THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 12 Issue 9

REVIEW ARTICLE

Paraquat and Parkinson's Disease: A Systematic Assessment of Recent Epidemiologic Evidence

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OPEN ACCESS

PUBLISHED
30 September 2024

CITATION
Weed, D., 2024. Paraquat and Parkinson's Disease: A Systematic Assessment of Recent Epidemiologic Evidence. Medical Research Archives, [online] 12(9). https://doi.org/10.18103/mra.v12i9.5767

DOI
https://doi.org/10.18103/mra.v12i9.5767

ISSN
2375-1924

ABSTRACT

A systematic assessment of recent evidence of the possible relationship between exposure to paraquat and Parkinson's disease was undertaken. A literature search was performed to identify all recently published relevant papers investigating, reviewing, or commenting upon the potential relationship between exposure to paraquat and Parkinson's Disease. MEDLINE via PubMed and EMBASE library databases were searched from 2019 to 2024 using search terms "paraquat" and "Parkinson." PRISMA guidelines for reporting systematic reviews were consulted along with the AMSTAR2 evaluation tool used to assess the quality of reviews. A total of 517 publications were identified in the first search and 923 publications in the broader search. After removal of duplicates, 21 publications were determined to be potentially relevant. Identified cohort studies were published between 2019 and 2021 and represented analyses using data from the Agricultural Health Study (AHS) a study designed and funded by the U.S. National Institutes of Health. These studies revealed no association between paraquat exposure and Parkinson's disease. With the results of the most recent analyses, there is no compelling scientific argument for claiming causality. These studies examined not only general population groups but especially occupationally exposed populations and found no statistically significant increased risk and no evidence of an exposure-response relationship. In the absence of these key causal considerations, the fact that these studies contribute to the inconsistency of the entire epidemiologic database, nonexistent risk increases and dose-response relationships, a lack of experimental evidence, and the absence of a similar—analogous—example in the practice of causal inference, there is no scientific justification for a causal claim. Organizational conclusions are consistent.

Introduction

In 1817, a member of the Royal College of Surgeons, James Parkinson, published what is now considered to be the first careful description of the "shaking palsy" or "*paralysis agitans*"[1,2]. Over two centuries later, Parkinson's Disease has gained in prominence and prevalence. Public attention on this progressive neurodegenerative disease can be attributed at least in part to the activism of the actor, Michael J. Fox, but others in the entertainment industry have experienced the disease, e.g., Alan Alda, and in politics, e.g., George H.W. Bush, as have religious leaders such as Jesse Jackson, Billy Graham, and Pope John Paul II (www.parkinson.org, accessed 9.9.2023).

Parkinson's Disease (PD) has also found its way into many households. Based on five epidemiological cohorts in North America, it has been estimated that there would be 86,000 new cases of PD in the United States in 2020, up from 77,000 in 2012. Worldwide, there are approximately 6.1 million cases of PD and 1.02 million new cases per year. The global prevalence of PD has increased 155% from 1990 to 2019[3].

Age is the most consistent risk factor for PD [4,5]. Incidence rates for those 65 years and older in the U.S. are between 108 and 212 per 100,000 person-years with a prominent preference for males [6]. The search for non-genetic risk factors of PD continues with a long list of possible culprits including microorganisms, traumatic brain injury, air pollution, electromagnetic fields, heavy metals, medications, alcohol consumption, and various pesticides all receiving attention in the research community [5,7]. Of these, the herbicide paraquat has been the focus of epidemiological and toxicological research for at least 30 years [8].

In some countries, paraquat is a commonly used herbicide in agriculture. For example, in California in 2018, 1,301,934 pounds of paraquat were applied to 1,240,012 acres of land. In 2019, 1,340,825 pounds were applied to 1,237,110 acres. In contrast, paraquat use in Japan has fallen. Sales fell 74.4% between 1995 and 2011 due in part to governmental regulations.

Of particular concern in the scientific community is whether a causal association exists between exposure to paraquat and Parkinson's disease. Causality is a central problem in the practice of the environmental and medical sciences with broad implications for public health, commerce, and the law. On the question of causation, a recent review of reviews that addressed the relationship between paraquat and PD through 2018 observed that there were no assessments of the accumulating evidence that concluded that paraquat causes PD [9]. The purpose of this paper is to update the scientific research on this issue that has been published since 2018 and to examine whether any changes to that earlier conclusion should be made. A particular focus in this effort are epidemiological studies that have examined population groups exposed to paraquat. Epidemiology is the study of the causes of diseases and the application of that knowledge for prevention and control in public health and remains a basic science of public health. In addition, it will be important to carefully examine reviews that have opined on the question of causation after examining published studies.

Methodology

A systematic literature search was performed to identify all recently published relevant papers investigating, reviewing, or commenting upon the potential relationship between exposure to paraquat and Parkinson's Disease. MEDLINE via PubMed and EMBASE library databases were searched from January, 2019 to March, 2024 using search terms "paraquat" and "Parkinson." A similar but broader search was undertaken using PubMed using search terms "pesticides" and "Parkinson." Reference lists of relevant articles were inspected to identify potentially relevant articles that may have been missed by the database searches. In addition, the so-called "grey" literature was examined for reports and other relevant documents not typically found in PubMed and EMBASE searches. PRISMA guidelines for reporting systematic reviews were consulted along with the AMSTAR2 evaluation tool used to assess the quality of reviews [10,11]. Inclusion criteria were applied to ensure adequate coverage of publications that addressed the potential relationship between exposure to paraquat and PD.

Results

A total of 517 publications were identified in the first search and 923 publications in the broader search. After removal of duplicates and a careful read of the titles and abstracts, twenty-one publications were determined to be potentially relevant. Full-text versions of those papers were examined including reference lists. There were seven reviews [4,5,8,12-15], four ecologic studies [16-19], a case-series [20], three case-control studies [7,21,22], four cohort studies [23-26], and one meta-analysis [8]. In addition, at least one organizational report, by the U.S. Environmental Protection Agency, was identified [27]. Excluded were studies that did not measure pesticides but rather inferred the presence of pesticides by the presence of heavy metals, nitrates and phosphates [16]. Also excluded were the following studies:

- Gamache et al. [20] is the report of a case-series of PD patients some with exposure to pesticides or toxic metals and others who had no such exposure (by self-report). Comparisons were made between these two groups of patients and the age at onset of PD. Specific pesticides were not considered.

- Schneider Medeiros et al. [23] is the report of a follow-up study of 150 PD patients enrolled between 2008 and 2013 and followed until 2019. A small proportion (13.3%) of the cohort reported a history of occupational pesticide exposure. Specific pesticides were not considered. The investigators examined whether the pesticide-exposed patients had a higher mortality than those without.

- Belvisi et al. [7] is the report of an Italian case-control study of risk factors for Parkinson disease. Pesticides, but not paraquat specifically, were included in the analysis.

- Dardiotis et al. [22] is the report of a case-control study of 104 Greek PD patients and 110 controls. The investigators compared organochlorine pesticide level in the two groups. Paraquat was not evaluated.

- Andrew et al. [21] is the report of a case-control study of lifestyle factors and Parkinson's disease in rural New England. Although use of pesticides (as a single entity) was collected, there was no information on specifics, including paraquat.

- Perrin et al. [17] is the report of a French nationwide ecologic study of pesticide expenditures by farming type and incidence of Parkinson's disease. Paraquat was not evaluated.

Epidemiological Studies of Paraquat and Parkinson's Disease

Epidemiological studies can be organized in terms of their ability to test causal hypotheses. Cohort and case-control studies have that capability whereas ecologic studies and case reports (or case series) do not [28]. To be precise, making causal claims from ecologic studies is subject to the ecologic fallacy and other problems affecting validity and reliability.

Making causal claims from case reports and case series falls prey to the fundamental problem of causal inference [29]. Put another way, cohort and case-control studies can—with appropriate attention to the inferential challenges presented by chance, bias, and confounding—test causal hypotheses and thus are considered superior to ecologic studies and case reports or case series. The superiority of cohort and case-control studies is confirmed in the U.S. Preventive Services Task Force hierarchy of evidence [30].

The cohort studies identified in the searches identified above were published between 2019 and 2021. Shrestha et al. [25] and Shrestha et al. [26] are cohort analyses using data from the Agricultural Health Study (AHS) a study designed and funded by the U.S. National Institutes of Health.

The AHS is a large prospective cohort study of private and commercial applicators of pesticides as well as the spouses of the applicators [31]. The study was undertaken in the states of North Carolina and Iowa. "Private" applicators include farmers and nursery workers; "commercial" applicators include those employed by pest control companies or businesses that use pesticides (e.g. warehouses and grain mills).

The purpose of the AHS was several-fold:

1. to evaluate non-cancer health risks including but not limited to neurotoxicity, reproductive effects, immunologic effects, respiratory and kidney disease, as well as growth and development among children,
2. to identify and quantify cancer risks among men, women, whites and minorities associated with direct exposure to pesticides and other agricultural agents,
3. to evaluate disease risks among spouses and children of farmers potentially related to exposure to pesticides and other agricultural agents that may occur due to indirect contact, e.g. spray drift, laundering, contaminated food/water,
4. to assess current and past exposure to agricultural exposures,
5. to study the relationship between exposure to agricultural agents and biomarkers of exposure, biologic effects, and genetic susceptibility factors,
6. and to identify and quantify cancer and other disease risks associated with lifestyle factors, e.g., smoking, alcohol diet, cocking practices, and physical activity.

The AHS investigators sought to mitigate the many weaknesses of earlier studies of the potential health effects of pesticides, including recall bias—a prominent problem of case-control studies—low statistical power due to small study populations, and inadequate information on specific chemical exposures, e.g. types, duration of use. The AHS investigators collect detailed and extensive information on occupational and environmental exposures, lifestyle characteristics, and medical/family history prior to the onset of the disease of interest. After the initial interview (to collect baseline information), the study updates the information every 5 years using computer-assisted telephone interviews for the entire cohort.

Information collected in the AHS on occupational exposures to individual pesticides includes duration of use, frequency of use, and intensity of use. Biological measurements of pesticides and metabolites are included in some studies as well as direct observation of some members of the cohort.

In the first year of a 3-year enrollment period, 26,235 people enrolled in the AHS, with 19,776 registered pesticide applicators and 6459 spouses. By 2005, there were 89,658 people enrolled in the AHS, with 52,395 private applicators, 4916 commercial applicators, and 32,347 spouses. The AHS population is overwhelmingly white (94.6% of private applicators; 98.6% of commercial applicators, and 95.2% of spouses of private applicators.

As will be discussed in more detail, the AHS study is superior—on strict methodological grounds—to any of the other more recent epidemiological studies of paraquat and PD including studies of pesticides and PD.

Shrestha et al. [25] is the report of a cohort mortality analysis in the AHS study where Parkinson's disease is one of many outcomes (n = 113) analyzed. Mortality rates for the states of North Carolina and Iowa were obtained from the Centers for Disease Control and Prevention. Follow-up period was from 1999 through 2015. In the final analysis there were 13,104 total deaths with 153 from Parkinson's disease. The authors calculated three relative outcome measures, the standardized mortality

ratio (SMR), the cumulative mortality ratio (CMR) and the relative SMR (rSMR) along with 95% confidence intervals for each. Adjustments were performed for age, calendar year, race, and state. Results for private pesticide applicators and separately for female spouses of private pesticide applicators, representing the possible relationship between exposure to pesticides (not otherwise defined) and Parkinson's disease are shown in the following table, adapted from Shrestha et al. (2019, Table 2, p. 17-20 and Table 4, p. 24-26):

Outcome Measure	Private Applicators O/E	Private Applicators Result	Spouses of Private Applicators O/E	Spouses of Private Applicators Result
SMR (95% CI)	153/156	0.98 (0.83-1.14)	32/39	0.83 (0.57-1.13)
CMR (95% CI)	153/104	1.47 (1.25-1.71)	32/29	1.01 (0.75-1.51)
rSMR (95% CI)		1.42 (1.21-1.66)		1.34 (0.95-1.90)

[1]O/E = Observed/Expected

There was some evidence of an elevated CMR but not an elevated SMR in the private applicators' results for pesticide application and Parkinson's disease. However, for spouses of private applicators, there were no results with confidence intervals that did not include unity. The exact nature of the pesticide exposure was not determined in this study. However, in Shrestha et al. (2020), to be described below, the authors extended their analysis to focus specifically on Parkinson's disease and individual pesticides.

Shrestha et al. [26] performed an analysis of the incidence of Parkinson's disease and specific pesticides, again using data from the Agricultural Health Study (AHS). Information on specific pesticides used by the study participants was obtained during study enrollment that included duration and frequency of use for pesticides. An applicator take-home questionnaire was also employed. This study focused on the 50 pesticides for which detailed information on duration and frequency of use were collected either at enrollment or in the take-home questionnaire. In addition, supplemental questionnaires were filled out by the study participants. This analysis used information collected at Phase 2 (conducted 2 to 10 years after enrollment with a 5-year average). Participants were asked about pesticide use in the most recent year. Potential cases of PD were identified by self-report in all AHS surveys as well as by linkage to the National Death Index and state death registries. Self-reported PD cases in Phase 2 of the study were confirmed by movement disorder specialists, via structured clinical examinations and medical records with an 84% confirmation rate (compared to self-report). Self-reported prevalent cases of PD were excluded from the analysis. After exclusions for lack of information on age at diagnosis, cases without supporting PD symptoms or medications and those providing inconsistent information on questionnaires, there were 491 cases of PD for analysis. The study population for the analyses comprised 37,284 male applicators for analyses where sufficient information was available on frequency and duration of use, with 372 cases of PD. The investigators used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (95% CI) to examine possible associations between pesticide use and incident PD. Adjustments were made for age, state of residence, smoking status, and education. Results for use of paraquat and PD shown as hazard ratio (HR) and 95% confidence interval (95% CI)—with a total of 87 cases of PD—are shown below from Shrestha et al. (2020, Table 2, p. 22):

HR = 1.09 (95% CI: 0.84-1.19)

Results for a duration-of-use analysis of paraquat and PD by number of lifetime days using the herbicide are shown in the following table, adapted from Shrestha et al. (2020, Table 4, p. 28):

Lifetime Days	No PD/PD	HR (95% CI)
Never Use	15305/188	Reference
>0-≤289	961/13	1.03 (0.58-1.81)
>289-≤1232	975/18	1.42 (0.86-2.33)
>1232	960/9	0.74 (0.37-1.49)
p-value trend		0.25

No exposure-response relationship was observed between use of paraquat and PD.

Tomenson and Campbell [24] is the report of a cohort mortality analysis of workers exposed to paraquat on a daily basis because they worked at four plants in the United Kingdom that manufactured the herbicide between 1961 and 1995. Workers were followed for mortality through December 31, 2017 and thus represents an updated study of paraquat production workers published in 2011 (31). Both this and the previous study were funded by Syngenta, a producer of paraquat. Vital status of cohort members—926 males and 42 females—and causes of death were obtained from records of the National Health Service (NHS). Observed numbers of deaths were compared with expected numbers based on national (England and Wales) mortality rates as well as local mortality rates in an additional analysis. Standardized mortality ratios (SMRs) and 95% confidence intervals (95% CI) were calculated. For Parkinson's disease, the authors analyzed both that disease as the underlying cause of death as well as mentions of PD on the death certificate. The "mentions" analysis is an indication of incidence rather than mortality. Results for exposure to paraquat and Parkinson's disease in workers exposed at levels—according to the authors—as comparable to that of a paraquat sprayer or mixer/loader are shown in the

following table adapted from Tomenson and Campbell (2021, Table 2, p. 4):

Parkinson's Disease	Observed Deaths	SMR (95% CI) England & Wales	SMR (95% CI) Local
Underlying Cause of Death	2	0.60 (0.07-2.17)	0.67 (0.08-2.43)
Mentioned	4	0.67 (0.18-1.72)	0.68 (0.19-1.75)

As the authors note, there is no evidence of increased mortality or incidence from Parkinson's disease in this cohort of paraquat workers.

Other Epidemiological Studies of Parkinson's Disease and Pesticides

Hugh-Jones et al. [18] is the report of a study of the incidence (actually, prevalence) of PD in the state of Louisiana as measured by hospital discharge diagnoses and organized by zip codes in relation to local agricultural crops, pesticides, and aquifer recharge. As such, this is an ecologic study and thus subject to the ecologic fallacy and other limitations of this study design (28). The investigators collected all hospital discharge diagnoses of PD in Louisiana during the years 1999-2012 and then grouped by the zip code of the patient provided to the hospital. This information, along with population estimates by zip code, permitted the calculation of zip-code specific incidence—actually, prevalence—rates of PD in Louisiana during the study period. Estimates of paraquat use in Louisiana were found in the U.S. Geological Survey Pesticide National Synthesis Project database by parish. Note that a parish in Louisiana is the same as a county in other U.S. states. The authors compared diagnoses of PD in parishes to the type of crop grown in those same parishes and inferred that "high-risk PD areas match closely with arbor-pastoral areas of the state that are of deciduous and evergreen forests" (Hugh-Jones et al. (p. 11). The authors then claimed that this correlation—i.e., between PD prevalence and arboreal-pastoral areas—justifies a conclusion that "the major risks identified came from the pesticides used in relation to areas of forestry, woodlands, and pastures and were from 2,4-D and from paraquat and chlorpyrifos" (18, p. 14) despite the fact that the authors did not know how much paraquat, or for that matter, whether paraquat had ever been used in the parishes. Furthermore, the authors did not know whether the patients with PD had lived in the zip code listed on their discharge diagnosis for years, months, or days. Simply put, the conclusion stated by the authors—regarding PD and paraquat—is not valid.

Paul et al. [19] is the report of an ecologic study undertaken in California's Central Valley. The authors utilized paraquat application records from the California Department of Pesticide Regulation, then linking those records with the location of cases and controls in an established case-control study of Parkinson's disease. Given the ecologic study design, it is unclear whether the study participants were exposed to paraquat. Distance of residences and workplaces from the paraquat application and amount of paraquat applied were the only clues to potential exposure. Parkinson's disease diagnoses were confirmed by movement disorder physicians. The authors adjusted for several other potential pesticide exposures (using the same ecologically driven estimation procedure). Adjustments were also made for age, gender, race, study wave and index year. Odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated using unconditional logistic regression models. The authors reported at least 190 odds ratios and 95% CI estimates. Of these, the authors chose to feature in their abstract exactly 4 examples, all of which revealed odds ratios greater than 1.0 and 95% confidence intervals that did not include 1.0. The authors did not report in their abstract or in their description of the results the 77 ORs (41% of the total number) for which the 95% confidence intervals did include 1.0. The authors did not correct for multiple comparisons nor did they explain why that method was not employed given the large number of comparisons made of the same basic information. In the end, the authors concluded that their study "provides further indication that paraquat dichloride exposure increases the risk of Parkinson's disease" (Paul et al. 2024, p. 1). One final observation is relevant to a critical assessment of this paper. Two of the authors of the paper are involved in the paraquat-Parkinson's disease litigation, serving as expert witnesses for the plaintiffs.

Reviews and Meta-Analyses

Ball et al. [5] is a narrative review of the relationship between the environment and Parkinson's disease, including heavy metals, pesticides, and illicit substances. On the topic of pesticides and herbicides in particular, the authors write "Parkinson's disease associated risk and herbicide exposure are still unclear" (5, p. 4). In addition, the authors write that "individual herbicide action has not been identified as causative" (5, p. 4).

Gunnarsson and Bodin [8] is the report of a systematic review and meta-analysis of occupational exposure to pesticides (as well as electromagnetic fields and metals) and neurodegenerative diseases, including Parkinson's disease, amyotrophic lateral sclerosis, and Alzheimer's disease. For pesticides and Parkinson's disease, the authors analyzed 24 epidemiological studies spanning 1992 to 2017. The result was a meta-relative risk (mRR) = 1.66 (95% CI: 1.42-1.94) with prominent heterogeneity ($I^2 = 74.2\%$) and positive publication bias ($p = 0.026$). No analysis for specific pesticides, including paraquat, was reported.

McKnight and Hack [12] is a narrative review of toxins and Parkinson's disease. On the topic of paraquat and Parkinson's disease, the authors cite one review [32] and one study [33] and claim that paraquat "has been associated with idiopathic Parkinson's disease through several case-control studies" but make no claim of causation.

DeMiranda et al. [13] is a narrative review outlining an environmental research agenda designed to prevent Parkinson's disease by identifying and acting on modifiable risk factors. The authors do not address paraquat specifically but claim that there is "strong

evidence that agricultural pesticide applicators are at increased risk."

Nabi and Tabassum [4] is a narrative review of the role of environmental toxicants on neurodegenerative disorders. According to the authors, the effect of paraquat on Parkinson's disease is limited to a single mouse study (34) and a mouse molecular study (35). No causal claim is made regarding paraquat and Parkinson's disease. In fact, the authors write that, at best, pesticides are a possible hazard without singling out paraquat.

Vellingiri et al. [14] is a narrative review of pesticides and Parkinson's disease. The authors write that "from the data, evidences [sic] are inconsistent and it is necessary to unwind the specific pesticide compounds associated with Parkinson's disease" (p. 3).

Sharma and Mittal [15] is a recent review of the possible relationship between exposure to paraquat and Parkinson's disease. The paper is entitled "Paraquat (herbicide) as a cause of Parkinson's Disease," although the authors do not make a causal claim in the text. The review focuses on various mechanistic considerations and cite only 2 out of a possible 27 human studies, neither of which reveals a statistically significant increase in PD given exposure to paraquat and both of which have been evaluated as methodologically inadequate (Weed, 2021). Nevertheless, the authors conclude from only 7% of the available epidemiological evidence that "Parkinson's disease (PD) is more likely to develop among people exposed to paraquat over an extended period of time, according to epidemiologic studies" (15, p. 4). Their claim is demonstrably false given the results of the entire body of epidemiological evidence including the critically important AHS results (25) described above.

Organizational Reports and Statements

The U.S. Environmental Protection Agency website (accessed 10.7.2023 and last revised 7.6.2023) states that "EPA has not found a clear link between paraquat exposure from labeled uses and adverse health outcomes such as Parkinson's disease and cancer." This conclusion emerged from a systematic review performed by the USEPA [27].

Conclusion

With the results of the most recent analyses of the possible relationship between exposure to paraquat and Parkinson's disease in hand, there is no compelling scientific argument for claiming that an association exists much less a causal association. The justification for this conclusion comes primarily from the fact that these epidemiologic studies examined not only general population groups but especially occupationally exposed populations and found no statistically significant increased risk and no evidence of an exposure-response relationship. In the absence of these key causal considerations, the fact that these studies contribute to the inconsistency of the entire epidemiologic database, nonexistent risk increases and dose-response relationships, also reviewed elsewhere as well as a lack of organizational support for causation [9], a lack of experimental evidence as defined by A.B. Hill [32], and the absence of a similar—analogous—example in the practice of causal inference [33], there is no scientific justification for a causal claim.

Scientific inquiry into paraquat and Parkinson's disease relies upon the fundamental principles of testability, replicability, and uncertainty with the ultimate goal being the identification of the best explanation given the application of well-established methods of causal inference to the available evidence. With these principles in mind, the evidence is clear. The basic hypothesis—does paraquat cause Parkinson's disease—has been tested and found wanting. The primary reasons for this conclusion include significant uncertainty due to imprecise exposure measurements, confounding, and bias, all challenges to the validity of epidemiological studies. Anyone willing to predict the results of the next epidemiologic study—count me out—would be unjustified in arguing that somehow all or nearly all of the previous studies were somehow wrong. In addition, the recent Agricultural Health Study [26] is about as good an epidemiologic study can be performed in these situations, and it was convincingly negative.

The most recent study of paraquat and Parkinson's disease, undertaken by investigators closely linked to the ongoing litigation, should be interpreted in the light of the problem of litigation-sponsored science [19]. While much has been discussed about the role that industry can play in the sponsoring of and impact on epidemiologic research [34-37], much less has been written about the fact that the attorneys who represent the plaintiffs in legal actions also represent a well-funded industry with the sole mission of winning cases against corporations. I will not discuss this matter in more detail here but the fact that two of the authors of the Paul et al. paper [19] are involved in the litigation as plaintiffs' experts cannot be ignored.

Simply put, the best explanation of the evidence available today is that a causal association has not been established, a conclusion the U.S. Environmental Protection Agency [17] agrees with. This best explanation comes ultimately from the application of well-established methods designed for the purpose of evaluating causality.

Several arguments that could be perceived as challenges to the conclusion need to be addressed. First, is it possible that the future could change the situation and move the arrow closer to causation? Predicting the future is a futile endeavor here. Put another way, it is at least, perhaps more likely, that the pattern already observed will continue furthering cementing the "not causal" conclusion. Scientists are good at many things but reading tea leaves is not one of them. If there were a fantasy league for scientific findings of causation, a safe bet would be "no;" things are unlikely to change in the future.

Second, anyone reading the available literature on this topic will be impressed with how often authors write that they believe pesticides have something to do with occurrence of Parkinson's disease. But even if we were to provisionally accept this vague hypothesis as possibly correct, it is illogical to conclude that, therefore, paraquat has something to do with the occurrence of Parkinson's disease. Pesticides are organized as insecticides, herbicides, and fungicides, each with dozens if not scores

of individual members. The sheer diversity of chemical structures, personal and professional use characteristics—e.g. whether protective equipment was used, how often applications occurred, etc.—and vastly different toxicological properties puts this challenge to bed.

Third, given that the evidence does not warrant a causal claim, it may seem reasonable to ask why there are no clear statements to that effect in the published literature. The answer is straightforward. The "system" of scientific discovery in biomedicine does not work that way. Reviews of Parkinson's disease do not typically list all the things that do not cause the disease. Rather, the authors describe what factors have been established as causal (if any), those deemed to be risk factors and those factors that have been studied but have not reached a level of certainty regarding risk. Paraquat falls into this last category. After decades of study, paraquat remains on the list as a factor of interest but not a causal factor.

Conflict of Interest Statement

I have no conflicts of interest to disclose.

Funding

This paper was conceived and written with no funding from any individual, private or public organization.

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