November 4, 2022

Tulio Macedo, Chief
Pesticide Registration Branch
Department of Pesticide Regulation
P. O. Box 4015
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Registration.Comments@cdpr.ca.gov

RE: Notice of Proposed Decision to Renew Pesticide Product Registrations For 2023, Director's Finding and Public Report (California Notice 2022-18)

Dear Pesticide Registration Branch Chief Macedo,

The undersigned Parkinson's disease researchers and practitioners thank you for the opportunity to comment on the proposed decision to renew paraquat pesticide product registrations for the year 2023. Collectively, we have decades of experience specifically studying Parkinson's disease or treating patients who suffer from the disease. We believe that our expertise makes us uniquely qualified to comment on paraquat's link to Parkinson's disease.

We urge the state of California to place paraquat into reevaluation in order to carefully address the links between paraquat and Parkinson's disease. The weight-of-evidence linking paraquat exposure to the development of Parkinson's disease is strong and getting stronger, bolstered by many recent studies that have not been formally reviewed and accounted for by CDPR scientists. A newly conducted systematic review of the literature, including epidemiological studies, animal studies and mechanistic studies, is necessary to inform the agency's position on whether paraquat can safely be used in the state.

An estimated 1 million people in the U.S. suffer from Parkinson's disease and countless millions of family members, caregivers and friends suffer indirectly by seeing their loved ones slowly succumb to a disease that has no known cure or therapy to stop its progression.[1] Parkinson's disease affects the central nervous system in a way that is both persistent and progressive, often leading to difficulty controlling movement, tremors, stiffness, lack of balance, cognitive impairment, behavioral problems and sleep disorders. Eventually dementia sets in. In addition to the human suffering. the societal and economic costs of this disease are enormous. The cost of medical care and indirect costs, such as lost productivity, are estimated to be over $52 billion each year in the U.S.[2]

Paraquat is one of the most widely used agricultural herbicides in California – among the top five herbicides used in the state – and has an enormous potential for human exposure in the rural environment.[3] A growing body of epidemiological literature has identified an association between paraquat exposure and Parkinson's disease – particularly in California communities. Residents of Fresno, Tulare, or Kern counties had an increased risk of developing Parkinson's disease when exposed to paraquat, and that risk increased when residents were exposed to paraquat in conjunction with the dithiocarbamate fungicide maneb.[4] In addition, multiple analyses of the Agricultural Health Study found a significant positive association between paraquat exposure and Parkinson's disease, including that licensed pesticide applicators who used paraquat were 2.5 times more likely to develop Parkinson's disease than those who did not.[5,6] The strength of the epidemiology includes findings of dose-dependent associations and increasing association when combined with other risk factors such as genetic and non-genetic predispositions.[7,8,9,10] This indicates that certain vulnerable populations in California may be at higher risk of developing this disease following paraquat exposure.

More recent meta-analyses provide additional support for a link between paraquat exposure and Parkinson's disease. Accounting for scientific quality of the available studies, two separate systematic review/meta-analyses of available case-control studies found a 25% and 64% increase in risk of developing Parkinson's disease.[11,12] Notably the risk was considerably higher when accounting for coexposure to paraquat and any other dithiocarbamate fungicide.[13] This is worrisome because the dithiocarbamate fungicides mancozeb and metam sodium are just as widely used as paraquat in California and are often used on the same crops, indicating that co-exposure may be common.[14]

In addition to epidemiology, animal and mechanistic studies also provide an important line of evidence to consider. Paraquat is known to pass the blood-brain barrier and accumulate in brain tissue in animal models – specifically the region of the brain that is implicated in Parkinson's disease.[15,16] In mice and rats, paraquat exposure mimics Parkinson's disease so well that it's considered a suitable model to study the disease.[17]

Paraquat exposure can induce dopaminergic neuron loss, alpha-synuclein aggregation and injury to the substantia nigra, all hallmarks of Parkinson's disease.[18,19] The mechanism of these paraquat-mediated effects is related to a process called 'redox cycling' by which paraquat generates superoxide anion, a form of reactive oxygen species (ROS), in brain cells, leading to a cascade of events that can culminate in Parkinson's disease.

Thus, the case against paraquat includes (1) strong human epidemiology, (2) a plausible mechanism of toxicity (oxidative stress - long implicated in Parkinson's disease), and (3) the fact that it faithfully reproduces in rodents the behavioral and pathological features of the human disease. Adding to the concern is the fact that epidemiological evidence suggests that current rates of exposure of people to paraquat is sufficient to cause the disease. This indicates that current mitigations and safeguards are insufficient to protect against paraquat-induced Parkinson's disease.

It is our expert opinion that paraquat presents a public health hazard to residents and workers in the state of California. We urge CDPR to place paraquat into reevaluation and conduct a systematic review of the literature to better understand the human health risks associated with paraquat use.

Sincerely,

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