THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

December 5, 2018

U.S. Environmental Protection Agency
Khanna Johnston
Acting Director
EPA Science Advisory Staff Office

Re: Docket ID No. EPA-HQ-ORD-2014-0859 (Integrated Science Assessment for Particulate Matter (External Review Draft))

Dear Acting Director Johnston:

Thank you for the opportunity to supply information on the impact of Particulate Matter (PM) on Parkinson's disease (PD) as the Clean Air Scientific Advisory Committee (CASAC) reviews the Integrated Science Assessment (Assessment) and ultimately decides on changes to the National Ambient Air Quality Standards for PM.

As the world's largest nonprofit funder of Parkinson's disease (PD) research, The Michael J. Fox Foundation is dedicated to accelerating a cure for Parkinson's and developing improved therapies for those living with the disease today. We have provided more than $800 million in research to date, including looking at the impact of environmental exposures on disease risk. As the Environmental Protection Agency (EPA) is tasked with safeguarding human health and the environment, it should continue to consider the impact of particle pollution on diseases like Parkinson's disease.

As you continue the review, we urge you to reinstate the Particulate Matter Review Panel. This group of 20 independent experts from a variety of health and science backgrounds was versed in the field of pollutants and disease risk. The panel was ideally positioned to review the dense scientific and medical information included in the 1,800 page draft Assessment. Given the document's size and scope, the current panel of just seven CASAC drawn from primarily non-academic and narrow backgrounds is likely incapable of adequately reviewing and analyzing its contents. To ensure the EPA adequately assesses the multitude of issues contained in the document, including sources of particulate matter and its dozens of impacts on American health, please reinstate the expert review panel before moving forward.

The rest of this letter will focus on the evidence surrounding PM's association with an increased risk of PD, which is primarily contained in Chapter 8 (Nervous System Effects) of the draft document.

The study of pollutants and their relationship with neurological disease continues to be a new and emerging field. Epidemiology studies examining the relationship require the ability to measure pollutants present in the air in a certain location over time. Most air monitoring procedures and technology were developed about 25 years ago and the period between exposure and a chronic illness diagnosis can span decades. Available studies and data, however,

indicate that particulate matter and other airborne pollutants, such as mercury, are correlated with an increased incidence of Parkinson's disease.

Though the evidence is relatively new, we agree it's proper to elevate the conclusion on whether PM causes neurological diseases, including Parkinson's disease, from "insufficient evidence" as presented in the 2009 review document to "likely causal" in the present assessment. Below, we summarize a portion of the relevant research as it relates to Parkinson's disease.

In a study looking at people living in six states, results suggested that exposure to particulate matter showed positive associations with Parkinson's disease risk.[1] This finding is replicated in other countries. A large-scale study from Denmark linked particulate exposures to Parkinson's disease.[2] This study used several thousand people with and without a current diagnosis of Parkinson's disease. Using extremely specific (within 5-50 meters of the front door) geo-coding to estimate participant's exposure to contaminants, the study estimated that ambient air pollution from traffic increased risk of developing Parkinson's disease by 9 percent. Researchers found an increased risk of Parkinson's disease after exposure to particulate matter in studies from a large-scale study in Taiwan as well.[3] In South Korea, study results suggest short-term air pollution exposure increases risk of Parkinson's disease aggravation and may cause neurological disease progression.[4]

The mechanisms of impact are not definitively known, but there are four proposed pathways through which particulate air pollution may induce neuroinflammation and neurodegeneration.[5]

First, particles induce chronic respiratory and systemic inflammation producing pro-inflammatory molecules which in turn affect the blood–brain barrier and the neural–immune response leading to chronic oxidative stress and neuronal death. Inflammation, along with neuroinflammatory processes, contribute to PD initiation and progression.[6] A study from Mexico City indicated that particulate matter may cause inflammation and damage neurons. This inflammation and damage may be responsible for the neuronal death seen in neurodegenerative diseases such as Parkinson's and Alzheimer's. Brain autopsies of people living in Mexico City and less polluted control cities with similar demographics found structural and chemical changes in the brains of

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[1] Liu R, Young MT, Chen JC, Kaufman JD, Chen H. 2016. Ambient air pollution exposures and risk of Parkinson disease. Environ Health Perspect 124:1759-1765.

[2] Ritz B, Lee P-C, Hansen J, Lassen CF, Ketzel M, Sørensen M., et al. 2016. Traffic-related air pollution and Parkinson's disease in Denmark: a case–control study. Environ Health Perspect 124(3):351–356.

[3] Chen C.Y., Hung H.J., Chang K.H., Hsu C.Y., Muo C.H., Tsai C.H., Wu T.N. Long-term exposure to air pollution and the incidence of Parkinson's disease: A nested case-control study. PLoS ONE. 2017;12:e0182834.

[4] Lee, H. et al. Short-term air pollution exposure aggravates Parkinson's disease in a population-based cohort. Sci. Rep. 7, 44741.

[5] Calderón-Garcidueñas, Lilian et al. 2008. "Long-Term Air Pollution Exposure Is Associated with Neuroinflammation, an Altered Innate Immune Response, Disruption of the Blood-Brain Barrier, Ultrafine Particulate Deposition, and Accumulation of Amyloid Beta-42 and Alpha-Synuclein in Children and Youn." Toxicologic pathology 36(2):289–310.

[6] Chung, Young Cheul et al. 2010. "The Role of Neuroinflammation on the Pathogenesis of Parkinson's Disease." BMB reports 43(4):225–32.

people from the more polluted Mexico City. Notably, researchers observed PM within brain matter along with signs of inflammation and oxidative stress. In their conclusion, the researchers state, "we strongly propose that neuroinflammation as a result of exposure to air pollution could have a causative role in both Alzheimer's and Parkinson's disease and that sustained brain inflammation confers a higher risk."[7] Second, particles do not have to pass the blood brain barrier but can access the brain directly through the olfactory bulb pathway.[8] The loss of smell is often considered a first sign symptom of the disease[9] and a study of feral dogs found that animals living in regions of high pollution showed enhanced oxidative damage, premature presence of plaques, and a significant increase in DNA damage in their olfactory bulbs and other parts of the brain.[10] Third, particles may use several cranial nerves to enter the nervous system from the respiratory or digestive systems.[11] Problems with digestion are also present in people with Parkinson's before other symptoms develop.[12] Fourth, ultrafine particles directly produce reactive oxygen species (which in turn causes oxidative stress), damage the blood–brain barrier, and enhance protein aggregates of the protein alpha-synuclein, all critical risk factors contributing to neurodegeneration in PD.[13]

EPA's recognition of the impacts that air pollution, including particulate matter and heavy metals, contribute to Parkinson's disease risk and cognitive decline is important as the panel moves forward with its level recommendations for the National Ambient Air Quality Standards for particulate matter. There is no "safe" threshold level for air pollutants in short-term association with mortality,[14] therefore reducing exposure by as much as possible is the best solution.

Thank you for the opportunity to respond.

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[7] Calderón-Garcidueñas, Lilian et. al. (2008). Long-term Air Pollution Exposure Is Associated with Neuroinflammation, an Altered Innate Immune Response, Disruption of the Blood-Brain Barrier, Ultrafine Particulate Deposition, and Accumulation of Amyloid -42 and -Synuclein in Children and Young Adults. Toxicologic pathology. 36. 289-310.

[8] Duda, John E. 2010. "Olfactory System Pathology as a Model of Lewy Neurodegenerative Disease." Journal of the Neurological Sciences 289(1–2):49–54.

[9] The Michael J. Fox Foundation, Smell Loss and Parkinson's Disease [Blog Post} retrieved from: https://www.michaeljfox.org/understanding-parkinsons/living-with-pd/topic.php?smell-loss.

[10] Calderon-Garciduenas L, et al. DNA damage in nasal and brain tissues of canines exposed to air pollutants is associated with evidence of chronic brain inflammation and neurodegeneration. Toxicol Pathol. 2003;31:524–538.

[11] Mutlu, Ece A. et al. 2011. "Particulate Matter Air Pollution Causes Oxidant-Mediated Increase in Gut Permeability in Mice." Particle and fibre toxicology 8(1):19.

[12] Levy, Jenna (2009, December 1) Reuters: Constipation: An Early Sign of Parkinson's? [Blog Post] retrieved from: https://www.michaeljfox.org/foundation/news-detail.php?reuters-constipation-an-early-sign-of-parkinsons.

[13] Cabezas, Ricardo et al. 2014. "Astrocytic Modulation of Blood Brain Barrier: Perspectives on Parkinson's Disease." Frontiers in cellular neuroscience 8:211.

[14] Lee H., Myung W., Kim D.K., Kim S.E., Kim C.T., Kim H. Short-term air pollution exposure aggravates Parkinson's disease in a population-based cohort. Sci. Rep. 2017;7:44741.