

August 4, 2023

Dr. Michal Freedhoff
Assistant Administrator
Office of Chemical Safety and Pollution Prevention
Environmental Protection Agency
1201 Constitution Avenue NW
Washington, DC 20004

Re: Additional Scientific Evidence Linking Paraquat to Parkinson's Disease

Dear Dr. Freedhoff:

The Michael J. Fox Foundation for Parkinson's Research (MJFF) is dedicated to finding a cure for Parkinson's disease through an aggressively funded research program and to ensuring the development of improved therapies for people living with Parkinson's. MJFF has funded over \$1.75 billion in research programs to date. MJFF submits this letter to ensure that EPA is aware of important, new research and investigative reporting linking paraquat dichloride (paraquat) to Parkinson's disease. We request that EPA include a copy of this letter and the accompanying attachments in the public docket for paraquat's registration review (Docket No. EPA-HQ-2011-0855).

MJFF is aware of investigative reporting in *The Guardian*, published most recently on June 2, 2023 ([Revealed: The secret push to bury a weedkiller's link to Parkinson's disease | US news | The Guardian](#)), alleging that, Syngenta, a manufacturer of paraquat, has internal documents setting forth their intent "to secretly influence scientific research regarding links between its top-selling weedkiller and Parkinson's." Earlier reporting in *The Guardian* is consistent with Syngenta's alleged attempts to obfuscate the scientific landscape (see October 20, 2022 ([Secret files suggest chemical giant feared weedkiller's link to Parkinson's disease | US news | The Guardian](#)), October 21, 2022 ([These farmers have Parkinson's disease - and claim a weedkiller is to blame | US news | The Guardian](#)), October 28, 2022 ([Why does the US allow a controversial weedkiller banned across the world?](#)), March 24, 2021 ([Scientist tells of relief after speaking out over weedkiller fears | Pesticides | The Guardian](#)), and March 24, 2021 (['A sip can kill': did a chemical company misrepresent data to avoid making a safer product? | Pesticides | The Guardian](#))). If true, the allegations are extremely concerning.

MJFF is a petitioner in *California Rural Legal Assistance Foundation, et al. v. U.S. Environmental Protection Agency, et al.* (21-71287), a lawsuit that is currently being held in abeyance while EPA reconsiders its assessment of paraquat's health risks, including the connection between paraquat and Parkinson's, and prepares an addendum to its human health risk assessment or a new standalone document related to such risks. We write with information that we believe is relevant to that reconsideration process, including primary scientific research on the connection between paraquat and Parkinson's that has been published since EPA's Interim Registration Review Decision for Paraquat Dichloride dated July 13, 2021 ("July 2021 Interim Decision"). That research is identified in the accompanying index and summarized below.

As background, Parkinson's disease is a chronic, progressive neurological disorder with motor and non-motor symptoms. Parkinson's occurs when dopamine neurons that coordinate movement stop working or

die. Parkinson's affects over 6.1 million people globally¹, and over 1 million of those individuals are in the United States². Parkinson's disease is the fastest-growing neurological disease in the world (by absolute prevalence)³. Parkinson's gradually worsens over time. Currently, there is no treatment to slow, stop, or reverse the progression of the disease, nor is there a cure. The treatment of patients diagnosed early with Parkinson's can aim to slow clinical progression, control motor and non-motor symptoms, maintain functioning in daily life activities, prevent motor complications, and minimize risk of side effects.

In 2017, the disease cost Americans at least \$52 billion each year². By 2037 – just 14 years from now – that total annual cost is estimated to balloon to \$79 billion². The emotional and mental cost to patients, their caregivers, and families is incalculable. The financial impact and rising prevalence, however, can be alleviated through mitigations that will reduce the number of Parkinson's cases, and by treatments developed through understanding the mechanisms and causes of the disease.

Between 10%⁴ and 27%⁵ of Parkinson's cases have a predominant genetic link. This means that most cases likely have an environment or gene-environment interactions component⁴. Environmental exposures such as exposure to pesticides⁶⁻⁸, particulate matter⁹⁻¹¹, other chemicals¹²⁻¹⁴, and head injuries¹⁵⁻¹⁸, have been linked to an increased risk for developing Parkinson's disease. Paraquat is one of these risks and MJFF is committed to reducing risks to prevent Parkinson's for future generations.

There is compelling scientific evidence linking paraquat to Parkinson's disease. In fact, paraquat is thought to increase Parkinson's risk by 100 to 500 percent, depending on overall exposure¹⁹. For this reason, MJFF and the Parkinson's community have long advocated for the elimination of this troubling suspected environmental risk. Since EPA's July 2021 Interim Decision, more published primary scientific research has been added to the strong body of evidence linking paraquat to Parkinson's. EPA's reconsideration of paraquat's risks and registration must carefully consider all available, relevant scientific evidence, including the additional research that has been published over the course of the approximately two-year period since the July 2021 IRR.

First, a recent *amicus curiae* brief by respected Parkinson's researchers Dr. Timothy Greenamyre, Dr. Michael Okun, and Dr. Beate Ritz details the evidence linking paraquat to Parkinson's disease. A copy of this brief, filed last summer as part of the above-mentioned case, is enclosed with this submission along with a folder of cited articles in pdf. Also enclosed with this submission is a compilation of recent peer-reviewed primary research, published from January 1st, 2018 through June 21st, 2023, further linking paraquat to Parkinson's. These studies consist of preclinical mechanistic studies examining how paraquat could be impacting Parkinson's disease-relevant pathological processes, and epidemiological studies linking probable paraquat exposures to increased incidence of the disease. Of note, excluded from the submitted list of publications are hundreds of other studies performed in the same period that use paraquat exposure as an extremely reliable inducer of Parkinson's-like symptoms and pathology in various species of laboratory animals, to test potential therapeutic strategies²⁰.

The *amicus* brief outlines that “[P]araquat likely has a causal relationship with Parkinson's” through three main points:

1. epidemiological studies demonstrate an association between paraquat and Parkinson's;
2. paraquat exposure can cause Parkinson's-like symptoms in animal studies; and

3. *in vitro* studies suggest a plausible mechanism for how paraquat can cause Parkinson's.

Second, additional paraquat and Parkinson's research has been published since the amicus brief was filed in June 2022. The most relevant studies of 2022 and January – June 2023 are summarized in the next few paragraphs.

In epidemiological studies, one study examined a cohort of farmers for dream enacting behaviors, which are a prodromal (precursor) symptom of Parkinson's and other neurodegenerative diseases²¹. The researchers found that farmers with past unusually high accidental exposures to paraquat had a 3.48 odds ratio, indicating positive associations of reporting dream enacting behaviors 16 - 22 years after the incident²¹. A separate study published in *Nature Communications* combined epidemiological data on real-life pesticide exposures and tested pesticide toxicity in a laboratory using neurons generated from one patient with Parkinson's²². In this study, the authors note "due to special considerations for paraquat dichloride, specifically strong experimental support for the hypothesis and the interest in estimating the effects of duration and intensity of exposure, we present results from these analyses in a separate manuscript"²². In that additional manuscript (which is in review and available as a preprint), the authors found that "Parkinson's disease patients lived and worked near agricultural facilities that applied greater amounts of the herbicide than community controls"²³. An advantage to these two studies is that they utilize the California commercial pesticide use record, which does not necessitate participant recall that can be difficult over long time periods.

Not only has additional research been completed in epidemiology, but also in laboratory mouse models. In one study, researchers found that "paraquat exposure alters lipid profile, elevates pro-inflammatory lipid production, elicits neuroinflammation in the midbrain, and induces motor deficits. These neurotoxic effects are mechanistically linked to the pathogenesis of PQ [paraquat] induced Parkinsonism"²⁴. The authors indicate that "moreover, results of this study emphasize the importance of controlling exposure to neurotoxic environmental pollutants for reducing the risk of Parkinsonism at population level"²⁴. In the Duan et al. 2023 study, the researchers "demonstrated that repetitive PQ [paraquat] exposure caused dopaminergic neuron loss, dopamine deficiency, and motor deficits dose dependently in mice"²⁵. The researchers concluded that "consistent with previous studies, we confirmed that cumulative paraquat exposure induced neurotoxicity and Parkinsonism in a dose dependent manner"²⁵.

Nuber and Selkoe cultured mouse neurons and exposed the cultures to differential dosages of paraquat²⁶. The researchers found that "paraquat-induced tetramer [4 subunits]-monomer [1 subunit] shift can induce alpha-synuclein containing aggregates and decreased neuron fibers and connectivity"²⁶. The researchers state that "mechanistically, we hypothesize that the reason paraquat induces alpha-synuclein aggregation is that the underlying event – chronically altering the neuronal tetramer/monomer equilibrium – is likely to occur in Parkinson's disease, dementia with Lewy bodies, and other human synucleinopathies"²⁶.

EPA's ongoing reconsideration of paraquat's risk assessment and registration is of great interest and importance not only to the scientific and medical community but also to individuals who are living with Parkinson's and their families. Some examples of these individuals, their stories and the impact on their caregivers are enclosed with this submission. These anecdotes describe individuals' exposure to paraquat in advance of their Parkinson's -symptom onset or diagnosis. In view of the widespread use of paraquat and the ongoing exposure to it by members of the public, we urge EPA to perform a robust review of all available relevant scientific evidence.

MJFF respectfully urges EPA to discharge its duty fully in its reconsideration of paraquat's risk assessment and registration, including the evidence contained or referenced in the attachments to this submission. The investigative reporting in *The Guardian* indicates that there may be documentation of paraquat harms in the ongoing torts case. We believe that these documents are critical for EPA staff to have access to the full information to reevaluate paraquat registration.

MJFF also respectfully requests a meeting with relevant EPA leadership and staff to discuss this extensive evidence, so that EPA has the benefit of the expertise of MJFF scientists and of experts with whom MJFF collaborates. MJFF would be happy to coordinate such a meeting of its experts with EPA to discuss this matter, which is so critical to public health and policy, prevention of future Parkinson's diagnoses, the continuing search for treatments, and the integrity of EPA's review process.

We can be reached at tthompson@michaeljfox.org or 202.638.4101, extension 382 should you or your team have any questions about this matter. Thank you for your consideration.

Sincerely,



Todd Sherer, Ph.D.
Chief Mission Officer



Ted Thompson, JD
Senior Vice President, Public Policy

Cc: Grant Cope, Senior Counselor to the EPA Administrator
Jake Li, Deputy Assistant Administrator for Pesticide Programs
Sonia Altieri, Manager and Program Analyst, EPA Office of Chemical Safety and Pollution Prevention
Michael Goodis, Deputy Director of Programs, EPA Office of Pesticide Programs
Elissa Reeves, Director, Pesticide Re-Evaluation Division, EPA Office of Pesticide Programs
Dana Vogel, Director, Health Effects Division, EPA Office of Pesticide Programs

Enclosures: Amicus brief, spreadsheet of articles, + folder of article PDFs
2 spreadsheets of paraquat and Parkinson's literature reviews + folder of article PDFs
Parkinson's disease paraquat exposure stories

References

- 1 Dorsey ER, Elbaz A, Nichols E, *et al.* Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2018; **17**: 939–53.
- 2 Yang W, Hamilton JL, Kopil C, *et al.* Current and projected future economic burden of Parkinson's disease in the U.S. *Npj Park Dis* 2020; **6**: 15.
- 3 Feigin VL, Nichols E, Alam T, *et al.* Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019; **18**: 459–80.
- 4 Ball N, Teo W-P, Chandra S, Chapman J. Parkinson's Disease and the Environment. *Front Neurol* 2019; **10**: 218.
- 5 Billingsley KJ, Bandres-Ciga S, Saez-Atienzar S, Singleton AB. Genetic risk factors in Parkinson's disease. *Cell Tissue Res* 2018; **373**: 9–20.
- 6 Vellingiri B, Chandrasekhar M, Sri Sabari S, *et al.* Neurotoxicity of pesticides – A link to neurodegeneration. *Ecotoxicol Environ Saf* 2022; **243**: 113972.
- 7 Li S, Ritz B, Gong Y, *et al.* Proximity to residential and workplace pesticides application and the risk of progression of Parkinson's diseases in Central California. *Sci Total Environ* 2023; **864**: 160851.
- 8 Gatto NM, Cockburn M, Bronstein J, Manthripragada AD, Ritz B. Well-Water Consumption and Parkinson's Disease in Rural California. *Environ Health Perspect* 2009; **117**: 1912–8.
- 9 Nunez Y, Boehme AK, Weisskopf MG, *et al.* Fine Particle Exposure and Clinical Aggravation in Neurodegenerative Diseases in New York State. *Environ Health Perspect* 2021; **129**: 027003.
- 10 Kioumourtzoglou M-A, Schwartz JD, Weisskopf MG, *et al.* Long-term PM_{2.5} Exposure and Neurological Hospital Admissions in the Northeastern United States. *Environ Health Perspect* 2016; **124**: 23–9.
- 11 Liu R, Young MT, Chen J-C, Kaufman JD, Chen H. Ambient Air Pollution Exposures and Risk of Parkinson Disease. *Environ Health Perspect* 2016; **124**: 1759–65.
- 12 De Miranda BR, Greenamyre JT. Trichloroethylene, a ubiquitous environmental contaminant in the risk for Parkinson's disease. *Environ Sci Process Impacts* 2020; **22**: 543–54.
- 13 Goldman SM, Quinlan PJ, Ross GW, *et al.* Solvent exposures and parkinson disease risk in twins. *Ann Neurol* 2012; **71**: 776–84.
- 14 Goldman SM, Weaver FM, Stroupe KT, *et al.* Risk of Parkinson Disease Among Service Members at Marine Corps Base Camp Lejeune. *JAMA Neurol* 2023; published online May 15. DOI:10.1001/jamaneurol.2023.1168.
- 15 Gardner RC, Byers AL, Barnes DE, Li Y, Boscardin J, Yaffe K. Mild TBI and risk of Parkinson disease: A Chronic Effects of Neurotrauma Consortium Study. *Neurology* 2018; **90**: e1771–9.

- 16 Gardner RC, Burke JF, Nettiksimmons J, Goldman S, Tanner CM, Yaffe K. Traumatic brain injury in later life increases risk for Parkinson disease: TBI Increases Risk for PD. *Ann Neurol* 2015; **77**: 987–95.
- 17 Gao J, Liu R, Zhao E, *et al.* Head injury, potential interaction with genes, and risk for Parkinson's disease. *Parkinsonism Relat Disord* 2015; **21**: 292–6.
- 18 Camacho-Soto A, Warden MN, Searles Nielsen S, *et al.* Traumatic brain injury in the prodromal period of Parkinson's disease: A large epidemiological study using medicare data: TBI in the Prodromal Period of PD. *Ann Neurol* 2017; **82**: 744–54.
- 19 Costello S, Cockburn M, Bronstein J, Zhang X, Ritz B. Parkinson's Disease and Residential Exposure to Maneb and Paraquat From Agricultural Applications in the Central Valley of California. *Am J Epidemiol* 2009; **169**: 919–26.
- 20 Chia SJ, Tan E-K, Chao Y-X. Historical Perspective: Models of Parkinson's Disease. *Int J Mol Sci* 2020; **21**: 2464.
- 21 Yuan Y, Shrestha S, Luo Z, *et al.* High Pesticide Exposure Events and Dream-Enacting Behaviors Among US Farmers. *Mov Disord* 2022; **37**: 962–71.
- 22 Paul KC, Krolewski RC, Lucumi Moreno E, *et al.* A pesticide and iPSC dopaminergic neuron screen identifies and classifies Parkinson-relevant pesticides. *Nat Commun* 2023; **14**: 2803.
- 23 Kimberly C Paul, Myles Cockburn, Yufan Gong, Jeff Bronstein, Beate Ritz. Agricultural paraquat dichloride use and Parkinson's disease in California Central Valley. *medRxiv* 2022; 2022.12.28.22284022.
- 24 Tong T, Duan W, Xu Y, *et al.* Paraquat exposure induces Parkinsonism by altering lipid profile and evoking neuroinflammation in the midbrain. *Environ Int* 2022; **169**: 107512.
- 25 Duan W, Liu C, Zhou J, *et al.* Upregulation of mitochondrial calcium uniporter contributes to paraquat-induced neuropathology linked to Parkinson's disease via imbalanced OPA1 processing. *J Hazard Mater* 2023; **453**: 131369.
- 26 Nuber S, Selkoe DJ. The Parkinson-Associated Toxin Paraquat Shifts Physiological α -Synuclein Tetramers toward Monomers That Can Be Calpain-Truncated and Form Oligomers. *Am J Pathol* 2023; **193**: 520–31.