April 1, 2024

Environmental Working Group Comments to the Environmental Protection Agency on the Interim Decision for Paraquat specifically EPA's Preliminary Supplemental Consideration of Certain Issues in Support of its Interim Registration Review Decision for Paraquat; Docket ID: EPA-HQ-OPP-2011-0855-0321

The Environmental Working Group, or EWG, a nonprofit research and policy organization headquartered in Washington, D.C., urges the Environmental Protection Agency to ban the use of paraquat in the United States. Paraquat has been banned in more than 50 countries, many that are large agricultural economies. Paraquat has high acute and chronic toxicity, leading to several unintentional poisoning and deaths, as well as increasing the risk of developing Parkinson's disease. The agency needs to follow the science and example of other nations and ban the use of this toxic herbicide.

Below, we highlight several flaws with EPA's current assessment of paraquat as rationale for why prohibiting paraquat use is the best course of action.

1) **The agency has not recognized and considered the tremendous body of evidence linking paraquat exposure to increased risk of developing Parkinson's disease.**
2) **The agency has not taken all the necessary steps to protect communities near paraquat spraying sites from paraquat impacts.**
3) **The agency has ignored the continued acute toxicity of paraquat despite restrictions that have been put into place.**
4) **The agency has ignored possible risks to children's health near paraquat exposure.**
5) **The agency's cost benefit and alternatives analysis are insufficient.**
6) **The agency's proposed mitigation does not alleviate all risks to people working with paraquat or harm to wildlife and the environment.**

The agency has not recognized and considered the tremendous body of evidence linking paraquat exposure to increased risk of developing Parkinson's disease.

The EPA's human health risk assessment for chronic health risk posed by paraquat focuses primarily on respiratory toxicity caused by paraquat exposure either through the oral or inhalation routes of exposure, relying on registrant submitted studies in dogs from the 1980's. Over the last 50 years, the body of scientific work identifying paraquat as an agent capable of inducing Parkinson's disease-like symptoms in animal

studies has extensively developed[1]. The chemical is routinely used in animal models of Parkinson's disease, used by researchers to understand how Parkinson's disease develops[2]. The agency discounts many of these studies, claiming that the route of exposure typically used, intraperitoneal injection, is not relevant for realistic paraquat exposure in humans. Yet the agency fails to acknowledge that high doses or alternate routes of exposure are routinely used in studies considered by the agency to understand a chemical's potential toxicological effects. Additionally, the National Toxicology Program considered these studies relevant in a systematic review of paraquat and Parkinson's disease[3]. Lastly, there are multiple studies that describe chronic, low-dose exposure to paraquat in animal studies that also observe hallmarks of Parkinson's disease including degeneration of dopaminergic neurons and decrease in motor function, increases in oxidative stress, mitochondrial dysfunction and increase in alpha-synuclein aggregates.[4,5,6,7] These studies as well as studies in cells that support the mechanistic plausibility of paraquat causing Parkinson's disease were recently reviewed.[8]

Numerous epidemiological studies, most of which come from occupationally exposed individuals, consistently find a statistically significant association between paraquat exposure and the likelihood of developing Parkinson's disease. Yet, the agency dismisses all of these studies despite the fact that two meta-analyses published in 2019

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[1] Zhang XF, Thompson M, Xu YH. Multifactorial theory applied to the neurotoxicity of paraquat and paraquat-induced mechanisms of developing Parkinson's disease. Lab Invest. 2016 May;96(5):496-507. doi: 10.1038/labinvest.2015.161. Epub 2016 Feb 1. PMID: 26829122.

[2] McDowell K, Chesselet MF. Animal models of the non-motor features of Parkinson's disease. Neurobiol Dis. 2012 Jun;46(3):597-606. doi: 10.1016/j.nbd.2011.12.040. Epub 2012 Jan 3. PMID: 22236386; PMCID: PMC3442929.

[3] Boyd WA, Blain RB, Skuce CR, et al. NTP Research Report on the Scoping Review of Paraquat Dichloride Exposure and Parkinson's Disease: Research Report 16 [Internet]. Research Triangle Park (NC): National Toxicology Program; 2020 Sep. Results. Available from: https://www.ncbi.nlm.nih.gov/books/NBK563358/

[4] Ren JP, Zhao YW, and Sun XJ. 2009. Toxic influence of chronic oral administration of paraquat on nigrostriatal dopaminergic neurons in C57BL/6 mice. *Chin Med J.* 122(19): 2366-2371.

[5] Lou D, Wang Q, Huang M, and Zhou Z. 2016. Does age matter? Comparison of neurobehavioral effects of paraquat exposure on postnatal and adult C57BL/6 mice. *Toxicol Mech Method.* 26(9): 667-673.

[6] Cristóvão AC, Campos FL, Je G, Esteves M, Guhathakurta S, Yang L, Beal MF, Fonseca BM, Salgado AJ, Queiroz J, Sousa N, Bernardino L, Alves G, Yoon KS, Kim YS. Characterization of a Parkinson's disease rat model using an upgraded paraquat exposure paradigm. Eur J Neurosci. 2020 Aug;52(4):3242-3255. doi: 10.1111/ejn.14683. Epub 2020 Feb 3. PMID: 31958881.

[7] Anselmi L, Bove C, Coleman FH, Le K, Subramanian MP, Venkiteswaran K, Subramanian T, Travagli RA. Ingestion of subthreshold doses of environmental toxins induces ascending Parkinsonism in the rat. NPJ Parkinsons Dis. 2018 Sep 27;4:30. doi: 10.1038/s41531-018-0066-0. PMID: 30302391; PMCID: PMC6160447.

[8] Sharma P, Mittal P. Paraquat (herbicide) as a cause of Parkinson's Disease. Parkinsonism Relat Disord. 2024 Feb;119:105932. doi: 10.1016/j.parkreldis.2023.105932. Epub 2023 Nov 21. PMID: 38008593.

found significant associations between paraquat and Parkinson's disease[9,10], and additional epidemiological studies supporting this association that have been published since then. These include a follow up to the Agricultural Health Study[11], which found increased risk of Parkinson's disease in pesticide applicators with head injury, a known risk factor for PD, a study that supports the link between paraquat and dream enacting behavior[12], a Parkinson's disease precursor, and an assessment of residential and workplace ambient exposure to paraquat in California's Central Valley[13].

The agency notes that the points of departure and reference doses identified to protect against respiratory outcomes are sufficiently protective of possible paraquat neurotoxicity, yet we strongly disagree with this statement. The agency only uses a 100X safety factor to account for inter and intra species differences. Yet, the body of evidence on paraquat neurotoxicity suggests the agency should also use a 10X database uncertainty factor to account for potential risks of Parkinson's disease. The agency also incorrectly states that "paraquat administered via inhalation has been shown to sequester entirely in the olfactory bulb in small amounts", but a study published by Anderson et al. (2021) reported paraquat "inhalation resulted in an appreciable burden in all examined brain regions."[14] Lastly, the agency has made no attempt to perform a dose response assessment on studies with evidence of paraquat exposure causing Parkinson's disease, so the agency cannot know if in fact other points of departure are more sensitive.

The agency also openly acknowledges that it has not considered all the articles of evidence submitted by Michael J. Fox Foundation and Earthjustice in letters submitted to the agency in August 2023, which include additional scientific studies, as well as personal testimony from ongoing court cases all of which are relevant to assessing the health risk associated with paraquat use. This information must be considered by the agency.

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[9] Tangamornsuksan W, Lohitnavy O, Sruamsiri R, Chaiyakunapruk N, Norman Scholfield C, Reisfeld B, Lohitnavy M. Paraquat exposure and Parkinson's disease: A systematic review and meta-analysis. Arch Environ Occup Health. 2019;74(5):225-238. doi: 10.1080/19338244.2018.1492894. Epub 2018 Nov 25. Erratum in: Arch Environ Occup Health. 2019;74(5):292-293. PMID: 30474499.

[10] Vaccari C, El Dib R, Gomaa H, Lopes LC, de Camargo JL. Paraquat and Parkinson's disease: a systematic review and meta-analysis of observational studies. J Toxicol Environ Health B Crit Rev. 2019;22(5-6):172-202. doi: 10.1080/10937404.2019.1659197. Epub 2019 Sep 2. PMID: 31476981.

[11] Shrestha S, Parks CG, Umbach DM, Richards-Barber M, Hofmann JN, Chen H, Blair A, Beane Freeman LE, Sandler DP. Pesticide use and incident Parkinson's disease in a cohort of farmers and their spouses. Environ Res. 2020 Dec;191:110186. doi: 10.1016/j.envres.2020.110186. Epub 2020 Sep 10. PMID: 32919961; PMCID: PMC7822498.

[12] Yuan Y, Shrestha S, Luo Z, Li C, Plassman BL, Parks CG, Hofmann JN, Beane Freeman LE, Sandler DP, Chen H. High Pesticide Exposure Events and Dream-Enacting Behaviors Among US Farmers. Mov Disord. 2022 May;37(5):962-971. doi: 10.1002/mds.28960. Epub 2022 Feb 13. PMID: 35152487; PMCID: PMC9524747.

[13] Paul KC, Cockburn M, Gong Y, Bronstein J, Ritz B. Agricultural paraquat dichloride use and Parkinson's disease in California's Central Valley. Int J Epidemiol. 2024 Feb 1;53(1):dyae004. doi: 10.1093/ije/dyae004. PMID: 38309714.

[14] Anderson T, Merrill AK, Eckard ML, Marvin E, Conrad K, Welle K, Oberdörster G, Sobolewski M, Cory-Slechta DA. Paraquat Inhalation, a Translationally Relevant Route of Exposure: Disposition to the Brain and Male-Specific Olfactory Impairment in Mice. Toxicol Sci. 2021 Feb 26;180(1):175-185. doi: 10.1093/toxsci/kfaa183. PMID: 33372994; PMCID: PMC7916739.

The agency has not taken all the necessary steps to protect communities near paraquat spraying sites from paraquat impacts.

There is scientific evidence and support that living and working near agricultural applications can impact health, and increase the risk of developing disease, including from paraquat exposure. A study published in February 2024, which investigation long term paraquat use in California's central valley use pesticide use records, found strong associations, a more than doubling in some cases, of the likelihood of developing Parkinson's diseases for patients living near the greatest amounts of paraquat applications, compared to community controls[11]. This study supported and built off the findings of a previous study. Furthermore, research by EWG highlights that Latinos and vulnerable communities in California face the greatest burden of paraquat exposure[15]. The agency has not considered paraquat use through an environmental justice lens, or how paraquat use impacts fence line agricultural communities.

In addition to Parkinson's disease, several studies on agricultural communities find association between paraquat exposure and other health effects including childhood leukemia[16], thyroid cancer[17], and kidney disease[18]. These studies have also not been considered by the agency, nor as the agency reevaluated cancer risk associated with paraquat despite additional evidence from occupational cohorts that paraquat exposure is associated with increased risk of non-Hodgkin's lymphoma[19]. Additionally, EPA is not considering possible exposure and risk from paraquat adhered to dust which has been identified as a serious route of exposure for paraquat, especially since paraquat adheres tightly to soil.

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[15] Rabine Al. Paraquat disproportionately threatens California's low-income Latino communities. Environmental Working Group. March 27, 2024. https://www.ewg.org/research/paraquat-disproportionately-threatens-californias-low-income-latino-communities

[16] Park AS, Ritz B, Yu F, Cockburn M, Heck JE. Prenatal pesticide exposure and childhood leukemia - A California statewide case-control study. Int J Hyg Environ Health. 2020 May;226:113486. doi: 10.1016/j.ijheh.2020.113486. Epub 2020 Feb 19. PMID: 32087503; PMCID: PMC7174091.

[17] Omidakhsh N, Heck JE, Cockburn M, Ling C, Hershman JM, Harari A. Thyroid Cancer and Pesticide Use in a Central California Agricultural Area: A Case Control Study. J Clin Endocrinol Metab. 2022 Aug 18;107(9):e3574-e3582. doi: 10.1210/clinem/dgac413. PMID: 35881539.

[18] McGwin G Jr, Griffin RL. An ecological study regarding the association between paraquat exposure and end stage renal disease. Environ Health. 2022 Dec 12;21(1):127. doi: 10.1186/s12940-022-00946-9. PMID: 36503540; PMCID: PMC9743741.

[19] Park SK, Kang D, Beane-Freeman L, Blair A, Hoppin JA, Sandler DP, Lynch CF, Knott C, Gwak J, Alavanja M. Cancer incidence among paraquat exposed applicators in the agricultural health study: prospective cohort study. Int J Occup Environ Health. 2009 Jul-Sep;15(3):274-81. doi: 10.1179/oeh.2009.15.3.274. PMID: 19650582; PMCID: PMC3058830.

The agency has ignored the continued acute toxicity of paraquat despite restrictions that have been put into place.

In the interim decision for paraquat that was published in 2016, EPA determined that several mitigations were needed to reduce the paraquat incidents that occurred from accidental and intentional ingestion of the herbicide. These mitigations included label changes and supplemental warning materials to highlight the risks of ingestion, increased training for pesticide applicators, restricting paraquat use only to certified applicators and packaging changes to prevent spills and pouring paraquat into other containers. The mitigations were implemented between 2017 and 2020. Yet, an analysis of the annual reports from the National Poison Data System from 2016 through 2022 indicated that over 700 cases mentioned exposure to paraquat alone, the overwhelming majority of these were unintentional, more than half resulted in adverse outcomes, included 15 that resulted in death, with at least one death occurring each year from paraquat ingestion[20, 21, 22, 23, 24, 25, 26]. Simply observing a reduction in these events is not acceptable, but an elimination of these events must be a public health priority, which can only be achieved through removing paraquat from the market.

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[20] Gummin DD, Mowry JB, Spyker DA, Brooks DE, Fraser MO, Banner W. 2016 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 34th Annual Report. Clin Toxicol (Phila). 2017 Dec;55(10):1072-1252. doi: 10.1080/15563650.2017.1388087. Epub 2017 Nov 29. Erratum in: Clin Toxicol (Phila). 2017 Dec;55(10):1256. PMID: 29185815.

[21] Gummin DD, Mowry JB, Spyker DA, Brooks DE, Osterthaler KM, Banner W. 2017 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 35th Annual Report. Clin Toxicol (Phila). 2018 Dec;56(12):1213-1415. doi: 10.1080/15563650.2018.1533727. Epub 2018 Dec 21. PMID: 30576252.

[22] Gummin DD, Mowry JB, Spyker DA, Brooks DE, Beuhler MC, Rivers LJ, Hashem HA, Ryan ML. 2018 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 36th Annual Report. Clin Toxicol (Phila). 2019 Dec;57(12):1220-1413. doi: 10.1080/15563650.2019.1677022. Epub 2019 Nov 21. Erratum in: Clin Toxicol (Phila). 2019 Dec;57(12):e1. PMID: 31752545.

[23] Gummin DD, Mowry JB, Beuhler MC, Spyker DA, Brooks DE, Dibert KW, Rivers LJ, Pham NPT, Ryan ML. 2019 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 37th Annual Report. Clin Toxicol (Phila). 2020 Dec;58(12):1360-1541. doi: 10.1080/15563650.2020.1834219. PMID: 33305966.

[24] Gummin DD, Mowry JB, Beuhler MC, Spyker DA, Bronstein AC, Rivers LJ, Pham NPT, Weber J. 2020 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 38th Annual Report. Clin Toxicol (Phila). 2021 Dec;59(12):1282-1501. doi: 10.1080/15563650.2021.1989785. PMID: 34890263.

[25] Gummin DD, Mowry JB, Beuhler MC, Spyker DA, Rivers LJ, Feldman R, Brown K, Nathaniel PTP, Bronstein AC, Weber JA. 2021 Annual Report of the National Poison Data System© (NPDS) from America's Poison Centers: 39th Annual Report. Clin Toxicol (Phila). 2022 Dec;60(12):1381-1643. doi: 10.1080/15563650.2022.2132768. PMID: 36602072.

[26] Gummin DD, Mowry JB, Beuhler MC, Spyker DA, Rivers LJ, Feldman R, Brown K, Pham NPT, Bronstein AC, DesLauriers C. 2022 Annual Report of the National Poison Data System® (NPDS) from America's Poison Centers®: 40th Annual Report. Clin Toxicol (Phila). 2023 Oct;61(10):717-939. doi: 10.1080/15563650.2023.2268981. Epub 2023 Dec 12. PMID: 38084513.

The agency has ignored possible risks to children's health near paraquat exposure.

Paraquat has been detected in maternal serum and cord serum with higher exposures associated with people living in agricultural areas, digging in soil or working in farm fields[27,28]. This could be an important route of exposure that is entirely missed by EPA's current assessment. To remedy this severe shortcoming, the EPA should include the full 10-X Food Quality Protection Act children's health safety factor.

Please find EWG's previously submitted comments on this matter, since the agency has not addressed these concerns:

> In the draft human health risk assessment for paraquat, the EPA presented its rationale for reducing the Food Quality Protection Act, or FQPA, Safety Factor to 1X for all exposure scenarios relevant to children by asserting that "the toxicity database, with contributions from the open literature, is adequate to evaluate the potential for susceptibility in infants and young children resulting from exposure to paraquat" and that "the [Points of Departure] are protective of all known health effects resulting from paraquat exposure including evidence of susceptibility and neurotoxicity in the open literature." EWG strongly disagrees with the EPA's statement that the points of departure chosen for the draft assessment for paraquat are "protective of all known health effects." As summarized in section 1 above, the EPA's approach used studies on dogs from the 1980s and fails to adequately consider the risk of neurotoxicity. Moreover, EPA's own assessment finds that "limited evidence of age-related sensitivity [to paraquat] was observed in the open literature…" (section 4.4 of the draft human health risk assessment, "Safety Factor for Infants and Children"). These effects are particularly significant for exposure to paraquat in combination with other contaminants, such as the fungicide maneb.[29]
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> EPA dismissed the findings of age-related sensitivity to paraquat, stating that these effects are applicable only to "exposure to a high purity paraquat

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[27] Kongtip P, Nankongnab N, Phupancharoensuk R, Palarach C, Sujirarat D, Sangprasert S, Sermsuk M, Sawattrakool N, Woskie SR. Glyphosate and Paraquat in Maternal and Fetal Serums in Thai Women. J Agromedicine. 2017;22(3):282-289. doi: 10.1080/1059924X.2017.1319315. PMID: 28422580.

[28] Konthonbut P, Kongtip P, Nankongnab N, Tipayamongkholgul M, Yoosook W, Woskie S. Paraquat Exposure of Pregnant Women and Neonates in Agricultural Areas in Thailand. Int J Environ Res Public Health. 2018 Jun 3;15(6):1163. doi: 10.3390/ijerph15061163. PMID: 29865285; PMCID: PMC6025106.

[29] Li B, He X, Sun Y, Li B. Developmental exposure to paraquat and maneb can impair cognition, learning and memory in Sprague-Dawley rats. Mol Biosyst. 2016 Oct 20;12(10):3088-97. doi: 10.1039/c6mb00284f. Epub 2016 Jul 27. PMID: 27460631.

> product (>98% purity), which is not representative of the lower purity technical paraquat products and formulations (<48% purity) undergoing Registration Review." EWG disagrees with the agency's rationale and finds that the above statement is inconsistent with the basic principles of toxicology. If a high-purity material is associated with a particular type of toxicity, this indicates that the above-referenced toxicity represents the feature of the compound itself. Therefore, if age-related neurodevelopmental sensitivity from exposure to high purity paraquat was observed, the same effects would be reasonably expected for all preparations of paraquat. In sum, because of the risk of harm to children's health, and concern about paraquat's developmental neurotoxicity, a 10X children's health safety factor should be used for paraquat human health risk assessment.

Additional evidence has been published in the literature highlighting the potential health risks from prenatal paraquat exposure including in epidemiological studies that reported increased risk of hypospadias with paraquat exposure in North Carolina[30], and increased risk of preterm birth in California agricultural areas[31]. Animal studies continue to report prenatal oral paraquat exposure and adverse neurological outcomes in offspring[32, 33].

The agency's cost benefit and alternatives analysis are insufficient.

In the agency's cost benefit and alternatives analysis, the agency is flawed in its approach in several ways. Firstly, the agency does not consider the potential cost to human health from continuing to use paraquat, especially for Parkinson's disease, in its assessment. Additionally, the agency only considers two potential alternative *chemical* herbicides to replace paraquat. However, there is extensive research and practice of using non-chemical methods, or integrated pest management tools to eliminate the need for paraquat. There are also several other potential alternatives that are described in

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[30] Rappazzo KM, Warren JL, Davalos AD, Meyer RE, Sanders AP, Brownstein NC, Luben TJ. Maternal residential exposure to specific agricultural pesticide active ingredients and birth defects in a 2003-2005 North Carolina birth cohort. Birth Defects Res. 2019 Apr 1;111(6):312-323. doi: 10.1002/bdr2.1448. Epub 2018 Dec 28. PMID: 30592382; PMCID: PMC6445756.

[31] Ling C, Liew Z, von Ehrenstein OS, Heck JE, Park AS, Cui X, Cockburn M, Wu J, Ritz B. Prenatal Exposure to Ambient Pesticides and Preterm Birth and Term Low Birthweight in Agricultural Regions of California. Toxics. 2018 Jul 21;6(3):41. doi: 10.3390/toxics6030041. PMID: 30037110; PMCID: PMC6160921.

[32] Ait Lhaj Z, Ibork H, El Idrissi S, Ait Lhaj F, Sobeh M, Mohamed WMY, Alamy M, Taghzouti K, Abboussi O. Bioactive strawberry fruit (Arbutus unedo L.) extract remedies paraquat-induced neurotoxicity in the offspring prenatally exposed rats. Front Neurosci. 2023 Oct 12;17:1244603. doi: 10.3389/fnins.2023.1244603. PMID: 37901424; PMCID: PMC10600521.

[33] Liu F, Yuan M, Li C, Guan X, Li B. The protective function of taurine on pesticide-induced permanent neurodevelopmental toxicity in juvenile rats. FASEB J. 2021 Jan;35(1):e21273. doi: 10.1096/fj.202001290R. PMID: 33368748.

agricultural extension resources, and the agency should consider these alternate herbicides, as well as their potential impact on health and the environment. A recent publication highlighted that in countries where paraquat use was banned, crop yields were not impacted, and a combination of non-chemical weed management tools can replace paraquat use.[34]

The agency's proposed mitigation does not alleviate all risks to people working with paraquat or harm to wildlife and the environment.

Although the agency has recommended mitigations for paraquat use, some of which are already in effect, the interim decision openly states and acknowledges that these mitigations do not cover all risks of concern identified. This includes occupational inhalation risk from aerial applications on cotton and ground applications by open or closed cab, and dermal risks to workers during cotton harvest as well as risk to birds, mammals, and bees for harms to wildlife[35]. This finding also directly contradicts EPA's conclusion that EPA's approach will be protective of Parkinson's disease risks because the EPA has protected for dermal and respiratory risks which are more sensitive, yet clearly the EPA has not protected for these risks, leaving the conclusion that there is no risk of developing Parkinson's disease, especially in these high exposure scenarios, completely baseless. Furthermore, these mitigations overly rely on changes to pesticide labels, or requirements for personal protective equipment, even though research has shown these types of mitigations are hard to enforce and not always followed in real world use of pesticides[36].

In conclusion, to fully protect public and environmental health from the health harms associated with paraquat exposure, the EPA must cancel all uses of this toxic herbicide.

On behalf of the Environmental Working Group,

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[34] Stuart AM, Merfield CN, Horgan FG, Willis S, Watts MA, Ramírez-Muñoz F, U JS, Utyasheva L, Eddleston M, Davis ML, Neumeister L, Sanou MR, Williamson S. Agriculture without paraquat is feasible without loss of productivity-lessons learned from phasing out a highly hazardous herbicide. Environ Sci Pollut Res Int. 2023 Feb;30(7):16984-17008. doi: 10.1007/s11356-022-24951-0. Epub 2023 Jan 9. PMID: 36622585; PMCID: PMC9928820.

[35] U.S. Environmental Protection Agency. Paraquat. Preliminary Ecological Risk Assessment. https://www.regulations.gov/document/EPA-HQ-OPP-2011-0855-0128

[36] Donley N, Bullard RD, Economos J, Figueroa I, Lee J, Liebman AK, Martinez DN, Shafiei F. Pesticides and environmental injustice in the USA: root causes, current regulatory reinforcement and a path forward. BMC Public Health. 2022 Apr 19;22(1):708. doi: 10.1186/s12889-022-13057-4. PMID: 35436924; PMCID: PMC9017009.