

Commentary

The Use of Standardized Diesel Exhaust Particles in Alzheimer's Disease Research

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Abstract. The mechanisms underlying how urban air pollution exposure conveys Alzheimer's disease risk and affects plaque pathology is largely unknown. Because particulate matter, the particle component of urban air pollution, varies across location, pollution source, and time, a single model representative of all ambient particulate matter is unfeasible for research investigating the role of air pollution in central nervous system diseases. More specifically, the investigation of several models of particulate matter with enrichment of source-specific components are essential to employ, in order to more fully understand what characteristics of particulate matter affects Alzheimer's disease, including standardized diesel exhaust particles.

Keywords: Air pollution, Alzheimer's disease, diesel exhaust particles, particulate matter models

Increasing evidence points to urban air pollution in increased Alzheimer's disease risk [1, 2] and elevated amyloid PET signal in humans [3], emphasizing the importance of current research focused on understanding the underlying mechanisms. Urban air pollution is a complex mixture comprised of diverse components such as gases, organic molecules, metals, and particulate matter, where the composition is variable and influenced by multiple factors, including the source of the exposure, temperature, photochemistry, and geography. Due to these influencing factors, the composition of real-world ambient particulate matter (PM) is highly variable in a temporal and spatial manner, and therefore, no one model ambi-

ent PM composition is fully representative of what people are exposed to. As such, correctly researching how this complex mixture, with pulmonary, peripheral, and central nervous system effects influences Alzheimer's disease relies heavily on model particles which reflect more limited, but targeted environmentally relevant exposures, such as diesel exhaust particles (DEPs).

Recently, Farahani et al. concluded that based on differences in composition of the exposure "standardized DEPs", such as those obtained from the National Institute of Standards (NIST) "are not suitable representatives of traffic emissions nor typical ambient PM to be used in toxicological studies" [4]. We would posit that while advances in the diesel engine technology and regulatory restrictions have resulted in successful reduction in diesel emission in the U.S. and that the specific exposure of these diesel exhaust particles unarguably fails as an exact replica of ambient

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air pollution, this should not preclude the experimental use of the diesel exhaust particulate matter in AD research today. Diesel exhaust is a component of urban air pollution and a prominent source of ultrafine particulate matter, where individuals diagnosed with or developing Alzheimer's disease today were likely exposed to pollution from these older diesel engine sources. Further, several CNS effects of diesel exhaust particulate matter [5, 6], including the fully characterized and commercially available diesel exhaust particulate matter reference material [6–9], have been published and validated. Notably, the wide catalogue of air pollution exposures used in inhalation toxicology research, including complex mixtures, concentrated ambient PM, and individual components of air pollution, such as ozone, each present their strengths and weaknesses, depending on the hypotheses being tested and the biological effect in question. For example, the concentration of PM 2.5 per cubic meter of air, which varies ~5 orders of magnitude worldwide, has been shown to correlate with the mutagenicity of ambient air [10, 11], rather than the chemical characteristics of the PM 2.5. Thus, as this field moves forward, reporting the limitations of the model, the full characterization of the air pollution exposure employed, the route of administration, and the pulmonary/peripheral effects will be essential for the integration of the findings from these diverse exposures. As ambient air pollution changes over time due to climate and regulation changes, comparative insights are needed into the potential mechanisms underlying how source-specific as well as urban air pollution can impact Alzheimer's disease to aid in identifying novel potential therapeutic targets, and/or potentially informing future policy.

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