daily life exposures encountered in street canyons of our cities during rush hour. Controlled exposure is provided by a real-word diesel engine running on real-world diesel fuel.

The seminal study of 2007 revealed mechanistic cardiovascular pathways that may explain the association between ambient air pollution and myocardial infarction.[9] Men with a stable coronary heart disease were exposed to diesel exhaust and clean air. Diesel exhaust promoted myocardial ischaemia and inhibited endogenous fibrinolytic capacity. For cardiologists dedicated to counselling patients with coronary heart disease, the study poses some challenges as their patients can usually not escape exposure to air pollution if they live in traffic-jammed communities. The same research team then showed that diesel exhaust also affected thrombus formation in healthy young men.[10] The new study of Mills *et al.* links the bench with the community in a further policy-relevant way. The experiment attempted to apportion the vascular effects of diesel exhaust into effects of (i) untreated diesel exhaust; (ii) the gas phase of diesel exhaust after removal of the particles; and (iii) pure nano-sized carbon particles. Only unfiltered diesel exhaust compromised the vasodilatation mediated by bradykinin, acetylcholine, and sodium nitroprusside. Filtered diesel and pure carbon particles had no effect on these outcomes. In the complementary tissue model, acetylcholine- and sodium nitroprusside-mediated vasorelaxation of aortic rings from rats was attenuated under exposure to diesel exhaust particles but not to pure carbon nanoparticles.

These findings highlight the specific relevance of the real-world combustion-related nano-sized particles. The identity of the surface constituents of the nanoparticles that may have caused these effects cannot be determined with this experiment. This led the authors to the policy-related statement that 'understanding of

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the detrimental components of diesel exhaust particulate will be necessary for the future evaluation of technologies designed to modify vehicle exhaust emissions'.[8] A research agenda that looks even more closely at what is happening under the lamp post will certainly be very relevant to reveal the mechanisms in more detail. I wonder though whether tailoring technologies and policies to the light under the lamp post would effectively serve public health. Would this lead to diesel engines that emit particles of lower toxicity, of different shape or surface, or other size? Had such a 'surgical approach' to policy in dealing with the detrimental effects of smoking been followed, public health strategies would probably look very different these days. Instead of highly effective smoking bans,[11] cigarettes might have been designed that reduce or eliminate single constituents of tobacco smoke, one by one, following the evidence from research carried out under the lamp post.

Looking under the lamp post has the great advantage of removing many challenging heterogeneities of the 'real world'. In fact, Mills *et al.* discuss several reasons for obtaining partly 'inconsistent' results such as observing no effect of diesel exhaust on fibrinolytic function in this experiment whereas they found such effects in two previous studies.[10,12] What one observes in a small sample of volunteers put under one lamp post depends on a range of factors that need to be defined in the experiment while being more complex and not standardized at all in the real world. Examples are the type of the diesel engines and fuel, temperature, and humidity; the distributions in the particle size, surface, reactivity, or its constituents or co-pollutants; the time lags of measurements and the chosen outcomes; as well as a range of host factors including age, sex, lifestyle, nutrition, physical activity, medication, and certainly genetic make up. Most importantly, the lamp post requires focusing on a few well-defined pathways and outcomes while the effects of the complex mixture of diesel exhaust—and air pollution in general—are far broader.[2,13] In fact, numerous epidemiological studies investigated the health of those living within a few metres of busy roads where traffic-related nanoparticles reach very high concentrations.[14] Those living in such environments—a possible marker for high exposure to ultrafine particles—may have increased risks for a range of health problems; evidence is at this stage sufficient for childhood asthma and suggestive for cardiovascular death.[14,15]

Figure 1 Californian school bus prior to retrofitting, Boyle Heights, Los Angeles. Picture acknowledged to Professor Andrea Hricko, USC Los Angeles.

Thus, reading the work of Mills *et al.*, my policy-related conclusions are 2-fold. First, the study underscores the relevance of policies that will lead to the elimination of vehicles like the one shown in the picture from Los Angeles (*Figure 1*). The experiment of Mills *et al.* used a highly effective Teflon filter system rather than a filter used in modern diesel cars. However, the same research team has shown that the commercially used diesel filters also effectively abolish cardiovascular and prothrombotic effects of diesel exhaust.[16] Vehicles like the one in *Figure 1* need to be banned or retrofitted. These policies must also reach the many cities in low income countries where such vehicles remain the norm rather than the picturesque exception.

Secondly, looking under the most interesting lamp post of Mills *et al.* further supports the call to embark on a serious discussion about whether and how to add a new air quality standard for nano-sized ambient particles (or ultrafine PM). Environmental studies clearly indicate that ultrafine particles (UFPs) are not just a marker for the already regulated coarser PM2.5 and PM10, as spatial and temporal correlations between the ultrafine and the coarser fractions can be low.[17–19] In other words, strategies to reduce PM10 and PM2.5—important as they are—will not necessarily take care of the ultrafine fractions. There is also substantial evidence that different size fractions have different toxicological properties, and thus act through different mechanistic pathways.[20] A European expert panel already agreed 3 years ago that UFPs most probably do cause death independently of the effects of coarser particles.[18] The panel also had little doubt that UFPs would cause respiratory inflammation and thrombotic effects.[21] The literature available at that time was limited. Studies published since—such as that of Mills *et al.*[8]—further support the conclusion that ambient nanoparticles do affect people's health independently and partly differently from effects related to larger particles. The direct translocation of those nanoparticles to the brain is of particular additional concern.[22] While many open questions remain, one should not forget that air quality standards for PM2.5 and PM10 were adopted based on rather limited data.

I conclude that the time has come to discuss how to regulate combustion-related ambient nanoparticles to protect public health. Given the high concentrations of these particles along traffic arteries, these hot spots of urban areas may be the specific target of such regulations. Whether the new standards ought to be based on particle number, mass, reflectance, or more complex characteristics such as surface or redox activity[23] needs to be discussed. Findings seen under the lamp post at the bench ought to be linked with those at the bedside and in the community to develop pragmatic policy solutions to protect public health from adverse effects of ambient nano-sized particles.

Conflict of interest: none declared.

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