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LETTER TO THE EDITOR

Response to: Neurotoxicity of paraquat and paraquat-induced Parkinson's disease

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Dear Editor,

We are pleased that Cook *et al*[1] have taken interest in our Mini Review article[2] and appreciate the opportunity to respond to their concerns. However, it is unfortunate that Cook *et al* did not fully grasp the purpose of our review or the theory behind it. The primary purpose of our manuscript was to apply a multifactorial theory approach in our review of applicable literature on the etiology of idiopathic Parkinson's disease (PD) in relation to paraquat (PQ) exposure. We took specific aim at PQ herbicide as we presented evidence and adduced hypotheses on its relation to the pathology of PD at a sub-cellular level and potential exposure routes through a varied environmental context.

The main critique from Cook *et al* is directed toward the second part of our review, the environmental context. Of key importance in this matter is the body of meta-analytical research showing significant risk association between PQ use or exposure and the onset or increased risk of developing PD. For example, Pezzoli and Cereda[3] identified PQ as a significantly associated factor for the onset of PD with a 2.2-fold increase in risk among individuals who had ever used the herbicide. Ritz *et al*[4] provide a recent review of gene–environment interactions in the etiology of PD including the factors that implicate PQ.

Much of the debate that is used to address discrepancies from laboratory research is based on unifactorial approach assuming a simple or singular cause. Our review of the literature using the multifactorial approach allows us to establish a number of hypotheses in consideration of environmental factors that may have been previously overlooked through the unifactorial approach. We postulate a pathology that requires low-dosage exposure, an increased risk in onset of PD if low-dose exposure occurs for an extended time, and multiple causes are implicated in the identified risk and incidence.

We do not claim that our review gives an exhaustive review of all literature concerning relations between PQ and PD. We certainly omitted numerous papers during the review and editing process as is the norm of practice. The nature of the problem is outlined in our review, where we state that 'cross-study results are somewhat inconsistent, which leaves a degree of uncertainty in the divide between correlation and causation' (p. 497). Hence, we did not neglect to mention studies that demonstrate no effect of PQ in relation to PD as Cook *et al* claim in their letter, but clearly recognize that there is disagreement. For example, we reference Jackson-Lewis *et al*[5] who note that the nigrostriatal (dopamine) system seems to be unaffected in the laboratory animal studies included in their review. Hence, we fully understand and give explicit examples of inconsistencies between laboratory-based studies into the potential linkages between PQ and PD. We would like to give assurances to Cook *et al* that there was nothing untoward in our approach as we reformulated the problem using multifactorial theory to examine active areas of research implicating PQ to PD.

There are two possible directions when there is disagreement between studies. First, we can ignore contrary data. However, this seems unwise generally and could even be unethical in terms of the potential harm that may be caused inadvertently by release of PQ into the environment. However, there may be important reasons for ignoring results, including faulty data, problems with auxillary hypotheses, misapplication of statistics, faulty logic, or faulty experimentation. The second direction is to change the theory and reformulate the hypotheses in relation to the new theory. We adopt the second direction in our review. We re-emphasize a point from our paper in light of this approach that the 'significance of meta-analysis indicating higher incidence of PD development in areas subject to PQ exposure (eg, farmland and use in undeveloped nations) requires explanation' (p. 504).

Cook *et al* cite a paper by Tomenson and Campbell[6] as an example of a study that contradicts our premise that low-dose long-term exposure to PQ is involved in the etiology of PD. It is important to note that Tomenson and Campbell[6] cite a key limitation to their study includes its size and power and 'only information from death certificates of deceased workers was available, and it was not possible to study the morbidity of the entire group' (p.1). A key corollary of Ioannidis[7] states that: 'The smaller the studies conducted in a scientific field, the less

likely the research findings are to be true.' Further, Wu and Song[8] note (and we agree) that Tomenson and Campbell[6] use of death certificates might introduce bias as PD may not have been recorded as the cause of death, but may have been present or a contributing factor.

However, the aforementioned limitations do not identify not the primary concerns that we have with Tomenson and Campbell's study.[6] Placing the Tomeson and Campbell's[6] study under the multifactorial lens gives new perspective on the results. For example, van Maele-Fabry *et al*[9] utilize the Tomenson and Campbell[6] data in a meta-analysis and find 'support for the hypothesis that occupational exposure to pesticides increases the risk of PD' (p.30). Similarly, Breckenridge *et al*[10] also used Tomenson and Campbell's[6] results in another meta-analysis. They found support for increased risk of developing PD that was associated with smoking, but note the limitations of other studies in characterizing 'the onset of PD and its relation to rural living, farming and exposure to pesticides.' (p. 1). Allen and Levy[11] includ cohort studies in their analysis and identified positive association between PQ and PD; although their study mentions Tomeson and Campbell,[6] their cohort data were outside of their literature search time frame. Hence, there are contradictions in the results and a multi-causal situation is supported by the research.

Breckenridge *et al*[10] also cite Minnema *et al*[12] as an example of conflicting results in the potential linkage between PQ and PD; Minnema *et al*[12] is the second paper that Cook *et al* cite in their attack on the premise behind our review. However, the problem again has more to do with a misunderstanding of multifactorial theory. A multifactorial approach leads us to question the wider applicability of Minnema *et al*'s[12] results since a particular genetic strain of mice was used in a controlled laboratory setting. The mice were fed a particular kind of diet per the study design and conditions were set under the leading premise of an unifactorial cause. Although there is nothing fundamentally wrong with the experimental design that was used, the results can only go so far to tell us about that particular strain of mice under a set of controlled conditions. Can these results be extrapolated to global circumstances or circumstances under varying environmental states in different regions?

Jones *et al*[13] also ask why the disparity exists between these particular studies, citing Breckenridge *et al*[10] as a particular case in point. They note that the studies all use the same mouse strain C57BL/6 (as in Minnema *et al*[12]), but they also note age differences in the mice used; an important causal factor 'since age is the most critical variable in sporadic PD.' A problem with the applicability Minnema *et al*'s[12] study is the length of time, which may not be optimally designed to address exposure under real-life scenarios. Another experimental or interacting parameter is the appropriate dose, which is unknown. Koch and Hill[14] provide an insightful review into some of the experimental work using PQ in relation to dose and oxidative stress in animals. Although 13 weeks is a long time for an unifactorial laboratory design, the long-term repeated exposure we consider in our theory extends over decades with repeated seasonal exposure as it relates to increasing risk of developing PD. The appropriate experimental parameters for time and dose of exposure are unknown and should be a target question for research based in multi-factorial theory.

Cook *et al* take particular aim at our premise of multiple avenues for chronic low-dose exposure of PQ through the environmental context, suggesting that it is not possible. However, we are very clear in our review on the binding properties and sorption of PQ in different kinds of soil and stand by the papers we cite. We do not agree with Cook and colleagues' contention that we have provided information that 'is fundamentally incorrect and misleading.' The binding and degradation process is not equal under all soil types or environmental circumstance.[15,16] We agree that the level of direct exposure from such routes is expected to be low (the exact value is unknown), but the potential exists for pulsed and persistent exposure depending on local application rates and the types of environment being investigated. Amondham *et al*[16] conclude: 'Because of high adsorption, coupled with low mobility and a short half-life, the potential environmental risk associated with paraquat movement through the soil profile into the groundwater would be minimal. Nevertheless, paraquat residues have been found in groundwater and surface water of humid tropical regions.' (p. 504).

We do not share the confidence of Cook *et al* in regard to the assured end of life of PQ after its release into the environment. Many questions remain unanswered on the environmental chemistry of PQ. Cook and colleagues' claim 'that it does not leach into groundwater' is incorrect. We cited the research by Santos *et al*[17] on PQ in drinking water networks. PQ can reach water through runoff from agricultural lands. Once in the water it becomes absorbed into suspended material, sediment, or aquatic organisms where it can cause physiological harm and increase mortality.[18,19] Fernández *et al*[20] reviews PQ in soil and water noting that application of fertilizer may increase PQ mobility in soils and they report on varied concentrations of PQ in water samples they analyze. Khan *et al*[21] found 'the potential of paraquat and linuron residues to persist in organic soil, and their uptake by vegetable crops' (p.407). However, an important limitation is that very little research has been published on the quantification of PQ in drinking water deposits or in soil.[22] Our article cites additional papers detecting PQ in groundwater. New advances in detection techniques may prove useful in ecotoxicological studies investigating the environmental chemistry of PQ.[23]

Insufficient research has gone into the potential for the desorption of PQ under different environmental circumstances for us to fully resolve that varied routes of environmental exposure are non-existent. In light of our review of environmental research into PQ and risk of developing PD, we maintain the importance and purpose of our review to

stimulate new directions of 'laboratory investigation to match the environmental context and to test animal models, farm animals, or captured wild animals that have been subject to PQ exposure in the environment where PD prevalence has been previously noted' (p. 504). In no place in our article do we claim that PQ exposure results from intake of plants or roots. Cook *et al* also claim 'statements relating to the risk of trophic accumulation of paraquat owing to its accumulation in animal tissues are equally implausible, since paraquat does not bioaccumulate.' It is true that PQ becomes strongly bound to clays and mostly becomes inactive in when bound to soil and suspended materials in water, but there is sufficient evidence to suggest that PQ accumulates in animal or algal tissues.

Consider Wiegand *et al*'s[24] study of PQ uptake into the oligochaete worm (*Lumbriculus variegatus*) via consumption of dissolved organic matter. Wiegand *et al*'s[24] study contradicts Cook and colleagues' claim that PQ does not bioaccumulate. The toxicity of PQ on algae and biofilms also gives varied thresholds for tolerance.[25–27] Is there potential for desorption of PQ within the digestive tracts of organisms such as anurans or earthworms? Amphibians have received little attention as non-target aquatic organisms in relation to PQ ecotoxicology and PQ mobility in the environment, but could be an important target group for study. They can inhabit small temporary ponds around farmland where overspray may occur and become concentrated. Amphibians also make a substantial contribution to the gastronomy of different cultures around the globe.[28] Amphibians modulate sediment deposition rates via bioturbation or ingestion of sediment mixed with biofilm and algae.[29] Uptake of PQ by aquatic or soil organisms, such as the heterotrophic consumption of organic matter, absorption through permeable skin, by means of bioturbation, or feeding on biofilms and how this relates to the longevity and transportation of PQ in the environment is relevant to the problem of environmental exposure.

We direct Cook *et al* to studies showing that PQ accumulates in skeletal muscle tissue.[30,31] 'Paraquat is stored in different tissues, especially the lung, but also in brain, liver, kidney, bile and muscle in varying amounts from where it is only released slowly.'[32] Our review paper provides citation to examples wildlife markets in different countries where amphibians were cited as an example food item, but many different kinds of foods may be collected locally from habitats exposed to PQ runoff and consumed. There is sufficient reason to infer that these socio-ecological variables are relevant to the theory behind PQ and PD contrary to the claims of implausibility by Cook *et al* that potential avenues for long-term low-dose chronic exposure is implausible.

The hypotheses we adduce in our review would not be considered in an univariate context. The multivariate approach leads to new kinds of research questions. What is the environmental context in terms of aquatic to terrestrial composition in the landscape were PQ is in use? Are the farmlands where the risk factor for developing PD surrounded by large lakes or small amphibian ponds? A higher density of local wetlands or different kinds of groundwater conditions is also likely to be relevant factors and we have no data or research that has moved in this direction. These are the kinds of environmental context that are of importance in consideration of a different regional or cultural contexts that we highlight in our paper.

Two final points were raised by Cook *et al* concerning incorrect statements in our article. The first involves our statement that 'organophosphate PQ is produced commercially Gramoxone.' This is an error that was either obtained from an obscure reference to Cermák *et al*[33] who make this claim or it was a language translation error. Their second statement involves our use of language that 'PQ is banned in the European Union since 2007.' They are correct that this is a wrong choice of words that is repeated often in the literature and should be corrected to state that the authorization for use of PQ has been withdrawn from the European Union since 2007. However, Cook and colleagues' reasons for the change in authorization is misleading in stating that the court's decision was entirely due to failure 'to satisfy certain administrative and procedural requirements' as Section 181 of the ruling states: 'In the light of the foregoing, the Guatemalan study appears to constitute solid evidence which may reasonably raise doubts as to the safety of paraquat for operators applying it.'

The problem we identify here is not particular to PQ and PD. Indeed, there is a similar problem identified in the relationship between the risk of glyphosate on amphibians with large-scale experiments showing no effect, whereas small-scale toxicity studies under laboratory conditions showing toxic effects.[34] These discrepancies between research findings are important and must be resolved. Ioannidis[7] identify a list of potential reasons for such discrepancies in scientific research. Similarly, Bellou *et al*[35] employ a systematic umbrella review of previously published meta-analyses concerning PD certainly brings many of the cited findings into question. They identify 75 potential risk factors, which is why multifactorial theory is the correct tool to address the problem of potentially multiplicative environmental covariates and multiple risk factors.

There are many new statistical tools available for addressing this research problem in an environmental context, including statistical software and mixed effects models that are suited to this kind of problem. Ecologists, for example, use mixed effects models to investigate multiple factors in inferential investigations using the R-stats environment, as they identify the most likely model given the data.[36] This debate has spread into modern times questioning the value of and abuse of null hypotheses statistical testing in scientific research.[37,38]

Our review proposes a new kind of research direction to the outlined problem that goes beyond controlled experimentation of singular cause on a case by case basis. Researchers applying multifactorial theory need to be well versed on the logic of scientific inference. In particular, laboratory investigators may be less familiar with the multiple

cause approach to investigation, which is more familiar to the historical- or field-based sciences. There are fundamental differences in the way that scientists address experimental-based research *versus* studies that address questions about past events in the world;[39,40] for example, an associated risk of the onset of PD associated with use and exposure to PQ is a field-based historical research study, whereas administering PQ to a particular strain of a laboratory animal fits the classical experimental model.[3,12] There are no advantages to either approach (experimental *vs* field-historical) when it comes to testing of hypotheses.[39,40] Evans *et al*[41] discuss how more 'complex models can be both desirable and general, and how simple and complex models can be linked together to produce broad-scale and predictive understanding of biological systems.' However, a multiple cause situation will make the discovery of 'smoking gun trace' more difficult; that is 'a trace that picks out one of the competing hypotheses as providing a better causal explanation for the currently available traces than the others.'[39]

Test evidence should have the lowest probability of occurrence if the hypothesis being tested is not true and be as narrowly associated with to the effects stemming from the hypothesized causal conditions.[42] Laboratory tests on particular strains of mice do not meet the narrow association standards for testing or manifesting the type of effect that should occur in diverse population level scenario.[3,12] However, laboratory investigations have historically provided the supporting 'smoking gun trace' for field-based sciences.[39,40] The approaches need to be complementary and researchers need to be familiar with the different scientific approaches.

We also offer a word of caution on the meta-analytical approach that is being adopted in relation to scientific inference on the problem reviewed (ie, PQ–PD associations) and how it relates to multifactorial theory more generally. Bellou *et al*[35] offer words of caution in the strength of inference that is offered by many of the meta-analytical studies on PQ–PD associations. An additional problem is that there is a tendency to treat hypotheses as the 'data' for inferring a more inclusive hypothesis. Hypotheses are specific to a particular experiment or study, whereas theory can go beyond and is used for the inference of new hypotheses in retrodictive fashion. While there is a requirement for all relevant evidence (ie, inclusion in the analysis will affect the conclusion) must be considered,[43,44] it is erroneous to conflate hypotheses as data in a meta-analytical framework. Likewise, a statistical *P*-value does not give information on the causal effects or members of the sample, it is not an inference from population parameters, and it is not a measure of the probability that the obtained results occurred by chance. Although meta-analysis may narrow down potential factors of causal importance (eg, increasing risk of onset of PD following exposure to PQ),[3] it does not provide an actual test. The evidence (ie, more studies report significant effect of onset of PD following exposure of PQ) is far removed from the causal conditions (exposure to PQ) leading to the effect (onset of PD) and its inferential value is lessened beyond the original investigations by necessarily increasing the number of auxiliary hypotheses required in the inferential process.

It is our hope that our review will stimulate new research directions that will take a multifactorial approach into the study of PQ–PD relations. We are not convinced that Cook *et al* have considered all relevant evidence in their baseline assertion (ie, auxiliary hypothesis) that PQ becomes fully immobilized and inert once released into the environment. We are pleased to have had the opportunity to summarize evidence to the contrary. Deeper insight into ways to better integrate research from the environmental field context with results from experimentally based laboratory investigations will improve testing of multifactorial relations between PQ and PD. This is a difficult and yet to be fully resolved problem that will require the application and better understanding of scientific technique in laboratory investigations coupled with environmental field research designed to test environmental exposure of PQ as it relates to PD.

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DISCLOSURE/CONFLICT OF INTEREST

The authors declare no conflict of interest.

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