Neurotoxicology 86 (2021) 180–184

Contents lists available at ScienceDirect

Neurotoxicology

journal homepage: www.elsevier.com/locate/neuro

Does paraquat cause Parkinson's disease? A review of reviews

Douglas L. Weed

DLW Consulting Services, LLC, 1302 N. Oak Forest Rd., Salt Lake City, UT, 84103, USA

ARTICLE INFO

Edited by Dr. P. Lein and Dr. R. Westerink

Keywords:
Paraquat
Parkinson's disease
Causality
Systematic reviews
Methodology

ABSTRACT

To examine the extent to which a consensus exists in the scientific community regarding the relationship between exposure to paraquat and Parkinson's disease, a critical review of reviews was undertaken focusing on reviews published between 2006 and the present that offered opinions on the issue of causation. Systematic searches were undertaken of scientific databases along with searches of published bibliographies to identify English language reviews on the topic of paraquat and Parkinson's disease including those on the broader topic of environmental and occupational risk factors for Parkinson's disease. Of the 269 publications identified in the searches, there were twelve reviews, some with meta-analyses, that met the inclusion criteria. Information on methods used by the reviewers, if any, and source of funding was collected; the quality of the reviews was considered. No author of any published review stated that it has been established that exposure to paraquat causes Parkinson's disease, regardless of methods used and independent of funding source. A consensus exists in the scientific community that the available evidence does not warrant a claim that paraquat causes Parkinson's disease. Future research on this topic should focus on improving the quality of epidemiological studies including better exposure measures and identifying specific mechanisms of action. Future reviews of emerging evidence should be structured as systematic narrative reviews with meta-analysis if appropriate.

1. Introduction

Interest in the relationship between exposure to the herbicide, paraquat, and the occurrence of Parkinson's disease (PD) has been growing ever since the hypothesis was introduced in the mid-1980's (Calne and Langston, 1983; Snyder and D'Amato, 1985). Paraquat is not the only factor of interest to the scientific community which has been examining whether a wide range of environmental, occupational, lifestyle, and genetic factors increase the risk of if not cause PD (Wirdefeldt et al., 2011; Ascherio and Schwarzschild, 2016; Breckenridge et al., 2016; Marras et al., 2019). Paraquat, however, has become a special focus of research in part because the paraquat molecule is structurally similar to a chemical—N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine or MPTP—used to induce PD in experimental animal models (Vaccari et al., 2017). In addition, PD has seen rising prevalence rates especially among the elderly in an aging population (Dorsey et al., 2018). Some have predicted that the number of PD cases in North America will rise to 1,238,000 by 2030 from 680,000 in 2010 (Marras et al., 2018). Simply put, PD is an important medical and public health problem. As Chen (2016, p. 919) has recently noted, PD "presents substantial physical, emotional, and economic burdens to patients and family members as well as to society at large." It follows that the identification of a modifiable risk factor—a cause—could represent progress in the fight against this disease.

The scientific community is not the only place where the paraquat-Parkinson's disease relationship is of current concern. Recently, there has been an increasing number of civil lawsuits brought to the courts in the United States regarding paraquat and Parkinson's disease. At the center of the scientific and legal communities' interests is this basic scientific question: does exposure to paraquat cause Parkinson's disease? The purpose of this paper is to provide insight into an answer to this question focusing primarily upon published reviews, systematic reviews, and meta-analyses where authors have opined on causation.

2. Methods

A review of reviews was undertaken, focusing primarily on publications where epidemiological studies on paraquat and PD were collected, described, and interpreted along with discussions of biological plausibility, that is, the mechanism by which paraquat could induce PD at the molecular level. Decisions about causation have, in recent decades, been made in review papers—which may include meta-analyses—more often than in the discussion section of individual studies. This reflects the importance the toxicological community has placed on the

E-mail address: douglaslweed@aol.com.

https://doi.org/10.1016/j.neuro.2021.08.006
Received 7 June 2021; Received in revised form 9 August 2021; Accepted 10 August 2021
Available online 13 August 2021

objective process of reviewing the literature using systematic review methodology (Birnbaum et al., 2013; Hoffmann et al., 2017). As Hoffmann et al. (2017, p. 2551) note, systematic reviews provide a "transparent, methodologically rigorous and reproducible means of summarizing the available evidence on a precisely framed research question."

A comprehensive search of the English-language literature was conducted in PubMed and EMBASE to identify reviews, systematic reviews, and meta-analyses that evaluated the relationship between paraquat and PD. Search terms included "pesticides," "paraquat," and "Parkinson's disease." In addition, reference lists of reviews identified in the search were examined for additional publications. Identified was a combined total of 275 potentially relevant articles, including 6 duplicates, leaving 269 unique articles. From an examination of titles and abstracts, 24 publications were selected for full text review. After this review and including those identified from reference lists, 12 publications were selected for inclusion. Of these, five were focused solely on the paraquat-PD relationship Dinis-Oliveira et al. (2006); Berry et al. (2010); Mandel et al. (2012); Tangamornsuksan et al. (2019), and Vaccari et al. (2019) and seven examined the broader issue of pesticides and PD, including but not limited to paraquat as well as other potential environmental and lifestyle risk factors Brown et al. (2006); Wirdefeldt et al. (2011); Freire and Koifman (2012); Van der Mark et al. (2012); Goldman (2014); Ascherio and Schwarzschild (2016), and Breckenridge et al. (2016). Excluded were reviews that did not specifically address the paraquat-PD relationship other than those that provided conclusions on the extent to which specific pesticides are associated with Parkinson's disease. In addition, attention was paid to the so-called "grey literature," that is, reports and websites of relevant organizations. Finally, a separate search was performed looking for any epidemiological study on paraquat and PD published after 2019, the year the most recent reviews were published. No studies were identified other than a single ecologic study from which causal conclusions are inappropriate given the ecologic fallacy (Hugh-Jones et al., 2020; McLaren and Hawe, 2005) as well as an updated cohort mortality study of paraquat production workers (Tomenson and Campbell, 2021) that revealed no evidence of an increased risk with a standardized mortality ratio (SMR) of 0.67 (95 % CI: 0.18–1.72).

From each review paper included, the following information was collected: author and year of publication, the number and citations of studies reviewed, including information on outcome measures, study design, and the quality of studies as assessed by authors of the three most recent systematic reviews (Breckenridge et al., 2016; Vaccari et al., 2019; and Tangamornsuksan et al., 2019). Also determined was whether a methods section appeared in the publication along with the methods used, the conclusion regarding the paraquat-PD relationship, and the source of funding for the research. Descriptive information other than conclusions can be found in Table 1 and information on the epidemiological studies can be found in Table 2.

3. Results

Twelve reviews have examined and interpreted the evidence on paraquat and PD. Nine, published between 2006 and 2012, are narrative reviews Dinis-Oliveira et al. (2006); Brown et al. (2006); Berry et al. (2010); Wirdefeldt et al. (2011); Freire and Koifman (2012); Mandel et al. (2012); Van der Mark et al. (2012); Goldman (2014); Ascherio and Schwarzschild (2016). Three, published between 2016 and 2019, are systematic reviews and meta-analyses Breckenridge et al. (2016); Tangamornsuksan et al. (2019), and Vaccari et al. (2019). Funding sources for the reviews include public and private organizations. Three reviews Mandel et al. (2012); Breckenridge et al. (2016), and Wirdefeldt et al. (2011), were funded by a corporation that manufactures and sells paraquat including one of the more recent systematic reviews with an accompanying meta-analysis. The two other systematic reviews, published in 2019, were funded by a university, a non-profit organization, and a government agency Tangamornsuksan et al. (2019) and Vaccari et al. (2019).

As shown in Table 3, no authors of the twelve reviews conclude that paraquat causes Parkinson's disease. On the other hand, several authors, including those of the two most recent publications, conclude that an association exists between exposure to paraquat and Parkinson's disease. Association, however, is not the same as causation as Bradford-Hill made clear in his classic paper (1965).

The conclusions of the reviews are consistent with organizational statements, such as one found on the website of the National Institute of Environmental Health Sciences which states only that the "evidence, from animal and human studies, suggests that exposure to certain types of pesticides can increase a person's risk of developing Parkinson's disease" and that "the exact cause of Parkinson's disease is unknown" (@ www.niehs.nih.gov/health/topics/conditions/parkinson/index.cfm). Similarly, the Mayo Clinic states that "exposure to certain toxins or environmental factors may increase the risk of later Parkinson's disease, but the risk is relatively small" without specifying paraquat (@ www.mayoclinic.org/diseases-conditions/parkinsons-disease/symptoms-causes/syc-20376055).

The most recent systematic reviews provide insight into reasons for the authors' decisions not to conclude that paraquat causes PD. Breckenridge et al. (2016), for example, in their effort to examine the role of cigarette smoking, rural living, well-water consumption, farming and

Table 1
Characteristics of Reviews of Paraquat and Parkinson's Disease (2006–2019).

Author, Year	Type of Review	Methods Section?	Methods Used	Funding	Studies Included
Brown et al., 2006	Narrative	Yes	"Weight of Evidence"	UK Dept Environment, Food, Rural Affairs	4
Dinis-Oliveira et al., 2006	Narrative	No	None	None Described	2
Berry et al., 2010	Narrative	No	None	Advisor to Industry	7
Wirdefeldt et al., 2011	Narrative	No	None	Syngenta	15
Freire and Koifman, 2012	Narrative	No	None	Fogarty at NIH	9
Mandel et al., 2012	Narrative	No	None	Syngenta	18
Goldman et al., 2012	Narrative	No	None	International Parkinson's Foundation	11
Breckenridge et al., 2016	Systematic Review + Meta-Analysis	Yes	Study Quality, Bradford-Hill + Meta-Analysis	Syngenta	19
Tangamornsuksan et al., 2019	Systematic Review + Meta-Analysis	Yes	NOS, Meta-Analysis	Naresuan University + Fulbright	15
Vaccari et al., 2019	Systematic Review + Meta-Analysis	Yes	MOOSE + GRADE + Bradford-Hill + Meta-Analysis	Brazilian Ministry of Science + Technology	17

UK = United Kingdom, NIH = National Institutes of Health, NOS = Newcastle Ottawa Scale, MOOSE = Meta-Analysis of Observational Studies in Epidemiology Statements.

Table 2
Epidemiological Study Results: Paraquat and Parkinson's Disease with Quality Assessments.

Year	Author	Study Design	RR (95 % CI)	Exposure	Quality[1]	Quality[2]	Quality[3]
1992	Semchuk et al., 1992	Case-Control	6.03 (0.24–149.2)	Prevalent Cases			4
1994	Hertzman et al., 1994	Case-Control	1.25 (0.34–4.63)	General Pop	Tier 2	High	4
1996	Seidler et al., 1996	Case-Control	2.98 (0.12–73.29)	Prevalent Cases			5
1997	Liou et al., 1997	Case-Control	3.22 (2.41–4.31)	Use	Tier 2	High	4
1999	Kuopio et al., 1999	Case-Control	1.21 (0.28–5.13)	Use	Tier 2		
2001	Engel et al., 2001		0.80 (0.50–1.30)	Ever Use	Tier 2		
2004	Elbaz et al., 2004	Case-Control	1.04 (0.65–1.66)	Use, Men	Tier 2		
2005	Firestone et al., 2005		1.67 (0.22–12.76)	Occupational Men	Tier 1		
2007	Kamel et al., 2007	Cohort	1.00 (0.50–1.90)	Incident PD Cases	Tier 2		
2007	Kamel et al., 2007	Cohort	1.80 (1.00–3.40)	Prevalent PD Cases	Tier 2		
2008	Dhillon et al., 2008	Case-Control	3.50 (0.40–31.60)	Ever	Tier 2	High	
2009	Costello et al., 2009		1.01 (0.71–1.43)	Only 1974–1999	Tier 2		
2009	Elbaz et al., 2009	Case-Control	1.20 (0.70–2.10)	Use, Men	Tier 2	Low	4
2010	Gatto et al., 2010		1.10 (0.75–1.63)	Use	Tier 2		
2009	Tanner et al., 2009	Case-Control	2.80 (0.81–9.72)	Use	Tier 2		4
2010	Firestone et al., 2010	Case-Control	0.90 (0.14–5.43)	Men	Tier 1		
2011	Wang et al., 2011		1.50 (1.03–2.18)	Residential + Occupational	Tier 2		
2011	Rugbjerg et al., 2011	Case-Control	1.01 (0.20–5.01)	Exposure	Tier 2	High	
2011	Tanner et al., 2011	Case-Control	2.50 (1.40–4.70)	Ever	Tier 2	Low	5
2011	Tomenson and Campbell, 2011		0.32 (0.01–1.76)	Male Production Workers	Tier 2		
2012	Goldman et al., 2012		2.60 (1.30–5.00)	Ever, Men	Tier 2		
2012	Lee et al., 2012	Case-Control	1.36 (1.02–1.81)	Residential + Workplace	Tier 2		5
2014	Van der Mark et al., 2014	Case-Control	1.13 (0.73–1.76)	Prevalent Cases			4
2017	Brouwer et al., 2017	Case-Control	0.94 (0.72–1.22)	Ecologic Exposure		High	
2017	Sanders et al., 2017	Case-Control	1.54 (1.24–1.92)	Ecologic Exposure		Low	

[1] Assessed by Breckenridge et al. (2016) where quality of a Tier 1 study > Tier 2.
[2] Assessed by Vaccari et al. (2019) where "High" = High Risk of Bias and "Low" = Low Risk of Bias.
[3] Assessed by Tangamornsuksan et al. (2019) where quality of a 5 > 4.

pesticide use, note that the epidemiological studies on paraquat and PD are inconsistent. Tangamornsuksan et al. (2019) note that the epidemiological studies lack objective measurements of paraquat exposure. In addition, they write that a mechanism of action lacks sufficient evidence, pointing out that the animal studies were of short duration using high doses on young animals and protocols were not clearly creditable. The results of their meta-analysis for case control studies with incident cases and lacking data from the single cohort study revealed a summary odds ratio of 1.41 (95 % CI: 1.08–1.85). Vaccari et al. (2019) conclude that the association between paraquat and PD is weak with a meta-analytic result of 1.25 (95 % CI: 1.01–1.55). In addition, they conclude that a dose-response relationship has not been established, and the epidemiological studies are too few and of relatively low quality. Vaccari et al. (2019) recommend that better exposure measurements, perhaps through biomonitoring studies, be undertaken. Finally, having examined the animal studies, they write that neither the Bradford-Hill criteria of biological plausibility nor coherence of evidence are fulfilled.

Combining these recent assessments into terms found in the classic version of the Bradford-Hill criteria of (Hill, 1965), strength of association, consistency of association, dose-response, biological plausibility, and coherence are not satisfied. In such situations, by analogy with previous assessments of potential environmental causes of disease (Weed, 2018a), causality is not an appropriate, i.e., justified, scientific conclusion. The fact that the studies were judged to be of relatively low quality using objective study quality tools in the Vaccari et al. (2019) review adds considerable weight to this overall assessment.

4. Discussion

The assessment of causation is a complex process involving a family of methods, including study design and statistical methods, as well as the methods used to synthesize evidence. These research synthesis methods include narrative reviews, the systematic narrative review, meta-analysis, and the so-called "causal criteria." Added to these methods are those used to evaluate the quality of studies and to assess bias.

All the methods mentioned are represented in the reviews examined here. The recent systematic review and meta-analysis by Vaccari et al. (2019) is a good example. The Vaccari et al. (2019) review also represents the evolution of methods used in causal assessments that has a long and illustrious history. To cite just a few examples, the authors employed the systematic narrative review the origin of which can be traced to the late 1980's (Mulrow, 1987, 1994) and the Bradford-Hill criteria from 1965. The formal bias assessment method used in that same review is a more recent development popularized by the National Toxicology Program's Office of Health Assessment and Technology or "OHAT" (Birnbaum et al., 2013; Vaccari et al., 2017).

What the reader could glean from this review of reviews in addition to the fact a causal conclusion regarding paraquat and Parkinson's disease is not warranted is that the biomedical community is increasingly committed to making causal assessments as objectively as possible using systematic reviews. This methodologic maxim has been discussed more extensively in oncology (Weed, 2018b) and nutrition science (Lichtenstein et al., 2008) among other disciplines including toxicology (Hoffmann et al., 2017). Systematic reviews with or without meta-analysis are preferred over narrative reviews which tend to reflect the author's subjective interpretation of the evidence and are prone to selection bias (Walker and Hopkins, 2018). Systematic reviews are defined as reviews with a clearly formulated research question that use explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies included in the review (Volmink et al., 2004).

Future assessments of the possible link between paraquat and Parkinson's disease should employ rigorous systematic review methods rather than narrative reviews that rely more heavily on an author's judgment. By no means am I suggesting that judgment is not involved in causal assessments but, as a mental facility, judgment is difficult to define and should not trump the results of methods applied appropriately to the available evidence (Weed, 2007). Furthermore, I am not suggesting that narrative reviews and commentaries may not have legitimate arguments to make about specific concerns. There is room for them in the published literature if their limitations (and strengths) are made clear. What remains unclear in published accounts of the paraquat-PD relationship is a good estimate of the risk if paraquat were a causal factor. The Tangamornsuksan et al. (2019) meta-analysis

Table 3
Conclusions of Reviews on Paraquat and Parkinson's Disease.

Brown et al. (2006, p. 162)	"In conclusion, the weight of evidence is sufficient to conclude that a generic association between pesticide exposure and PD exists, but it is not sufficient to conclude that this is a causal relationship exists for any particular pesticide compound…"
Dinis-Oliveira et al. (2006, p. 1118)	"Despite the suggestive results of epidemiological investigations, some of the data are equivocal and more detailed information about the association between PQ exposure and risk for PD is needed."
Berry et al. (2010, p. 1123)	"The epidemiological and clinical evidence that PQ may favor the onset of PD is inconclusive."
Wirdefeldt et al. (2011, p. S1)	"Evidence that one of several pesticides increase PD risk is suggestive but further research is needed to identify specific compounds that may play a causal role."
Freire and Koifman (2012, p. 969–70)	"Epidemiologic studies published over the past decade have added to the evidence of an association between pesticide exposure and PD, but a causal relationship has not yet been definitely established."
Mandel et al. (2012, p. 391)	"…without significant improvements on the existing research, it will not be possible to reach a definitive conclusion on the relationship between paraquat and PD."
Van der Mark et al. (2012, p. 346)	"Although classes of pesticides have been linked to PD, it remains important to identify the specific chemical responsible for this association."
Goldman (2014, p. 155)	"Epidemiologic, animal, and in vitro data strongly support associations with pesticides—specifically with rotenone, paraquat, and organochlorine compounds."
Ascherio et al. (2016, p. 1259)	"Overall, evidence that pesticide exposure increases Parkinson's disease risk is substantial, but the risk associated with specific compounds remains uncertain."
Breckenridge et al. (2016, p. 26)	"Overall, the epidemiological data are inconsistent across studies and collectively they do not support a conclusion that a causal relationship exists between exposure to paraquat and PD."
Tangamornsuksan et al. (2019, p. 236)	"Our analysis with new data re-affirms the association of paraquat use with PD. However, objective measurement of paraquat exposure was inadequate and future studies are need(ed) to focus on exposure assessment, disease progression and clinical manifestations thereby providing clues about the mechanism of this insidious disease."
Vaccari et al. (2019, p. 26)	"The relatively low estimates of risk and low quantity of evidence gathered by this systematic review (SR) and meta-analysis does not enable one to propose a definitive conclusion regarding a causal relationship between paraquat and PD."

estimated the odds to be 1.41 (95 % CI: 1.08–1.85) based primarily on four case-control studies. Vaccari et al. (2019), on the other hand, note that the odds of PD given paraquat exposure from the only cohort study was a non-significant 1.08 (95 % CI: 0.57–2.04) and 1.25 (95 % CI: 1.01–1.51) from case-control studies.

Another interesting observation from the collection of reviews published on paraquat and Parkinson's disease is that industry funding appears not have had an impact on the results. After all, the conclusion that the available evidence does not warrant a causal conclusion regarding paraquat and Parkinson's disease emerged independent of funding source. This fact represents a simple and single refutation of the perception, especially in epidemiology, that research funded by industry is necessarily biased (Pearce, 2008). That did not occur here. I am not suggesting that funding cannot have an influence, but it is important to remember that research funding comes from many sources, including corporations, non-governmental organizations, and government agencies each of which has "interests" that could potentially affect the scientific process.

One final comment is relevant. As mentioned earlier, there are civil lawsuits currently making their way through the U.S. legal system that allege, contrary to the scientific consensus described in this paper, that paraquat causes Parkinson's disease. Indeed, that scientific consensus presents a significant hurdle for the scientific experts hired by the attorneys representing the claimants, i.e., the plaintiffs. After all, those experts can only prevail if they can legitimately claim that the science to date on paraquat and Parkinson's disease represents a causal relationship in direct contrast to the consensus presented here. That will not be easy if objective—i.e., systematic—methods are employed. It is important to keep in mind that, in general, the role of scientific evidence and expertise in the courts is not any different than its role in the scientific community. As Stephen Breyer, a Supreme Court justice, has noted, legal decisions "should reflect a proper scientific and technical understanding so that the law can respond to the needs of the public" (Breyer, 2000, p. 2). Scientific experts are not engaged to evaluate evidence in ways not representative of the methods used in the peer-reviewed published literature; that is precisely what the well-known *Daubert* decision requires (Berger, 2000). As discussed here and revealed in the review of reviews above, the methods used to assess causation are complex, labor-intensive, and support the conclusion that, given the evidence to date, paraquat does not cause Parkinson's disease.

In conclusion, this review of review provides an up-to-date assessment of the state of the science on paraquat and Parkinson's disease in terms of the published reviews on this topic which has not been done since Breckenridge et al. (2016). Although objective assessments of the quality of the reviews described here was not undertaken, the most recent reviews are of superior quality to those published early on given that systematic approaches were used. If new studies of the potential relationship between paraquat and Parkinson's disease are published, then updates of these systematic reviews and meta-analyses will be required.

Funding

This research did not receive any specific grant or funding of any kind from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Ascherio, A., Schwarzschild, M.A., 2016. The epidemiology of Parkinson's disease: risk factors and prevention. Lancet Neurol. 15, 1257–1272.
Berger, M.A., 2000. The Supreme Court's trilogy on the admissibility of expert testimony. Reference Manual on Scientific Evidence, 2nd ed. Federal Judicial Center, Washington, D.C, pp. 9–38.
Berry, C., La Vecchia, C., Nicotera, P., 2010. Paraquat and Parkinson's disease. Cell Death Differ. 17, 1115–1125.
Birnbaum, L.S., Thayer, K.A., Bucher, J.R., Wolfe, M.S., 2013. Implementing systematic review at the National Toxicology Program: status and next steps. Environ. Health Perspect. 121, A108–109.
Breckenridge, C.B., Berry, C., Chang, E.T., Sielken Jr., R.L., Mandel, J.S., 2016. Association between Parkinson's disease and cigarette smoking, rural living, well-water consumption, farming and pesticide use: systematic review and meta-analysis. PLoS One 11, e0151841. https://doi.org/10.1371/journal.pone.0151841.
Breyer, S., 2000. Introduction. Reference Manual on Scientific Evidence, 2nd ed. Federal Judicial Center, Washington, D.C, pp. 1–8.
Brouwer, M., Huss, A., Van der Mark, M., Nijssen, P.C.G., Mulleners, W.M., Sas, A.M.G., van Laar, T., de Snoo, G.R., Kromhout, H., Vermeulen, R.C.H., 2017. Environmental exposure to pesticides and the risk of Parkinson's disease in the Netherlands. Environ. Int. 107, 100–110. https://doi.org/10.1016/j.envint.2017.07.001.
Brown, T.P., Rumsby, P.C., Capleton, A.C., Rushton, L., Levy, L.S., 2006. Pesticides and Parkinson's disease—is there a link? Environ. Health Perspect. 114, 156–164. https://doi.org/10.1289/ehp.8095.
Calne, D.B., Langston, J.W., 1983. Aetiology of Parkinson's disease. Lancet. 322, 1457–1459.
Chen, H., 2016. Are we ready for a potential increase in Parkinson incidence? JAMA Neurol. 73, 919–921.

Costello, S., Cockburn, M., Bronstein, J., Zhang, X., Ritz, B., 2009. Parkinson's disease and residential exposure to maneb and paraquat from agricultural applications in the Central Valley of California. Am. J. Epidemiol. 169, 919–926. https://doi.org/10.1093/aje/kwp006.

Dhillon, A.S., Tarbutton, G.L., Levin, J.L., Plotkin, G.M., Lowry, L.K., Nalbone, J.T., Shepherd, S., 2008. Pesticide/environmental exposures and Parkinson's disease in East Texas. J. Agromed. 13, 37–48. https://doi.org/10.1080/10599240801986215.

Dinis-Oliveira, R.J., Remiao, F., Carmo, H., Duarte, J.A., Navarro, A.S., Bastos, M.L., Carvalho, F., 2006. Paraquat exposure as an etiological factor of Parkinson's disease. Neurotoxicol. 27, 1110–1122.

Dorsey, E.R., Sherer, T., Okun, M.S., Bloem, B.R., 2018. The emerging evidence of the Parkinson pandemic. J. Parkinson Dis. 8, S3–S8. https://doi.org/10.3233/JPD-181474.

Elbaz, A., Clavel, J., Rathouz, P.J., Moisan, F., Galanaud, J.P., Delemotte, B., Alperovitch, A., Tzourio, C., 2009. Professional exposure to pesticides and Parkinson disease. Ann. Neurol. 66, 494–504. https://doi.org/10.1002/ana.21717.

Elbaz, A., Levecque, C., Clavel, J., Vidal, J.S., Richard, F., Amouyel, P., et al., 2004. CYP2D6 polymorphism, pesticide exposure, and Parkinson's disease. Ann. Neurol. 55, 430–434.

Engel, L., Checkoway, H., Keifer, M., Seixas, N., Longstreth, W., Scott, K., Hudnellh, K., Angerf, W.K., Camicioli, R., 2001. Parkinsonism and occupational exposure to pesticides. Occup. Environ. Med. 58, 582–589. https://doi.org/10.1136/oem.58.9.582.

Firestone, J.A., Smith-Weller, T., Franklin, G.M., Swanson, P.D., Longstreth, W.T., Checkoway, H., 2005. Pesticides and risk of Parkinson disease: a population-based case-control study. Arch. Neurol. 62, 91–95.

Firestone, J.A., Lundin, J.I., Powers, K.M., Smith-Weller, T., Franklin, G.M., Swanson, P. D., Longstreth, W.T., Checkoway, H., 2010. Occupational factors and risk of Parkinson's disease: a population-based case-control study. Am. J. Ind. Med. 53, 217–223. https://doi.org/10.1002/ajim.20788.

Freire, C., Koifman, S., 2012. Pesticide exposure and Parkinson's disease: epidemiological evidence of association. Neurotoxicology 33, 947–971.

Gatto, N.M., Cockburn, M., Bronstein, J., Manthripragada, A.D., Ritz, B., 2010. Well-water consumption and Parkinson's disease in rural California. Environ. Health Perspect. 177, 1912–1918. https://doi.org/10.1289/ehp.0900852.

Goldman, S.M., 2014. Environmental toxins and Parkinson's disease. Annu. Rev. Pharmacol. Toxicol. 54, 141–164. https://doi.org/10.1146/annurev-pharmtox-011613-135937.

Goldman, S.M., Kamel, F., Ross, G.W., Bhudhikanok, G.S., Hoppin, J.A., Korell, M., Marras, C., Meng, C., Umbach, D.M., Kasten, M., 2012. Genetic modification of the association of paraquat and Parkinson's disease. Mov. Disord. 27, 1652–1658. https://doi.org/10.1002/mds.25216.

Hertzman, C.M., Wiens, B., Snow, S., Kelly, S., Calne, D., 1994. A case-control study of Parkinson's disease in a horticultural region of British Columbia. Mov. Disord. 9, 69–75. https://doi.org/10.1002/mds.870090111.

Hill, A.B., 1965. The environment and disease: association or causation? Proc. Roy. Soc. Med. 58, 295–300.

Hoffmann, S., de Vries, R.B.M., Stephens, M.L., Beck, N.B., Dirven, H.A.A.M., Fowle III, J. R., Goodman, J.E., Hartung, T., Ian Kimber, I., Lalu, M.M., Thayer, K., Whaley, P., Wikoff, D., Tsaioun, K., 2017. A primer on systematic reviews in toxicology. Arch. Toxicol. 91, 2551–2575.

Hugh-Jones, M.E., Peele, R.H., Wilson, V.L., 2020. Parkinson's disease in Louisiana, 1999-2012: based on hospital primary discharge diagnoses, incidence and risk in relation to local agricultural crops, pesticides, and aquifer recharge. Int. J. Environ. Res. Public Health 17, 1584. https://doi.org/10.3390/ijerph17051584.

Kamel, F., Tanner, C., Umbach, D., Hoppin, J.A., Alavanja, M.C.R., Blair, A., Comyns, K., Goldman, S., Korell, M., Langston, J., 2007. Pesticide exposure and self-reported Parkinson's disease in the agricultural health study. Am. J. Epidemiol. 165, 364–374. https://doi.org/10.1093/aje/kwk024.

Kuopio, A.M., Marttila, R.J., Helenius, H., Rinne, U.K., 1999. Environmental risk factors in Parkinson's disease. Mov. Disord. 14, 928–939.

Lee, P.C., Bordelon, Y., Bronstein, J., Ritz, B., 2012. Traumatic brain injury, paraquat exposure, and their relationship to Parkinson disease. Neurology. 79, 2016–2066. https://doi.org/10.1212/WNL.0b013e3182749f28.

Lichtenstein, A.H., Yetley, E.A., Lau, J., 2008. Application of systematic review methodology to the field of nutrition. J. Nutrition 138, 2297–2306.

Liou, H.H., Tsai, M.C., Chen, C.J., Jeng, J.S., Chang, Y.C., Chen, S.Y., Chen, R.C., 1997. Environmental risk factors and Parkinson's disease: a case-control study in Taiwan. Neurology 48, 1583–1588. https://doi.org/10.1212/wnl.48.6.1583.

Mandel, J.S., Adami, H.O., Cole, P., 2012. Paraquat and Parkinson's disease: an overview of the epidemiology and a review of two recent studies. Regul. Toxicol. Pharmacol. 62, 385–392. https://doi.org/10.1016/j.yrtph.2011.10.004.

Marras, C., Canning, C.G., Goldman, S.M., 2019. Environment, lifestyle, and Parkinson's disease: implications for prevention in the next decade. Mov. Disord. 34, 801–811. https://doi.org/10.1002/mds.27720.

McLaren, L., Hawe, P., 2005. Ecological perspectives in health research. J. Epidemiol. Commun. Health. 59, 6–14.

Mulrow, C.D., 1987. The medical review article: state of the science. Ann. Intern. Med. 106, 485–488.

Mulrow, C.D., 1994. Rationale for systematic reviews. Br. Med. J. 309, 597–599.

Pearce, N., 2008. Corporate influences on epidemiology. Int. J. Epidemiol. 37, 46–53.

Rugbjerg, K., Harris, M.A., Shen, H., Marion, S.A., Tsui, J.K., Teschke, K., 2011. Pesticide exposure and risk of Parkinson's disease—a population-based case-control study evaluating the potential for recall bias. Scand. J. Work Environ. Health 27, 427–436. https://doi.org/10.5271/sjweh.3142.

Sanders, L.H., Paul, K.C., Howlett, E.H., Lawal, H., Boppana, S., Bronstein, J.M., Ritz, B., Greenamyre, J.T., 2017. Editor's highlight: base excision repair variants and pesticide exposure increase Parkinson's disease risk. Toxicol. Sci. 158, 188–198. https://doi.org/10.1093/toxsci/kfx086.

Seidler, A., Hellenbrand, W., Robra, B.P., Vieregge, P., Nischan, P., Joerg, J., 1996. Possible environmental, occupational, and other etiologic factors for Parkinson's disease: a case-control study in Germany. Neurology 46, 1275–1284. https://doi.org/10.1212/wnl.46.5.1275.

Semchuk, K.M., Love, E.J., Lee, R.G., 1992. Parkinson's disease and exposure to agricultural work and pesticide chemicals. Neurology 42, 1328–1335. https://doi.org/10.1212/wnl.42.7.1328.

Snyder, S.H., D'Amato, R.J., 1985. Predicting Parkinson's disease. Nature. 317, 198–199.

Tangamornsuksan, W., Lohitnavy, O., Sruamsiri, R., Chaiyakunapruk, N., Scholfield, C. N., Reisfeld, B., Lohitnavy, M., 2019. Paraquat exposure and Parkinson's disease: a systematic review and meta-analysis. Arch. Environ. Occup. Health 74, 225–238. https://doi.org/10.1080/19338244.2018.1492894.

Tanner, C.M., Ross, G.W., Jewell, S.A., Hauser, R.A., Jankovic, J., Factor, S.A., Bressman, S., Deligtisch, A., Marras, C., Lyons, K.E., 2009. Occupation and risk of parkinsonism. A multicenter case-control study. Arch. Neurol. 66, 1106–1113. https://doi.org/10.1001/archneurol.2009.195.

Tanner, C.M., Kamel, F., Ross, G.W., Hoppin, J.A., Goldman, S.M., Korell, M., Marras, C., Bhudhikanok, G.S., Kasten, M., Chade, A.R., et al., 2011. Rotenone, paraquat, and Parkinson's disease. Environ. Health Perspect. 119, 866–872. https://doi.org/10.1289/ehp.1002839.

Tomenson, J.A., Campbell, C., 2011. Mortality from Parkinson's disease and other causes among a workforce manufacturing paraquat: a retrospective cohort study. BMJ Open 1 (2), e00283. https://doi.org/10.1136/bmjopen-2011-000283.

Tomenson, J.A., Campbell, C., 2021. Mortality from Parkinson's disease and other causes among a workforce manufacturing paraquat: an updated retrospective cohort study. J. Occup. Med. Toxicol. 16, 20. https://doi.org/10.1186/s12995-021-00309-z.

Vaccari, C., El Dib, R., de Camargo, J.L.V., 2017. Paraquat and Parkinson's disease: a systematic review protocol according to the OHAT approach for hazard identification. Sys. Rev. 6, 98. https://doi.org/10.1186/s13643-017-0491-x.

Vaccari, C., El Dib, R., Gomaa, H., Lopes, L.C., de Camargo, J.L., 2019. Paraquat and Parkinson's disease: a systematic review and meta-analysis of observational studies. J. Toxicol. Environ. Health Part B. https://doi.org/10.1080/10937404.2019.1659197.

Van der Mark, M., Brouwer, M., Kromhout, H., Nijssen, P., Huss, A., Vermeulen, R., 2012. Is pesticide use related to Parkinson disease? Some clues to heterogeneity in study results. Environ. Health Perspect. 129, 340–347. https://doi.org/10.1289/ehp.1103881.

Van der Mark, M., Vermeulen, R., Nijssen, P.C.G., Mulleners, W.M., Sas, A.M., Van Laar, T., Brouwer, M., Huss, A., Kromhout, H., 2014. Occupational exposure to pesticides and endotoxin and Parkinson disease in the Netherlands. Occup. Environ. Med. 71, 757–764. https://doi.org/10.1136/oemed-2014-102170.

Volmink, J., Siegfried, N., Robertson, K., A. Gülmezoglu, M., 2004. Research synthesis and dissemination as a bridge to knowledge management: the Cochrane Collaboration. Bull. World Health Organ. 282, 778–783.

Walker, A., Hopkins, C., 2018. Systematic reviews and meta-analysis in rhinosinusitis: a critical review of reviews. Curr. Allergy Asthma Rep. 18 (8) https://doi.org/10.1007/s11882-018-0762-1.

Wang, A., Costello, S., Cockburn, M., Zhang, X., Bronstein, J., Ritz, B., 2011. Parkinson's disease risk from ambient exposure to pesticides. Eur. J. Epidemiol. 26, 547–555. https://doi.org/10.1007/s10654-011-9574-5.

Weed, D.L., 2007. The nature and necessity of scientific judgment. J. Law Policy 15, 135–164.

Weed, D.L., 2018a. Analogy in causal inference: rethinking Austin Bradford Hill's neglected consideration. Ann. Epidemiol. 28, 343–346.

Weed, D.L., 2018b. The need for systematic reviews in oncology. JNCI J. Natl. Cancer Inst. 110, 812–814.

Wirdefeldt, K., Adami, H.O., Cole, P., Trichopoulos, D., Mandel, J., 2011. Epidemiology and etiology of Parkinson's disease: a review of the evidence. Eur. J. Epidemiol. 26, S1–S58. https://doi.org/10.1007/s10654-011-9581-6.