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Evaluating Neural Reflex Activation as a Potential Mode of Action for the Cardiovascular and Respiratory Effects of Ambient Fine Particulate Matter ($PM_{2.5}$) Using a Human Relevance Framework

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Background and Purpose: In 2019, US EPA reviewed the epidemiology literature and concluded a causal relationship exists between short- and long-term exposure to fine particulate matter ($PM_{2.5}$) and total non-accidental mortality, primarily attributable to mortality from cardiovascular and respiratory health conditions. While a mode of action (MoA) for underlying respiratory and cardiovascular morbidities has remained elusive, it has been proposed that some effects of $PM_{2.5}$ occur through activation of neural reflexes. In this proposed MoA, oxidative components of $PM_{2.5}$ are postulated to activate sensory receptors within the vagus nerve, leading to reflex responses, modulation of the autonomic nervous system, and increased sympathetic tone, with apical effects that include bronchoconstriction, shortness of breath, airway inflammation, impaired vascular function, and arrhythmia. However, the evidence regarding this potential MoA and its relevance to humans has not been evaluated. We applied the International Programme on Chemical Safety (IPCS) MoA/human relevance framework to critically assess whether the available scientific evidence supports neural reflex activation as a biologically plausible MoA by which $PM_{2.5}$ could contribute to cardiovascular and respiratory morbidities.

Methods: We critically reviewed the experimental studies of $PM_{2.5}$ and neural reflex activation, which included an evaluation of their study design and quality. Then, we applied the principles of the IPCS MoA/human relevance framework to evaluate the plausibility of neural reflex activation as the MoA for the relationship between $PM_{2.5}$ and mortality induced by altered respiratory and cardiovascular function. In our analysis, we considered the consistency, essentiality, temporality, and exposure-response relationships of the key events underlying the toxic responses. Similarly, we evaluated the biological concordance of the proposed MoA with other available evidence to inform biological plausibility. Finally, we assessed the relevance of the MoA in humans, considering the exposure levels at which the key events occur and any differences in the key events between animals and humans.

Results: We identified eight studies of the respiratory system and seven studies of the cardiovascular system relevant to the proposed MoA. These studies were conducted in several different experimental animal models and used various sources of $PM_{2.5}$ (*i.e.*, diesel exhaust, diesel exhaust particles, concentrated ambient particles, and cigarette smoke). We did not identify any relevant studies in humans. Our analysis found relatively consistent evidence that $PM_{2.5}$-induced respiratory effects are mediated by a neural pathway, and the animal studies demonstrated essentiality of multiple key events, including production of reactive oxygen species and stimulation of transient receptor potential ion channels. These results are also consistent with the proposed temporality of the key events. The evidence across experimental studies was concordant and indicated that neural reflex activation is a biologically plausible MoA by which $PM_{2.5}$ could cause respiratory morbidities. However, the human relevance of the key events is unclear; exposure-response relationships and thresholds for the key events could not be determined, as a majority of the studies used only one exposure level that was higher than typical ambient exposures. The studies that evaluated cardiovascular endpoints provide

inconsistent evidence for a role of the proposed MoA and suggest that a different MoA may be more plausible.

Conclusions: Our analysis found that the proposed MoA of neural reflex activation is biologically plausible for $PM_{2.5}$-induced respiratory effects, but a role for the proposed MoA in $PM_{2.5}$-induced cardiovascular effects is less clear. Further studies are needed to determine whether neural reflex activation is the MoA by which $PM_{2.5}$ could induce respiratory or cardiovascular morbidities in humans exposed to environmentally relevant $PM_{2.5}$ concentrations.