March 29, 2024

Office of Pesticide Programs
Environmental Protection Agency, (28221T)
1200 Pennsylvania Ave., NW
Washington, DC 20460-0001

Re: Paraquat Interim Registration Review [EPA-HQ-OPP-2011-0855]

Dear Madam/Sir,

These comments are submitted on behalf of Beyond Pesticides. Founded in 1981 as a national, grassroots, membership organization that represents community-based organizations and a range of people seeking to bridge the interests of consumers, farmers and farmworkers, Beyond Pesticides advances improved protections from pesticides and alternative pest management strategies that eliminate a reliance on pesticides. Our membership and network span the 50 states and the world.

We are writing with concerns in response to EPA’s preliminary reconsideration of the issues raised by the California Rural Legal Assistance Foundation, et al. (Petitioners) in a Petition filed in September 2021 in the U.S. Court of Appeals for the Ninth Circuit for review of the Paraquat Interim Registration Review Decision (ID) completed by EPA in July 2021. As part of that litigation, EPA has further considered several substantive issues raised by the Petitioners, including concerns related to human health and EPA’s balancing of risks and benefits. We additionally are raising concerns with the ID not highlighted by the Petitioners filing.

Paraquat (PQ) is one of the most widely used herbicides in the world and is applied annually in the U.S. to more than 100 crops—including cotton, corn, and soybeans. PQ is a dangerous pesticide responsible for a large number of deaths from accidental and intentional ingestion with no proven antidote or cure for such poisoning. It is prohibited in over 30 countries, including all of the EU, China, and several others. PQ has been linked to numerous adverse health and environmental effects including increased risk of Parkinson’s disease (PD) and possible endocrine disruption, which has motivated numerous public interest campaigns and proposed legislation\(^1\) to ban its uses in the U.S.

PQ linkage to PD represents a key concern with the human health risk assessment supporting the ID. When the weight of epidemiologic evidence on the causal role of an environmental contaminant is debatable or not consistent enough for an unequivocal conclusion, other relevant information is crucial for a causal association to be considered, such as information provided by experimental animal

\(^1\) Protect Against Paraquat Act of 2019 (HR 3817)
studies and/or mechanistic studies. PD is a neurodegenerative disorder caused by progressive and substantial loss of dopaminergic neurons with accompanying gliosis in the substantia nigra. Several important contributing factors have been identified at the sub-cellular level in cases of idiopathic PD, including the excess production of reactive oxygen species (ROS). PQ is implicated as a potential cause or contributor in idiopathic PD due to its mechanism of action that disrupts electron transport within the mitochondria and thereby increase generation of ROS. Excessive ROS formation is a major mechanism related to PD and can trigger many types of damage, including neuroinflammation, characterized by the presence of activated microglia and reactive astrocytes in the brain parenchyma (indicated by the expression of Iba-1 and GFAP, respectively) and proinflammatory cytokines release. Indeed, PQ is used commonly as a mimic in researching the initiating events of PD. This provides substantial and credible evidence for a distinct molecular initiating event and additional intermediate events in an adverse outcome pathway (AOP) for PQ culminating in PD or other neurodegenerative conditions.

EPA failed to assess a common mechanism of toxicity for PQ and any other substance in its review for the ID, erroneously concluding that PQ does not have a common mechanism of toxicity or combined toxic action with other substances that may interact and potentiate its action. PQ exposure does not only occur in isolation but can also occur in combination with other pesticides such as the ethylene bis (dithiocarbamate) class fungicide maneb (manganese ethylene-bis dithiocarbamate) as an example. In animal models, the combined administration of PQ and maneb, to a greater extent than administration PQ or maneb alone, was found to cause PD-like nigrostriatal degeneration, microglial activation, lipid peroxidation and motor deficits that manifest as hunched posture and a decline in locomotor activity. These data indicate occurrence of an additive or synergistic effect. Similarly, gastric co-administration of subthreshold dose of dietary lectins and PQ can induce a range of PD-like neurodegenerative processes and pathological changes, including misfolded α-synuclein in the dorsal motor nucleus and substantia nigra, a loss of dopaminergic neurons in the substantia nigra, and Parkinson-related behavioral deficits that are responsive to L-DOPA therapy.

Inexplicably, after its systematic review of the epidemiologic literature on PQ exposure, the agency determined in its subjective opinion that “there is limited, but insufficient epidemiologic

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2 Vaccari et al. Paraquat and Parkinson’s disease: a systematic review protocol according to the OHAT approach for hazard identification. Systematic Reviews (2017) 6:98
evidence at this time to conclude that there is a clear associative or causal relationship between occupational paraquat exposure and Parkinson’s disease”. For non-occupational PQ exposure, it was determined that epidemiologic evidence is simply “insufficient at this time to conclude a clear associative or causal relationship”. The agency is using the wrong standard for interpreting the results of its review. The agency is not responsible for finding a clear causal relationship between PQ and PD. According to the standard set forth in FIFRA, the agency must interpret the epidemiological evidence (which is clearly more plentiful than “limited”) such that PQ unequivocally does not cause or contribute to the development of PD. The burden of persuasion is with the proponents for registration to demonstrate no causation (no unreasonable adverse effect). Can the Agency assert based on the available evidence that exposure to PQ will not risk development of PD? No, the ample epidemiological evidence and additional mode of action evidence are more than sufficient to support a presumption that PQ exposure may risk initiating or directly contributing to development of PD. Such rebuttable presumption against registration should stand until evidence is presented that clearly demonstrate no such linkage.

PQ was also not fully assessed for potential endocrine disruption. Both the human health and ecological assessments deferred an assessment and provided canned language that endocrine disrupting potential will be further considered under the Endocrine Disruptor Screening Program (EDSP). Although mandated by the Food Quality Protection Act of 1996 (FQPA) nearly 30 years ago, the EDSP has only partially evaluated a meager 52 chemicals in the first group of chemicals to be assessed (List 1) out of the greater than 10,000 chemicals subject to evaluation. PQ was not included in List 1 of chemicals or included in the second group or List 2 chemicals which have yet to receive test orders. However, there is evidence available that PQ has endocrine disrupting effects. Use of PQ is significantly associated with hypothyroidism.\(^{12}\) PQ has been reported to decrease testosterone, follicle-stimulating hormone, luteinizing hormone and prolactin in male rats.\(^{13}\) In the frog *Rana esculenta*, PQ was found to inhibit the production of testosterone in the testis and 17-beta-estradiol in the ovary.\(^{14}\) More importantly, the endocrine disruption activity of PQ that causes excessive ROS production also links PQ to PD.\(^{15}\) Though somewhat limited, these data do indicate a potential for unreasonable adverse endocrine disruption in humans and wildlife and should be further investigated as mandated in FIFRA and FQPA.

Likewise, the agency’s ecological risk assessment in support of its ID did not consider risks to endangered/threatened species and potential jeopardy to their continued existence. As stated in the assessment: “Given that the agencies are continuing to develop and work toward implementation of the Interim Approaches\(^{16}\) to assess the potential risks of pesticides to listed species and their designated critical habitat, this ecological risk assessment for paraquat does not contain a complete ESA analysis that includes effects determinations for specific listed species or designated critical habitat.” Considering that the calculated risk quotients (RQs) exceed established levels of concern (LOCs) for most unlisted

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\(^{16}\) Available at http://www2.epa.gov/endangered-species/assessing-pesticides-under-endangered-speciesact#report
species, it can be inferred that listed plant and animal species in areas of PQ use could indisputably be at risk of jeopardy.

In the ID, the agency intentionally did not make any human health or environmental safety findings associated with EDSP screening requirements for PQ. Similarly, the agency did not make a complete endangered species finding, but presumed without foundation that the use mitigation imposed may be expected to reduce the extent of environmental exposure and may reduce risk to listed species whose range or critical habitat co-occur with the use of PQ. The agency will need to complete a listed-species assessment and any necessary Endangered Species Act (ESA) Section 7 consultation with the Services and make an EDSP determination before issuing a final registration review decision for PQ.

The risk benefit assessment presented in the ID is flawed. As previously indicated, the full gamut of potential risks has not yet been fully considered. The ID asserts that any potential risks of concern that are not fully mitigated by the measures prescribed are outweighed by the benefits associated with the use of paraquat and there are no direct alternatives to PQ. We disagree with this assertion as several effective alternatives, chemical and non-chemical, that pose less health and environmental risks are widely available. Given the availability of alternative pest management practices that incorporate alternative cultural practices and/or less toxic products, including other registered pesticides, the benefits of PQ are effectively nullified in comparison to the very serious known risks and potentially serious undefined risks posed (endocrine disruption, listed species, etc.) rendering these risks unreasonable. Therefore, the agency has a statutory duty to revoke all remaining registrations of PQ under its unreasonable adverse effects standard in FIFRA. To refute this rebuttable presumption against registration a more rigorous and robust reevaluation and meta-analyses of the epidemiological studies in combination with the substantial experimental data on PQ’s mechanisms of action than the agency’s flawed systematic review would need to be done to contradict and demonstrate conclusively that such linkage does not exist despite the existing evidence to the contrary.

In summary, we find EPA’s preliminary reconsideration of the issues raised by the Petitioners is insufficient and non-persuasive. Specifically, the agency’s risk benefit analysis fails to adequately consider the many alternatives available to PQ usage. These many alternatives negate any and all purported benefits the agency asserts rendering the many demonstrated adverse effects and presumed serious risks to human health and the environment as unreasonable.

Respectfully,

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