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National Toxicology Program

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NTP Research Report on the

Scoping Review of Paraquat Dichloride Exposure and Parkinson's Disease

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NTP Research Report on the Scoping Review of Paraquat Dichloride Exposure and Parkinson's Disease

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Foreword

The National Toxicology Program (NTP), established in 1978, is an interagency program within the Public Health Service of the U.S. Department of Health and Human Services. Its activities are executed through a partnership of the National Institute for Occupational Safety and Health (part of the Centers for Disease Control and Prevention), the Food and Drug Administration (primarily at the National Center for Toxicological Research), and the National Institute of Environmental Health Sciences (part of the National Institutes of Health), where the program is administratively located. NTP offers a unique venue for the testing, research, and analysis of agents of concern to identify toxic and biological effects, provide information that strengthens the science base, and inform decisions by health regulatory and research agencies to safeguard public health. NTP also works to develop and apply new and improved methods and approaches that advance toxicology and better assess health effects from environmental exposures.

NTP reports the findings from many of its studies in the NTP Technical Report and Monograph series. NTP uses the Research Report series, which began in 2016, to report on work that does not fit readily into one of those two series, such as pilot studies, assay development or optimization studies, literature surveys or scoping reviews, and handbooks on NTP procedures or study specifications.

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For questions about the reports and studies, please email NTP or call 984-287-3211..

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Peer Review

The National Toxicology Program (NTP) conducted a peer review of the draft *NTP Research Report on the Scoping Review of Paraquat Dichloride Exposure and Parkinson's Disease* by letter in April 2019 by the experts listed below. Reviewer selection and document review followed established NTP practices. The reviewers were charged to:

(1) Peer review the draft *NTP Research Report on the Scoping Review of Paraquat Dichloride Exposure and Parkinson's Disease* and comment on the adequacy of the scoping report in identifying and summarizing the relevant literature.

NTP carefully considered reviewer comments in finalizing this report.

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Conflict of Interest

Individuals identified as authors in the About This Report section have certified that they have no known real or apparent conflict of interest related to paraquat dichloride or Parkinson's disease.

Abstract

Introduction: Paraquat dichloride (commonly referred to as paraquat) is a restricted-use, broad-spectrum herbicide that is commonly used in the United States to control weeds in agricultural and horticultural crops. Because paraquat is not registered for home use, the highest exposures would likely be to those manufacturing and applying paraquat or to those living on or near farms or other areas where paraquat is manufactured or applied. Observational human studies of people who apply pesticides and data from experimental animal studies indicate that long-term, chronic exposure to paraquat might lead to central nervous system toxicity. The National Toxicology Program (NTP) identified paraquat as a potential candidate for systematic review while performing scoping activities to classify environmental exposures associated with Parkinson's disease. Subsequently, NTP became aware that the U.S. Environmental Protection Agency (EPA) Office of Pesticide Programs (OPP) was also evaluating paraquat as part of registration review activities and collaborated with EPA to avoid duplication of effort.

Objective: The objective of these scoping activities was to identify and characterize peer-reviewed, published scientific literature relevant to paraquat exposure and neurobehavioral and neuropathological endpoints associated with Parkinson's disease in humans and to related models in experimental animals or in vitro studies.

Methods: A scoping review was conducted that followed the NTP Office of Health Assessment and Translation (OHAT) method for systematic review through an abbreviated data extraction step. A comprehensive search strategy was used to retrieve original research records from multiple databases (i.e., Embase, PubMed, Scopus, Web of Science, and TOXLINE) through May 24, 2018. Relevant records included reports of exposure to paraquat dichloride and neurobehavioral or neuropathological endpoints relevant to Parkinson's disease in humans (such as clinical diagnoses, movement abnormalities, and effects on dopaminergic neurons) in epidemiological studies, experimental animal models of parkinsonism, and in vitro model systems. References were screened in duplicate for relevance and categorized by exposure, outcome, species, and cell type, where appropriate. An interactive evidence map was prepared using Tableau® software to enable researchers to explore the health outcome data by key feature (e.g., outcome, study type, animal model). Finally, data extraction of quantitative results was performed using the Health Assessment Workspace Collaborative (HAWC) software for those studies that were the most directly relevant to human Parkinson's disease (e.g., epidemiological studies reporting primary outcomes and studies of mammals exposed to paraquat via exposure routes most representative of human exposures including oral, dermal, and inhalation).

Results: The literature search identified 8,685 references, 458 of which were included after screening as relevant to describing the association between exposure to paraquat and the potential development of Parkinson's disease with some reports consisting of multiple lines of evidence and measured endpoints. The human epidemiological evidence consisted of 24 studies with the majority conducted in agricultural workers or people living in or near agricultural areas. A total of 143 experimental animal studies reported measurement of primary health endpoints; 11 were found to have high external validity to human exposure by exposing mammals via a route similar to human exposures (i.e., oral, inhalation, dermal). Supporting mechanistic information was reported in 190 experimental animal studies measuring secondary health endpoints and 244 in vitro studies.

Discussion: Using systematic review methodologies, NTP developed a scoping review and evidence maps of published scientific literature to support potential follow-up systematic review and to identify extant research gaps. The evidence maps are interactive, sortable visualizations of quantitative data from epidemiological studies and experimental study characteristics with links to publications. A considerable body of evidence was identified as relevant to paraquat exposure and Parkinson's disease that can be used in developing future systematic reviews as were data gaps and scientific challenges that could be addressed by future research.

Preface

NTP conducts scoping reviews to identify, categorize, and summarize the literature-based evidence evaluating whether exposure to environmental substances (e.g., chemicals, physical agents, and mixtures) may be associated with adverse health effects. These reviews serve as a foundational step in directing potential further inquiry by identifying areas that are data rich or data poor on project-specific key concepts such as: exposures, health effects, mechanisms, experimental model or study design, and evidence stream (human, experimental animal, in vitro models); however, they do not include a synthesis of the data. Depending on the goals and the available evidence, scoping reviews may include: (1) a summary of the research relating to specific questions or relatively broad topic areas, (2) a systematic evidence map—an interactive visual display of research relating to relatively broad topic areas that can be sorted, filtered, and categorized to illustrate the extent and types of evidence, or (3) both.

NTP conducts these health effects evaluations following the first three steps of the general methods outlined in the "Handbook for Conducting a Literature-Based Health Assessment Using the OHAT Approach for Systematic Review and Evidence Integration"[†]: (1) problem formulation, (2) literature search and selection of studies for inclusion, and (3) abbreviated data extraction to categorize published research by key concepts relevant to the goals of the review. The key feature in applying the systematic review approach to scoping reviews is the application of a transparent framework to document the methods.

[†]OHAT is the abbreviation for Office of Health Assessment and Translation, which is within the Division of the National Toxicology Program at the National Institute of Environmental Health Sciences.

Introduction

Parkinson's disease is a group of motor system disorders that are due to progressive degeneration of dopaminergic neurons within the substantia nigra of the brain. Although some genetic factors are known to contribute to familial Parkinson's disease, the cause of most cases remains unknown. Increasingly, the potential contributions of environmental factors—including exposures to pesticides, metals, and other environmental chemicals—have been investigated in observational human, experimental animal, and in vitro studies. Meta-analyses of epidemiological data have identified elevated risks of Parkinson's disease in farmworkers and others who handle pesticides or live near areas close to pesticide use or production (Ahmed et al. 2017).

Paraquat dichloride (1,1'-dimethyl-4,4'-bipyridinium ion, hereafter referred to as paraquat) is a quaternary ammonium compound used as a broad-spectrum, fast-acting contact herbicide. Paraquat is registered for use in both agricultural and nonagricultural settings, and is used to control weeds and as a post-harvest desiccant (Bromilow 2004). It is applied as a direct spray and kills the leaves that come in direct contact with the compound.

Importantly, paraquat is a restricted-use pesticide (i.e., it can only be purchased and used by people certified to apply pesticides) and is not registered for any homeowner or residential applications in the United States. Thus, the primary route of exposure for paraquat is occupational exposure during mixing, loading, and applying paraquat or during post-application processes. However, residential exposure can occur for those living on or near farms where paraquat has been applied. Normal use patterns suggest that paraquat is not expected to be a surface water or groundwater contaminant (US EPA 1997). Whereas high-level, acute exposure to paraquat is associated with pulmonary toxicity in humans and experimental animals, low-level, chronic exposure is reported to be associated with various health effects, including central nervous system toxicity, which can lead to Parkinson's disease (Dinis-Oliveira et al. 2008).

The association between paraquat exposure and Parkinson's disease was identified as a potential candidate for systematic review as a result of a National Toxicology Program (NTP) scoping activity of Parkinson's disease. The same topic was also identified as a topic for systematic review by two external groups. The U.S. Environmental Protection Agency (EPA) Office of Pesticide Programs (OPP) is evaluating paraquat as part of its pesticide registration review program and collaborated closely with NTP during the scoping process. A second academic group from Brazil also contacted NTP for advice on the planning and conduct of its separate, independent systematic review of paraquat and Parkinson's disease (Vaccari et al. 2019). Because of the interest and extent of the evidence, NTP conducted this targeted scoping review of the literature on paraquat exposure and Parkinson's disease. The literature was systematically collected and categorized to develop an interactive evidence map to enable researchers to explore the data by key Parkinson's disease-related health effects, types of evidence, and gaps in research. The information contained in this scoping report can be used to focus and support a full systematic review by any interested group or for consideration of future research on this topic.

Objective and Specific Aims

Objective

The primary objective of this scoping review was to identify and characterize the literature relevant to paraquat exposure and neurobehavioral or neuropathological endpoints associated with Parkinson’s disease in humans and to related models in experimental animal or in vitro studies.

Specific Aims

- Identify literature reporting the effects of paraquat exposure on neurobehavioral and neuropathological endpoints associated with Parkinson’s disease or clinical symptoms of parkinsonism (i.e., tremors of the extremities, slowed movement, postural rigidity, and changes in gait) in humans, animals, and in vitro model systems.
- Extract study design information from included studies, such as evidence stream, exposure scheme, and measured effects. Data extraction files of the included studies will be shared upon release of the final report.
- Summarize the available literature and create an evidence map of the health effects and mechanistic data relevant to Parkinson’s disease (i.e., the extent and types of health effects evidence available) associated with paraquat exposure.

Methods

The systematic review techniques applied in this scoping review adhered to the framework developed by the National Toxicology Program (NTP) Office of Health Assessment and Translation (OHAT) (Rooney et al. 2014). The OHAT systematic review and evidence integration framework consists of a seven-step process in which the first three steps are relevant to producing a scoping review, and the last four steps are applicable to assessing study quality and synthesizing evidence (NTP 2015). Therefore, this scoping review was restricted to the first three steps: (1) problem formulation, (2) literature search and study selection, and (3) abbreviated data extraction. Data extraction was primarily used to capture study characteristics of all included studies; quantitative results of epidemiological and experimental mammalian studies of high external validity to human exposure (e.g., oral, inhalation, or dermal) were also extracted as reported by study authors. Qualitative evidence synthesis was limited to grouping studies according to similar study characteristics, including experimental models and exposure categories (e.g., exposed populations in epidemiological studies, exposure routes in animal studies, and in vitro model systems). Study quality assessment was beyond the aims of this evaluation, as is customary for most scoping reviews, and thus was not performed for this review.

Problem Formulation

Parkinson’s disease was first chosen by NTP as a disease-focused scoping project due to high prevalence of cases of unknown etiology, questions about environmental exposures, and potential to inform future testing efforts. While performing scoping activities, NTP identified the association between paraquat exposure and Parkinson’s disease as a potential candidate for further review. In addition, NTP was made aware that EPA OPP and a research group from the University Estadual Paulista, São Paulo, Brazil, were also initiating systematic reviews on the same topic. Thus, to support a consistent process, promote access and data sharing, and avoid duplication of effort, NTP consulted with the research group from Brazil at the project’s initiation and collaborated closely with EPA OPP throughout scoping activities. NTP, in collaboration with EPA OPP toxicologists and epidemiologists and an expert on neurotoxicity from the EPA Office of Research and Development (ORD), defined the outcomes of interest and the inclusion/exclusion criteria for the title-and-abstract screen and full-text review. A scoping review protocol was developed using the OHAT systematic review framework for the literature screen and review and for data extraction (Appendix G).

PECO Statement

A PECO (**P**opulation, **E**xposure, **C**omparator, and **O**utcome) statement was developed in conjunction with EPA to address and understand the potential effects of paraquat on neurological outcomes associated with Parkinson’s disease or parkinsonism in humans, animals, and in vitro model systems (Table 1). The PECO statement is used to help develop the specific research questions, search terms, and inclusion/exclusion criteria for the systematic review (Higgins and Green 2011).

Table 1. Population, Exposure, Comparator, Outcome Statement

PECO Element	Evidence
Populations	**Human:** Humans, without restriction on age, sex, or life stage at exposure or outcome assessment **Animal:** Experimental animals without restriction on species (including nonmammalian and invertebrate species), age, sex, or life stage at exposure or outcome assessment **In vitro:** Human or animal cells, tissues, or model systems with in vitro exposure regimens; examples of cell lines typically used for in vitro Parkinson's disease mechanistic study include SK-N-SH, SH-SY5Y, PC12, RBE, astrocytes, and dopaminergic neurons
Exposure	Exposure to paraquat dichloride (CASRN 1910-42-5) based on administered dose or concentration, biomonitoring data (e.g., urine, blood, or other specimens), environmental measures (e.g., air, water levels), or indirect measures such as job title or occupational history
Comparators	**Human:** A comparison population exposed to lower levels (or no exposure/exposure below detection levels) of paraquat **Animal:** Comparable animal populations that were untreated or exposed to vehicle-only treatment in experimental animal studies **In vitro:** Comparable cells or tissues exposed to vehicle-only treatment or untreated controls
Outcomes	**Human:** ***Primary outcomes:*** Diagnosis of Parkinson's disease and/or clinical observations, neurobehavioral, or neuropathological outcomes typically associated with Parkinson's disease or parkinsonism following in vivo exposure, focusing on tissue level and functional abnormalities, descriptive and/or functional assessment of the central nervous system, including the nigrostriatal (dopamine) system; examples of relevant outcomes include tremor, bradykinesia, rigidity, postural instability, and any other movement abnormalities associated with parkinsonism ***Secondary outcomes:*** Tissue, cellular, biochemical, and/or molecular outcomes resulting from in vivo exposure that have a mechanistic association with Parkinson's disease or are evidence of toxicity in the nervous system, but are not specific to Parkinson's disease **Animal:** ***Primary outcomes:*** Neurobehavioral or neuropathological outcomes, focusing on whole body and tissue level abnormalities typically associated with Parkinson's disease following in vivo exposure; endpoints include motor activity and coordination, sensorimotor reflexes, effects on cognitive function, quantitative or qualitative assessment of dopaminergic neuron counts in the substantia nigra and dopaminergic neuron terminals in the striatum, and other descriptive and/or functional assessments of the central nervous system, including the nigrostriatal (dopamine) system, which are considered hallmarks of Parkinson's disease (e.g., detection of intracytoplasmic Lewy bodies) ***Secondary outcomes:*** Tissue, cellular, biochemical, and/or molecular outcomes resulting from in vivo exposure that have a mechanistic association with Parkinson's disease (e.g., dopamine and metabolite levels in the nigrostriatal pathway, tyrosine hydroxylase-positive neuron [TH+] immunoreactivity or density) or are evidence of toxicity in the nervous system, but are not specific to Parkinson's disease (e.g., oxidative stress, inflammation, mitochondrial, and/or proteasomal dysfunction) **In vitro:** In vitro assays investigating cellular responses commonly attributed to Parkinson's disease (e.g., assessment of functionality, integrity, and viability for nerve cells critical to the nigrostriatal [dopamine] system) and mechanistic assays investigating proposed pathways for the etiology of Parkinson's disease (e.g., enzyme interactions, cell signaling)

Primary and Secondary Outcomes

The publications selected during the paraquat literature screen included studies that examined primary and secondary outcomes related to Parkinson's disease. Both primary and secondary outcomes were used to evaluate the connection between pesticide exposure and the disease. Primary outcomes directly associate pesticide exposure with the manifestation of Parkinson's disease (or symptoms of neurological disruption commonly attributed to parkinsonism), whereas secondary outcomes elucidate mechanistic connections between exposure and Parkinson's disease or describe general toxicity in the nervous system. Secondary outcomes are considered with the corresponding primary health effects to examine support for biological plausibility of those outcomes, or support for the analysis of a causal relationship (or lack thereof), between paraquat exposure and Parkinson's disease. In humans, primary outcomes include abnormal neurobehavioral clinical observations, clinical diagnoses consistent with parkinsonism, and neuropathological aberrations. Animal primary outcomes include abnormal neurobehavioral clinical observations, neuropathological aberrations, including degeneration of dopaminergic neurons in the substantia nigra, and changes in locomotor activity. Secondary outcomes in human and animal studies cover other tissue, cellular, biochemical, or molecular changes in the nervous system that either have a mechanistic association with Parkinson's disease or reflect general toxicity in the nervous system that is not specific to Parkinson's disease. Indirect measures of a primary outcome (e.g., evaluating dopaminergic neuron health based on TH+ optical density) were grouped into this category because they provided supportive rather than direct evidence of the primary outcome. In vitro studies also contribute mechanistic information and can be used to assess the biological plausibility of outcomes observed in human and animal studies. Relevant in vitro outcomes include loss of nerve cell integrity and viability or altered functionality of nerve cells critical to the nigrostriatal system, and physiological changes attributed to paraquat exposure that are hypothesized to play a role in the etiology of Parkinson's disease but are not unique consequences of the disease (e.g. oxidative stress, proteasomal and mitochondrial dysfunction in nervous tissues, and epigenetic changes). No distinction was made between primary and secondary outcomes for in vitro studies because all in vitro data were considered supporting information for the other evidence streams.

Literature Search

Literature Search Strategy

Database search strategies were developed to identify all relevant published evidence that addresses the relationship between Parkinson's disease and paraquat exposure. To ensure inclusion of all relevant papers, the strategy for this search was broad for the consideration of neurobehavioral and neuropathological endpoints associated with Parkinson's disease and comprehensive for paraquat dichloride as an exposure or treatment. All searches included terms associated with paraquat including: (1) the common name of the chemical, (2) the Chemical Abstract Services Registry Number (CASRN), and (3) retrieval of synonyms from the ChemIDplus database, which currently contains chemical names and synonyms for more than 400,000 chemicals (NIH 2018). Keywords specific to Parkinson's disease were derived from review articles on proposed mechanistic pathways for the etiology of Parkinson's disease (Baltazar et al. 2014; Zhang et al. 2016) and through a systematic review that investigated the relationship between chemical exposure and Parkinson's disease (Choi et al. 2016). Searches were not limited by study design, language restrictions, or publication year. The following databases were searched most recently on May 24, 2018 (full details of the search strategies are presented in Appendix A):

- Embase (Elsevier)
- PubMed (NLM)
- Scopus (Elsevier)
- Web of Science (Thomson Reuters)
- TOXLINE

Searching Other Resources

The reference lists of all relevant published reviews identified during the initial search were hand searched to find studies that were not identified through the electronic searches. These studies were evaluated using the same inclusion and exclusion criteria used for screening the electronic search results. Relevant studies identified through these steps are marked as "identified through other sources" in the study selection flow diagram (Figure 1).

Study Selection

Evidence Selection Criteria

Inclusion/exclusion criteria were designed to identify relevant publications that comply with each aspect of the PECO statement (Table 1). The eligibility of each citation from the paraquat literature was considered using the criteria outlined in Appendix B.

Screening Process

Search results from each database were compiled in EndNote and duplicates were removed. The master reference list of original search results was filtered and sorted with the Document Classification and Topic Extraction Resource software (DoCTER), a machine-learning tool developed by ICF, to group the citations into clusters based on perceived relevance to the key questions and similarity to vetted studies. Clusters were used to prioritize manual screening in order of highest-to-lowest perceived relevance. The references in each cluster were then screened at each stage as described below for relevance and eligibility with the inclusion/exclusion criteria used by the online literature screening program, DistillerSR®, a web-based, systematic review software program with structured forms and procedures (http://systematic-review.net/).

Title-and-abstract Review

Screeners were trained using the detailed inclusion/exclusion criteria outlined in Appendix B with an initial pilot screening phase of a minimum of 150 references (actual n = 172) to improve clarity of the inclusion and exclusion instructions and to improve accuracy and consistency among screeners. Changes to the inclusion criteria resulting from the pilot phase were documented in a protocol amendment along with the date of modifications and the logic for the changes. After the pilot phase, trained screeners used updated inclusion/exclusion criteria to conduct a title-and-abstract screen of each reference in duplicate to determine study eligibility. If considered possibly relevant, studies were moved to a full-text review. In the case of screening conflicts, screeners independently reviewed their screening results to confirm the inclusion/exclusion decision and, if needed, discussed discrepancies with the other screeners. If a true disagreement existed between screeners, the study passed to the full-text review.

Full-Text Review

After completion of the title-and-abstract screen, full-text articles were retrieved for those studies that either clearly met the inclusion criteria or for which eligibility to meet the inclusion criteria was unclear. Two screeners who participated in the title-and-abstract screening independently conducted the full-text review. True disagreements were resolved by discussion through consultation with other members of the evaluation design team and technical advisors.

Reason for exclusion at the full-text-review stage was annotated and is reported in a study selection flow diagram using reporting practices outlined in Moher et al. (2009) (Figure 1). Although more than one reason might have applied, only one of the following reasons for exclusion was documented for simplicity: (1) lacked a comparator (e.g., a control or baseline group); (2) conducted with a nonanimal model (e.g., plants, fungi, protists, or bacteria); (3) lacked neurobehavioral or neuropathological health outcome information; (4) conducted on wildlife; (5) lacked paraquat exposure; (6) mixture study lacked paraquat-only exposure; (7) was a conference abstract, grant application/registration, thesis/dissertation, or otherwise not a peer-reviewed scientific publication; or (8) study was only available in non-English language.

Multiple Publications of Same Data

During full-text review, publications were examined for overlapping data by comparing author affiliations, study designs, cohort names, enrollment criteria, and enrollment dates. No publications with overlapping data were identified in this review.

Data Extraction

Data were extracted from the full-text records of individual studies by one member of the scoping review team and checked by a second member for completeness and accuracy. Any discrepancies in data extraction were resolved by discussion or consultation with a third member of the team.

Two levels of data extraction were performed during scoping activities depending on study type and design: abbreviated data extraction of study characteristics of all included studies to capture study characteristics including species tested, routes and levels of exposure, and endpoints measured; and full data extraction including quantitative health effects data from epidemiological studies and experimental animal studies of high external validity to human exposures reporting primary outcomes.

Secondary outcomes reported in experimental mammalian animal studies and all outcomes reported in nonmammalian animal and in vitro models were included only as supporting information because the measured effects were less specific to Parkinson's disease than those measured for primary outcome studies in mammals. Instead, only abbreviated data extraction was performed on these studies. These characteristics were identified in the full-text record and coded into Microsoft Excel spreadsheets to facilitate data visualization and summary using Tableau® software.

Full data extractions of included epidemiology studies and experimental studies of mammals exposed to paraquat via oral, dermal, or inhalation exposure routes, both reporting primary outcomes, were conducted using the Health Assessment Workspace Collaborative (HAWC) (https://hawc.readthedocs.io/en/latest/), a free and open-source, web-based software application. Partial data extraction for other studies was performed using Microsoft Excel. Full data extraction included information on author affiliations and funding, characteristics of the model organism, exposure methodology and conditions, the route of administration, comparators, and quantitative and qualitative data on health effects. Data extraction elements collected from epidemiological studies are listed in Appendix C and those from animal studies in Appendix D.

Data Availability

Interactive versions of each figure can be accessed directly using the link included beneath each figure. In addition, all interactive figures and additional study details can be viewed online and data can be downloaded from Tableau in Microsoft Excel format here: https://doi.org/10.22427/NTP-DATA-RR-16 (NTP, 2019b). Full data extraction results are available for download from HAWC in Microsoft Excel format here: https://hawcproject.org/assessment/475/ (NTP, 2019a).

Results

Literature Search Results

The screening results and reasons for exclusion are outlined in the study selection diagram (Figure 1). The electronic database searches retrieved 8,685 references, which resulted in 7,042 after duplicate removal. Review of reference lists of relevant published review articles yielded an additional 1,329 articles, which resulted in 124 references after duplicate removal. Thus, a total of 7,166 individual references were screened for relevance and eligibility in the title-and-abstract screen. Of these, 6,152 studies were excluded as not relevant to PECO and 120 records had no primary data, such as review articles and commentaries. This resulted in 894 studies reviewed in the full-text screen, of which 426 were excluded as not relevant to PECO along with 10 reviews, leaving 458 total included studies after screening (Figure 1). Five included articles were identified by the review of reference lists rather than through electronic database searches: three human primary-endpoint studies, one animal secondary study, and one in vitro study.

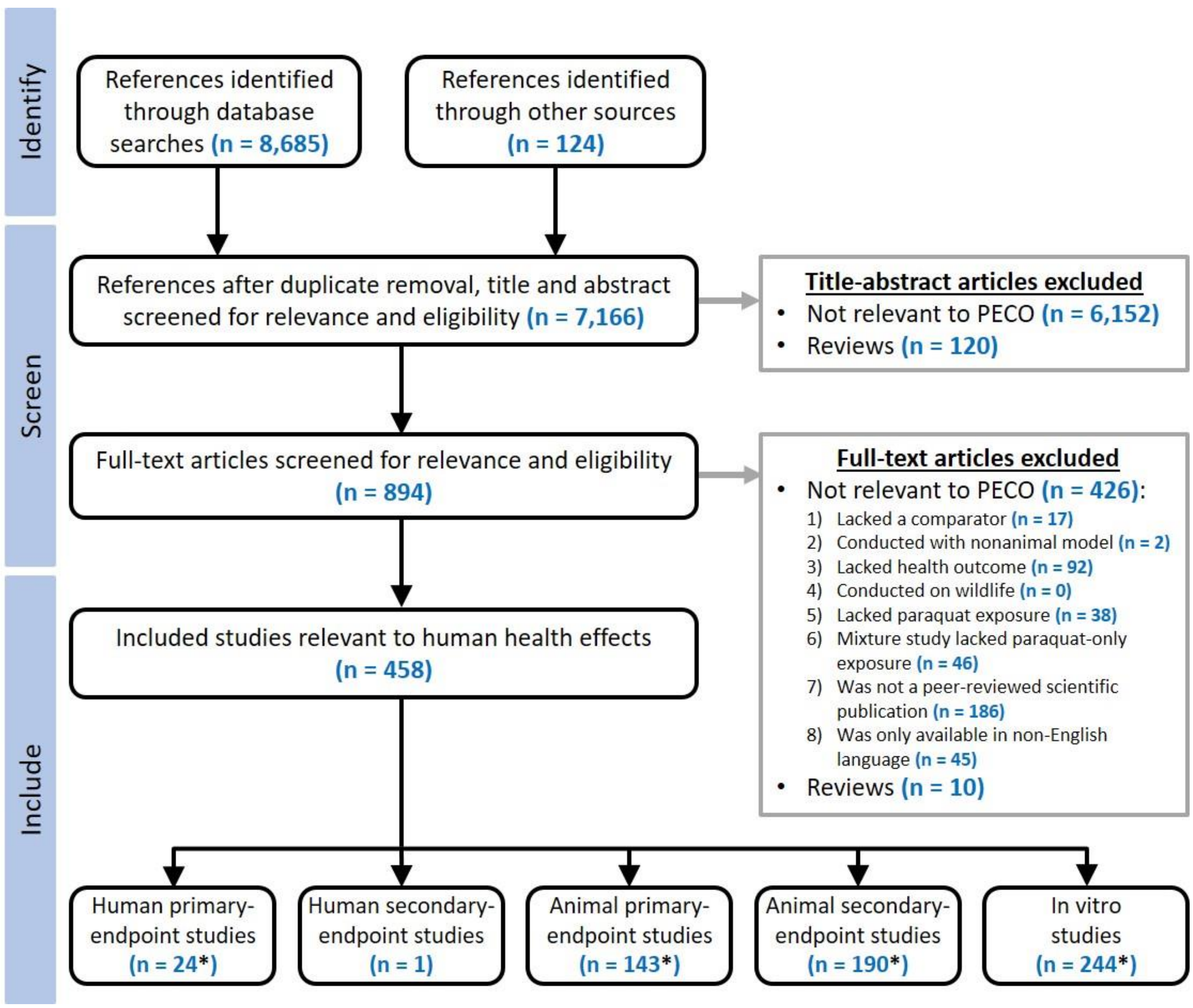


Figure 1. Study Selection Diagram

*Several included articles contain data for multiple evidence streams.

Human Health-relevant Studies

Figure 1 illustrates the breakdown of included studies by evidence stream and primary or secondary data. A total of 25 human epidemiological studies (24 primary endpoint studies and 1 secondary endpoint study) were identified that satisfied the PECO inclusion criteria along with 143 experimental animal studies reporting primary endpoints, 190 experimental animal studies reporting secondary endpoints, and 244 in vitro studies. Because some included studies reported data from multiple evidence streams or both primary and secondary outcomes, these numbers do not add up to the total number of studies considered relevant (i.e., 458). A list of included studies after full-text review is itemized in Appendix E of this scoping review report and high-level summaries of studies within each evidence stream (i.e., human, experimental animal, and in vitro) are provided in the following sections.

Human Studies

The epidemiological studies that evaluated the association between paraquat exposure and primary outcomes of Parkinson's disease, including Parkinson's disease diagnosis or clinical symptoms of parkinsonism, consisted of analysis of incidence in a prospective cohort study, 3 cross-sectional analyses of prevalence in this prospective cohort, 19 case-control studies, a retrospective cohort study, and an ecological study (Figure F-1). Many related publications or follow-up analyses were based on the same study populations as described in more detail in the following sections. All studies evaluated Parkinson's disease, although researchers defined and captured the outcomes differently, most commonly by self-report of diagnosis, but also by clinical observations of neurological effects associated with parkinsonism. Two studies reporting unique outcome assessment approaches included a retrospective cohort that evaluated mortality in workers at a paraquat manufacturing plant (Tomenson and Campbell 2011) and one that investigated the onset of Parkinson's disease (i.e., before or after the age of 68) in residents living near agriculture areas in California (Gatto et al. 2010). The majority of the studies (n = 17) were conducted in the United States; others were conducted in the Netherlands, France, Canada, Taiwan, and the United Kingdom.

Epidemiological studies were grouped by potential levels of exposure using the following exposure types as proxies for levels of exposure: (1) occupational studies that included pesticide applicators, farmers, and others who used paraquat on the job and were estimated to be exposed to the highest levels of paraquat (Table 2; Figure F-2); (2) environmental exposure studies in which residences and/or workplaces of participants were near agricultural areas or other situations with moderate paraquat exposure levels (Table 3; Figure F-3); and (3) general population studies that were more representative of typical exposures to people who do not work directly with paraquat or live in areas associated with higher usage of paraquat, although these studies might include subjects who used paraquat at work (Table 4; Figure F-4). Brief descriptions of epidemiological studies are provided in the following sections to provide an overview of the key studies and results.

Occupational Studies

The Agricultural Health Study (AHS) is a prospective cohort study of more than 50,000 licensed pesticide applicators and more than 30,000 of their spouses living in North Carolina and Iowa in the United States (https://www.aghealth.nih.gov/about/). All AHS participants are asked at enrollment, and at 5-year follow-up evaluation, to report whether they had ever been diagnosed with Parkinson's disease by a physician and at what age they were first diagnosed. A subset of participants completed a supplemental questionnaire that included additional information on paraquat and other pesticides suspected to be associated with Parkinson's disease (Kamel et al. 2007). An increase in odds ratio that was not statistically significant was observed for prevalent cases of Parkinson's disease (83 subjects who reported physician-diagnosed Parkinson's disease at enrollment; adjusted odds ratio [adjOR] 1.8; 95% confidence interval [CI] 1.0–3.4) for the paraquat-exposed workers, but not with incident cases (78 reported diagnosis during follow-up; adjOR 1.0; 95% CI 0.5–1.9) (Figure F-2).

Most of the self-reported Parkinson's disease cases were subsequently invited to participate in the Farming and Movement Evaluation (FAME) studies, which were nested case-control studies within AHS that confirmed self-reported Parkinson's disease cases by follow-up assessments, including clinical evaluation of movement disorders and completion of additional exposure assessment questionnaires designed to capture lifetime paraquat exposures (Tanner et al. 2011). All four FAME studies that were included as relevant to this scoping review (i.e., evaluated exposure to paraquat alone) reported significant increases in odds ratio for prevalent Parkinson's disease with paraquat exposure (Furlong et al. 2015; Goldman et al. 2012; Kamel et al. 2014; Tanner et al. 2011) (Figure F-2**)**. Compared with participants who had never applied paraquat (n = 396 unexposed; 87 of 110 cases and 309 of 358 controls), pesticide applicators who had been exposed to paraquat (n = 72; 23 of 110 cases and 49 of 358 controls) were at a higher risk of Parkinson's disease (adjOR 2.5; 95% CI 1.4–4.7) (Tanner et al. 2011). An even greater risk of Parkinson's disease was observed in pesticide applicators with a homozygous GSTT1 deletion who had been exposed to paraquat, although the number of exposed cases and controls were fewer (adjOR 11.1; 95% CI 3.0–44.6; n = 9 exposed cases and 6 exposed controls with deletion) (Goldman et al. 2012). In addition, a higher odds ratio for Parkinson's disease was observed with longer duration of paraquat exposure in those with a homozygous GSTT1 deletion (Goldman et al. 2012). Furlong et al. (2015) reported a greater risk in workers who used gloves ≤50% of the time (adjOR 3.9; 95% CI 1.5–10.2) than in those who used gloves more consistently (adjOR 1.6; 95% CI 0.6–4.2). Finally, Kamel et al. (2014) observed a higher risk with exposure to paraquat in subjects with low total dietary fat consumption (adjOR 4.7; 95% CI 1.7–12.6) compared with those who consumed higher total levels of fat in their diets (adjOR 1.4; 95% 0.5–3.7). The increase in Parkinson's disease risk with low-fat diets was related to lower consumption of unsaturated fats, including monounsaturated fatty acids (MUFAs; adjOR 3.8; 95% CI 1.4–10.4), polyunsaturated fatty acids (PUFAs; adjOR 4.2; 95% CI 1.5–11.6), and linoleic acid (adjOR 3.8; 95% CI 1.4–10.3). The paraquat exposure in subjects with a high-fat diet was significant when focusing on saturated fats only (adjOR 3.1; 95% CI 1.2–8.0).

The Agriculture and Cancer (AGRICAN) cohort is another large prospective cohort that follows active and retired agricultural workers from France. Researchers conducted a cross-sectional analysis using the AGRICAN enrollment questionnaire and reported a significant increase in prevalence of self-reported diagnosis of Parkinson's disease at enrollment in subjects exposed to paraquat (adjOR 1.43; 95% CI 1.17–1.75), but this increase was eliminated after adjusting for co-exposures to active ingredients of other pesticides (adjOR 1.01; 95% CI 0.41–2.49) (Pouchieu et al. 2018). An increase in odds ratio by duration in years compared with unexposed subjects was observed; however, the results were not statistically significant.

Other studies in subjects exposed occupationally to paraquat did not observe significant associations between paraquat exposure and Parkinson's disease. Similar to the FAME analyses, these studies reported few cases of the disease and many involved co-exposures to other pesticides. Tanner et al. (2009) evaluated occupations, including pesticide use among farmers, as a risk factor for Parkinson's disease in North America. Paraquat exposure occurred in 9 of the 519 cases and 4 of the 511 controls; however, 6 of the 13 subjects exposed to paraquat were also exposed to other pesticides. A cross-sectional analysis of 310 workers (238 with exposure to paraquat and 72 unexposed controls matched for similar physical activity levels in their occupations) selected from participants of a previous cohort study conducted by the Washington State Department of Health from 1972 to 1976 found no significant associations between paraquat exposure and parkinsonism based on prevalence ratios (estimated using a general linear model due to high prevalence of parkinsonism among participants) categorized by exposed versus unexposed, tertile of years of exposure, or tertile of acre-years of exposure (Engel et al. 2001). Outcome assessment consisted of confirmed clinical symptoms of parkinsonism rather than Parkinson's disease diagnosis; notably, only one participant self-reported a diagnosis of Parkinson's disease. A retrospective cohort of workers in a paraquat manufacturing plant did not find an increase in mortality from Parkinson's disease, as only 1 of 307 total deaths identified the disease as the underlying cause of death (Tomenson and Campbell 2011). Similarly, in a case-control study in British Columbia, occupational paraquat exposure did not significantly increase the risk of idiopathic parkinsonism using cardiovascular disease patients as controls (adjOR 1.11; 95% CI 0.32–3.87; 6 cases, 5 controls) or voters as controls (adjOR 1.25; 95% CI 0.34–4.63; 6 cases, 4 controls) (Hertzman et al. 1994). A hospital-based case-control study in the Netherlands did not find a significant association between paraquat exposure and Parkinson's disease using a crop-exposure matrix based on both self-reported exposure and corrected, active-ingredient exposure (van der Mark et al. 2014).

A single occupational exposure study reported the secondary outcome oxidative stress (Ranjbar et al. 2002). Oxidative stress was evaluated in paraquat formulation workers and compared with age-matched volunteers from Tehran University with no direct pesticide exposure. Paraquat workers had higher levels of plasma lipid peroxidation and lower levels of plasma antioxidant capacity and thiol levels. This study was not included in any summary figures or tables as it did not contain primary outcome data.

Table 2. Epidemiological Studies Evaluating Occupational Paraquat Exposure and Parkinson's Disease

Country; State/Region	Study Population	Study Design (n)	Exposure Assessment	Outcome Assessment	Results	Study
United States; Iowa and North Carolina	Pesticide workers and spouses in Agricultural Health Study cohort	Prospective cohort (incidence: 78 cases [11 exposed], 55,931 controls [7,382 exposed]) Cross-sectional (prevalence: 83 cases [14 exposed], 79,557 controls [11,266 exposed])	Ever exposed to paraquat based on self-reporting of duration and frequency of pesticide use, as well as, ever used paraquat	Parkinson's disease (incidence and prevalence) Self-reporting of doctor-diagnosed Parkinson's disease	**ns** adjOR for ever use of paraquat (incidence) ↑ adjOR for ever use of paraquat (prevalence)	(Kamel et al. 2007)
United States; Iowa and North Carolina	FAME participants[a]	Case-control (110 cases [23 exposed], 358 controls [49 exposed])	Ever exposed to paraquat based on computer-assisted telephone interviews to obtain detailed information on pesticide use from age 14 onward	Parkinson's disease Diagnosis determined by agreement of two neurologists after independent review of all available diagnostic information	↑* adjOR for ever use of paraquat	Tanner et al. (2011)
United States; Iowa and North Carolina	FAME participants[a]	Case-control (87 cases [21 exposed], 343 controls [52 exposed])	Estimated exposure using computer-assisted telephone interviews to determine ever use of paraquat and cumulative lifetime years of use	Parkinson's disease Diagnosis determined by consensus of two movement disorder specialists using all available information and applying NINDS/UK Brain Bank criteria	Paraquat use (Y/N): ↑* adjOR for ever use of paraquat Paraquat use (years–lifetime): ↑‡ adjOR for ever use of paraquat (≤4 years) ↑‡ adjOR for ever use of paraquat (>4 years) Homozygous deletion genotype for GSTT1: **ns** adjOR for paraquat exposure by genotype (9 exposed cases with deletion, 6 exposed controls with deletion), but there was a significant interaction between paraquat exposure and genotype	Goldman et al. (2012)

Country; State/Region	Study Population	Study Design (n)	Exposure Assessment	Outcome Assessment	Results	Study
United States; Iowa and North Carolina	FAME participants[a]	Case-control (89 cases [18 exposed, males only], 336 controls [46 exposed, males only])	Occupational exposure to paraquat was assessed via telephone interview; interviewers collected a complete occupational history and information on pesticide use from age 14 onward	Parkinson's disease Self-reported cases evaluated by neurologists during home visits; diagnosis determined by agreement of two movement disorder specialists using medical records and the in-home evaluation	🡅* adjOR for paraquat exposure with low total fat diet 🡅* adjOR for paraquat exposure with high saturated fat diet	Kamel et al. (2014)
United States; Iowa and North Carolina	FAME participants[a]	Case-control (69 cases [22 exposed], 237 controls [48 exposed])	Estimated exposure based on complete occupational history to evaluate paraquat exposure in each job held from age 14 to reference data; determination of hygiene practices and personal protective equipment use was also self-reported	Parkinson's disease Case status determined by agreement of two movement disorder specialists following established criteria and using information from medical records and the in-home evaluation; diagnosis dates determined from medical histories	Paraquat use: 🡅* adjOR for ever use of paraquat Based on hygiene practices 🡅* adjOR for paraquat (glove use ≤50% based on several different models)	Furlong et al. (2015)
United States; Washington	Pesticide workers who were previous participants in a Washington State Department of Health cohort during 1972–1976 (US EPA 1976)	Cross-sectional (310 workers [238 with exposure to paraquat and 72 unexposed controls matched for similar physical activity levels in their occupation])	Estimated exposure based on self-administered questionnaire on occupational pesticide use throughout their working career and years of use	Parkinsonism Diagnosed based on neurological examination by a trained nurse; defined as the presence of two or more of the following signs: bradykinesia, rest tremor, rigidity, and impairment of postural reflexes	**ns** adjPR for paraquat exposure, tertile years of exposure, and acre-years	Engel et al. (2001)

Country; State/Region	Study Population	Study Design (n)	Exposure Assessment	Outcome Assessment	Results	Study
North America; 7 in United States and 1 in Canada	Parkinson's patients and hospital controls from 8 centers	Case-control (519 cases [9 exposed], 511 controls [4 exposed])	Ever exposed was assessed based on occupational history information for all jobs held for at least 3 months acquired via computer-assisted telephone interview	Parkinson's disease Diagnosed by the enrolling investigator based on clinical features and Unified Parkinson's Disease Rating Scale score	**ns** adjOR for paraquat exposure (large OR, but not significant due to wide CI)	Tanner et al. (2009)
Canada; Okanagan Valley, British Columbia	Residents in horticultural region	Case-control (127 cases [6 exposed], 245 controls [5 cardiac disease controls exposed, 4 voter controls exposed])	Exposure to paraquat assessed via questionnaire; exposure defined as handling paraquat or working in an area that had been recently sprayed	Idiopathic parkinsonism Diagnosed by a neurologist based on patients having two of the following symptoms: resting tremor, rigidity, bradykinesia, and loss of postural reflexes	**ns** adjOR for paraquat exposure (cardiac disease controls) **ns** adjOR for paraquat exposure (voter controls)	Hertzman et al. (1994)
France	Agriculture workers in Agriculture and Cancer cohort	Cross-sectional[b] (149,810 participants, Parkinson's disease reported in 1,732 participants; 244 cases exposed and 25,298 non-cases exposed)	Exposure was assessed using the French crop-exposure matrix PESTIMAT, which reconstitutes pesticide use since 1950 in the main crops	Parkinson's disease Self-reporting of doctor-diagnosed Parkinson's disease, age range at diagnosis, and having at least two parkinsonian symptoms (tremor in hands or feet; rigidity of arms or legs; slowness or tightening in daily living, walking, or speaking)	**ns** adjOR for paraquat exposure (1–25 years) **ns** adjOR for paraquat exposure (26–46 years) **ns** adjOR for ever paraquat exposure (when adjusted for co-exposure between active ingredients)	Pouchieu et al. (2018)

Country; State/Region	Study Population	Study Design (n)	Exposure Assessment	Outcome Assessment	Results	Study
United Kingdom; Widnes	Paraquat production workers	Cohort (retrospective) (968 workers [1 case of Parkinson's disease])	Workers at a paraquat manufacturing plant in Widnes; although there were some monitoring data, there was insufficient sampling information available to perform a quantitative exposure assessment	Parkinson's disease (cause of death) Diagnosed based on review of death certificate	No significant change in standardized mortality ratio either with Parkinson's disease mentioned as cause of death or as an underlying cause of death	Tomenson and Campbell (2011)
The Netherlands	Parkinson's patients and controls from 5 hospitals	Case-control (444 cases [33 exposed], 876 controls [58 exposed])	Exposure estimated to specific active ingredient by linking self-reported crops cultivated at the subject's farm to a crop-exposure matrix	Parkinson's disease Medical files reviewed by neurologist to confirm case diagnosis	**ns** adjOR for exposure based on median of the distribution of the different exposures among controls	van der Mark et al. (2014)

FAME = farming and movement evaluation; adjOR = adjusted odds ratio; adjPR = adjusted prevalence rate; CI = confidence interval; **ns** = no change; 🡩 = increase; 🡩* = significant increase; 🡩ǂ = significant trend.
[a]Studies examining FAME participants were nested case-control studies.
[b]Agriculture and Cancer is a prospective cohort, but results were from the baseline questionnaire only; therefore, the study is considered a cross-sectional analysis.
Additional study details available in Figure F-2.

Table 3. Epidemiological Studies Evaluating Environmental Paraquat Exposure and Parkinson's Disease

Country; State/Region	Study Population	Study Design (n)	Exposure Assessment	Outcome Assessment	Results	Study
United States; California	Parkinson's Environment and Genes Study (PEG) participants Central Valley, CA residents	Case-control (368 cases [149 paraquat only], 341 controls [152 paraquat only])	Average annual exposure estimated using self-reported residence and workplace address histories combined with pesticide use data from California Department of Pesticide Regulation and land use maps from California Department of Water Resources	Parkinson's disease Diagnosed based on examination by a UCLA movement disorder specialist and confirmation of clinically probable or possible Parkinson's disease	*Exposure status (1974–1999):* **ns** adjOR for paraquat-only exposure	Costello et al. (2009)
United States; California	PEG participants Central Valley, CA residents	Case-control (368 cases [79 exposed], 341 controls [60 exposed])	Estimated ambient exposure for historical residential addresses inhabited between 1974 and 1999 using GIS modeling; exposure from private well water was estimated based on a combination of pesticide use and application data and self-reports of private wells as drinking water sources at a residential address	Parkinson's disease Diagnosis of clinically probable or possible Parkinson's disease cases confirmed by UCLA movement disorder specialist based on 5 criteria related to parkinsonian syndrome	**ns** adjOR for any of the paraquat exposure	Gatto et al. (2009)
United States; California	PEG participants Central Valley, CA residents	Case-control (333 cases, 336 controls [number of exposed ranged from 4 to 105, depending on exposure {high}, age of onset, and genotype])	Estimated ambient exposure from pesticide application to agricultural crops using a GIS-based exposure assessment tool using geocoded lifetime address data, historical pesticide use data from the California Department of Pesticide Regulation, and land use data	Parkinson's disease Diagnosis of incident idiopathic Parkinson's disease confirmed by UCLA movement disorder specialists	No significant changes in adjusted OR, but trend for increased OR with high paraquat exposure, with onset of Parkinson's disease ≤68 years old, and with α-synuclein variations	Gatto et al. (2010)

Country; State/Region	Study Population	Study Design (n)	Exposure Assessment	Outcome Assessment	Results	Study
United States; California	PEG participants Central Valley, CA residents	Case-control (362 cases [81 workplace, 109 residential paraquat-only], 341 controls [78 workplace, 125 residential paraquat only])	Average annual exposure estimated using residence and workplace address histories combined with pesticide use data from California Department of Pesticide Regulation and land use maps from California Department of Water Resources	Parkinson's disease Diagnosed based on examination by a UCLA movement disorder specialist and confirmation of clinically probable or possible Parkinson's disease	*Workplace exposure status:* **ns** adjOR for paraquat exposure *Residential exposure status:* **ns** adjOR for paraquat exposure	Wang et al. (2011)
United States; California	PEG participants Central Valley, CA residents Subjects are the same as those reported in Costello et al. (2009)	Case-control (357 cases [169 exposed], 754 controls [291 exposed])	Average annual exposure estimated using residence and workplace address histories combined with pesticide use data from California Department of Pesticide Regulation and land use maps from California Department of Water Resources	Idiopathic Parkinson's disease Diagnosed by UCLA movement disorder specialists	**↑*** adjOR for ambient residential and workplace exposures	Lee et al. (2012)
United States; California	PEG participants Central Valley, CA residents	Case-control (619 cases [245 exposed], 854 controls [296 exposed])	Ambient exposure was estimated using a GIS model combined with pesticide use data and land use maps from California	Parkinson's disease Clinical confirmation of Parkinson's diagnosis by a UCLA movement disorder specialist	**↑*** adjOR for ambient residence and workplace paraquat exposure *Paraquat exposure by genotype:* **↑*** adjOR for high exposure only with 2 risk genotypes (significant interaction)	Sanders et al. (2017)

OR = odds ratio; adjOR = adjusted odds ratio; **ns** = no change; **↑** = increase; **↑*** = significant increase.
Additional study details available in Figure F-3.

Table 4. Epidemiological Studies Evaluating Paraquat Exposure and Parkinson's Disease in the General Population

Country; State/Region	Study Population	Study Design (n)	Exposure Assessment	Outcome Assessment	Results	Study
United States; Nebraska	Residents of Nebraska	Ecological (6,557 cases [numbers of exposed in each quartile not reported])	Estimated from GIS modeling using combination of land use data, pesticide usage databases, and historical pesticide use surveys	Parkinson's disease Spatial analysis of Parkinson's disease—exposure associations based on statewide population-based Parkinson's disease registry	Higher risk of Parkinson's disease in Q3 (medium-high) and Q4 (high) exposure to paraquat compared with Q1 (low exposure group), but trend for risk was not significant (i.e., Q4 risk was not higher compared with Q3)	Wan and Lin (2016)
United States; Texas	Parkinson's patients and controls from East Texas neurology practice	Case-control (100 cases [4 exposed], 84 controls [1 exposed])	Exposure estimated from self-reported lifetime use of paraquat	Parkinson's disease Diagnosed by a neurologist specializing in movement disorders based on standard clinical/lab diagnostic criteria	**ns** OR for ever personally used/mixed or applied paraquat (large OR, but not significant due to wide CI)	Dhillon et al. (2008)
United States; Washington	Group Health Cooperative (GHC) of Washington State	Case-control (250 cases [2 exposed], 388 controls [2 exposed])	Paraquat exposure was based on self-reported occupational and home-based pesticide use during structured interview; occupational pesticide exposure based on checklist of common chemical agents, whereas home-based pesticide exposure was based on a checklist of commercial brand name products (paraquat was listed under chemicals for occupational exposure, but not specifically listed for home-based use)	Parkinson's disease Cases identified using provider referrals and computerized databases; Parkinson's disease diagnoses confirmed by a neurologist via medical chart review, requiring at least 2 of 4 signs of Parkinson's disease: bradykinesia, resting tremor, cogwheel rigidity, postural reflex impairment	*<u>Paraquat exposure vs. no exposure:</u>* **ns** adjOR for any paraquat exposure	Firestone et al. (2005)

Country; State/Region	Study Population	Study Design (n)	Exposure Assessment	Outcome Assessment	Results	Study
United States; Washington	GHC of Washington State	Case-control (404 cases, 526 controls; 252 male cases [2 exposed], 326 male controls [3 exposed]; 152 female cases [0 exposed], 200 female controls [0 exposed])	Paraquat exposure was based on self-reported workplace exposure to various toxicants from a checklist of other things including paraquat	Parkinson's disease Cases identified using provider referrals or computerized databases; a panel of neurologists confirmed Parkinson's disease diagnoses by medical chart review, requiring at least 2 of 4 signs of Parkinson's disease: bradykinesia, resting tremor, cogwheel rigidity, postural reflex impairment	*<u>Paraquat exposure vs. no exposure:</u>* **ns** adjOR for any paraquat exposure in males; OR could not be calculated for females	Firestone et al. (2010)
British Columbia	Parkinson's patients and controls from a mountainous rural area	Case-control (57 cases [4 exposed], 122 controls [0 exposed])	Exposure estimated based on self-reporting of private well-water use, occupational history, and past chemical handling (e.g., question asked ever handled paraquat)	Parkinson's disease Based on physician reporting of Parkinson's disease patients under their care and a follow-up neurologist examination	No OR could be calculated	Hertzman et al. (1990)
The Netherlands	Parkinson's patients and controls from five hospitals	Case-control (352 cases [181 exposed], 607 controls [322 exposed])	Exposure estimated using a spatio-temporal model to assign environmental pesticide exposure to residential addresses (based on crop cultivation within 100 m of the residence, then split into two different distance categories 0–50 m and >50–100 m)	Parkinson's disease Medical files reviewed by neurologist to confirm case diagnosis	**ns** adjOR for ever exposure to paraquat or by tertile regardless of distance category	Brouwer et al. (2017)
Taiwan, Province of China; Taipei	Parkinson's patients and hospital controls	Case-control (120 cases [31 exposed], 240 controls [22 exposed])	Exposure estimated based on self-reporting of residential and farming history, drinking water sources, and pesticide use/exposure (subjects were asked to identify specific herbicides/pesticides and chemicals they had used)	Parkinson's disease Diagnosed at the Movement Disorder Clinic of National Taiwan University Hospital, based on 2 or more cardinal signs of Parkinson's disease: resting tremor, cogwheel rigidity, bradykinesia, postural reflex instability, responsiveness to levodopa therapy	**↑*** OR for ever paraquat use **↑*** adjOR for paraquat use >20 years	Liou et al. (1997)

OR = odds ratio; adjOR = adjusted odds ratio; CI = confidence interval; **ns** = no change; **↑** = increase; **↑*** = significant increase.
Additional study details available in Figure F-4.

Environmental and General Population Studies

For this review, the epidemiological studies that did not specifically investigate occupational exposures were divided into environmental exposures where locations of residences or workplaces might be expected to contain moderate levels of paraquat (Table 3) and those with paraquat exposures representative of the general population with the lowest levels of paraquat exposures expected (Table 4). Few significant associations were observed in the studies classified in either of these categories (Figure F-3 and Figure F-4). The Parkinson's Disease, Environment, and Gene (PEG) Study recruited participants between 2001 and 2007 and between 2010 and 2015 and assessed the potential relationship between environmental susceptibility (including exposure to pesticides such as paraquat) and genetics in rural Parkinson's disease patients. The PEG study used a population-based approach to identify Parkinson's disease cases in three counties (Fresno, Tulare, and Kern) of California. Six resulting articles evaluated the association between paraquat exposure and Parkinson's disease in participants from the study. It was not clear in every case whether the report was officially a PEG study because some reports noted that cases were enrolled in the PEG study, whereas others cited a common reference for methods (Kang et al. 2005) but did not refer to the PEG study by name. The majority of these studies did not observe significantly higher adjusted odds ratios with paraquat exposure (Costello et al. 2009; Gatto et al. 2009; Gatto et al. 2010; Wang et al. 2011). Although Gatto et al. (2010) did not report any significant findings with paraquat exposure, adjusted odds ratios tended to increase with higher paraquat exposure for those subjects with onset of Parkinson's disease at ≤68 years old, and with α-synuclein gene variations (adjOR 3.15; 95% CI 0.74–13.37). Indications of increased risk with paraquat exposure were reported in some PEG studies. Lee et al. (2012) evaluated ambient residential and workplace exposures to paraquat and observed a significant increase in risk (adjOR 1.36; 95% CI 1.02–1.81). High paraquat exposures at residences or workplaces in subjects containing two risk genotypes (i.e., base excision repair single nucleotide polymorphisms in *APEX1* and *OGG1* genes) were observed to significantly increase risk (Sanders et al. 2017).

Two other studies in locations other than California found significant associations between paraquat exposure and Parkinson's disease. In a study in Taiwan evaluating environmental risk factors for Parkinson's disease, duration of paraquat use of >20 years was associated with a significant increased risk (adjOR 6.44; 95% CI 2.41–17.2) (Liou et al. 1997). An ecological study cross-referenced a statewide registry of patients diagnosed with Parkinson's disease in Nebraska with land use and pesticide exposure databases to perform a spatial analysis of paraquat exposure levels and risk of Parkinson's disease (Wan and Lin 2016). While the two highest quartiles of paraquat exposures were associated with higher risk than the lowest quartile, the risk did not increase significantly between the two highest exposure groups (i.e., the response did not increase in a concentration-dependent manner).

Animal Studies

Animal models do not develop Parkinson's disease per se and instead were categorized by neurocognitive effects that might be expected to correlate with parkinsonism symptoms in humans including primary effects such as motor activity, motor coordination, motor skills, number of dopaminergic neurons (i.e., number of tyrosine hydroxylase-positive [TH+] neurons), as well as other cognitive effects such as anxiety and memory. Secondary effects included mechanistic data such as levels of dopamine, density of TH immunoreactivity, or other biochemical changes associated with Parkinson's disease, as well as general effects to the nervous system such as measurements of oxidative stress levels.

A total of 143 experimental studies in laboratory animals were identified as measuring primary endpoints and 190 as measuring secondary endpoints (Figure 1); 119 studies reported both primary and secondary endpoints. Primary endpoints were measured in 113 mammalian studies (Figure 2). A variety of neurological effects were investigated, including 66 studies that estimated the number of dopaminergic cells by measuring the number of TH+ neurons. Changes in locomotor activity were the most often reported neurobehavioral effects, including locomotion (34 studies) and distance traveled (6 studies) followed by effects on motor skills (34 studies). Some studies reported qualitative results that were not eligible for quantitative data extraction but might provide relevant information about the link between paraquat exposure and parkinsonism (e.g., descriptive histopathology of the brain in 13 studies). The majority of the animal studies with endpoints specific for parkinsonism did not report administration of paraquat via a route that would be relevant to human exposures (i.e., oral, dermal, or inhalation) with 83 of the 113 studies using intraperitoneal injection and most others using subcutaneous or other methods of administration (including intracranial in a couple of cases) (Figure 2).

Effect	Endpoint	Route of Exposure: Oral Diet	Oral Gavage	Oral Drinking Water	Dermal	Intraperitoneal Injection	Subcutaneous Injection	Other	Unknown	Grand Total
Muscular Effects	Movement: distance traveled					3	2		1	6
	Movement: gait			1		3				4
	Movement: locomotion		3		1	26	3	1	1	34
	Movement: posture					1				1
	Muscle contraction					2		1		2
	Posture					1				1
	Total		3	1	1	33	4	2	1	43
Nervous System Effects	Nerve degeneration: total number of neurons					15				15
	Nerve degeneration: total number of TH+ neurons	1				58	3	3	1	66
	Seizures/Tremors					3		2		3
	Sensation disorders: olfactory perception					2		1		3
	Sensation disorders: pain perception					1				1
	Total	1				65	3	5	1	73
Psychomotor Effects	Behavior: exploratory				1	5	1	1	1	9
	Behavior: immobility					2				2
	Emotional effects: anxiety				1	3	1	1		6
	Emotional effects: depression					2		1		3
	Learning: avoidance					1				1
	Learning: spatial memory		2			2	1	1		6
	Memory						1		1	2
	Motor skills		2	2	1	22	4	2	1	34
	Task performance							1		1
	Total		4	2	1	29	4	2	1	43
Other	Qualitative histopathology		2	1	1	3	1	5		13
	Total activity (data not shown)					1				1
	Electrocorticogram results							1		1
	Acute effects (seizures/tremors)					1				1
	Acute toxicity study		1			1	1	2		5
	Induced activity assay							1		1
	Total		3	1	1	6	1	7		19
Grand Total		1	7	3	1	83	8	12	1	113

Figure 2. Number of Studies That Evaluated Primary Effects Following Paraquat Exposures in Mammalian Models

Numbers indicate the counts of studies that have investigated the identified endpoints; no indication of direction or significance of effect is provided. Some studies might have characterized multiple health effects or multiple routes of exposure and therefore could be listed multiple times. Row and column totals and grand total shown in the figure represent counts of distinct references. The endpoint movement: locomotion under Muscular Effects and the endpoint behavior: exploratory under Psychomotor Effects are interlinked and sometimes measured using the same open field test. However, exploratory behavior is used for endpoints that measured a specific behavior that reflected more than simple locomotor movement. This may include specific patterns of movement or other designations of exploration given by study authors.
Interactive figure and additional study details in Tableau (NTP, 2019b).

High External Validity Study Designs

Because humans are exposed to paraquat through diet or direct contact via inhalation or skin, study designs that administered paraquat through these routes and measured primary effects in mammals were considered to be the most informative to human exposure scenarios and Parkinson's disease (i.e., high external validity). Eleven studies in rats and mice reported administration of paraquat via dermal (n = 1), oral (n = 9), inhalation (n = 0), and intranasal (n = 1) exposures and evaluated a primary health effect, with most measuring neuromuscular effects including locomotor activity, motor skills, and cognitive behavior (Figure 3). Several studies using orally exposed rats or mice reported data for secondary animal effects and will be discussed in the following section on secondary effects.

		Direction of Effect			
Effect	**Subeffect**	**↑**	**↓**	**NS**	**Grand Total**
Muscular Effects	Movement: gait			1	1
	Movement: locomotion	1	2	3	4
Nervous System Effects	Nerve degeneration: total number of TH+ neurons			2	2
Psychomotor Effects	Behavior: exploratory		1	1	1
	Emotional effects: anxiety		1	1	1
	Learning: spatial memory	2	1	2	2
	Motor skills		2	4	5
Grand Total		3	5	9	11

Figure 3. Number of Studies and Direction of Effect for Primary Animal Effects Evaluated Following Oral, Dermal, or Inhalation Paraquat Exposures in Mammalian Models

Some studies might have characterized multiple health effects and therefore could be represented multiple times. Row and column grand totals represent counts of distinct references. The endpoint movement: locomotion under Muscular Effects and the endpoint behavior: exploratory under Psychomotor Effects are interlinked and sometimes measured using the same open field test. However, exploratory behavior is used for endpoints that measured a specific behavior that reflected more than simple locomotor movement. This may include specific patterns of movement or other designations of exploration given by study authors.
Interactive figure and additional study details in Tableau (NTP, 2019b).
Study data for these 11 studies are available on HAWC (NTP, 2019a).

Comparing across these studies, paraquat was reported to elicit neuromuscular effects more often in mice relative to rats. Two oral gavage studies in mice evaluated locomotor activity and observed decreases in activity (Fredriksson et al. 1993; Ren et al. 2009). Both studies used C57BL/6 mice, but the doses differed: Fredriksson et al. (1993) administered 0.07 and/or 0.36 mg/kg over two days depending on the age of the mice and Ren et al. (2009) administered 10 mg/kg/day for 4 months. A third oral gavage study noted effects on learning and spatial memory in C57BL/6 mice, as indicated by an increase in escape latency in the probe test of the Morris water maze (Lou et al. 2016). This study, however, evaluated latency to find the platform, which could have been affected by motor activity and was not discussed, even though some animals died. Chen et al. (2010) evaluated learning and spatial memory in Kunming mice using the Morris water maze. Mice were exposed to 0.89, 2.67, or 8 mg/kg/day via oral gavage, and the study reported both an increased latency to reach the platform (on multiple training days) and a decrease in the number of times passing the platform (as part of the spatial probe test). The study did not report whether motor activity was affected, nor any mortality or clinical signs in the animals. An oral gavage dose of 20 mg/kg/day to male Swiss mice was found to cause a significant change in motor skills as indicated by decreased latency to fall from the rotarod test (Satpute et al. 2017). Doses of 10–20 mg/kg/day in drinking water did not have significant effects on motor skills in female C57BL/6 mice (Naudet et al. 2017), or male wild-type CuZnSOD mice when tested at 4 months or 2 years of age (Peled-Kamar et al. 1997). Two studies investigated the number of TH+ neurons in C57BL/6 mice but did not report a significant change with doses up to 21.5 mg/kg/day in females exposed via diet for 13 weeks (Minnema et al. 2014) or male mice exposed to 20 mg/kg/day via intranasal inoculation for 30 days (Rojo et al. 2007) (Figure 3).

No significant effects on motor skills were noted in male AP rats orally exposed to 5 mg/kg/day paraquat (Widdowson et al. 1996). Dermal administration of 40 mg/kg/day paraquat to female Wistar rats did not cause a significant change in locomotor activity, but did decrease motor skills as measured by climbing on blocks less frequently (Luty et al. 1997). Luty et al. (1997) also observed no differences in exploration, as measured by interest in blocks, or anxiety, as measured by washing and defecations, in female Wistar rats dermally administered 40 mg/kg/day for 28 days. However, interest in blocks and defecations significantly decreased after 14 days of treatment (note: defecations were also lower prior to paraquat exposure). Two additional studies in rats that administered paraquat via relevant exposure routes reported qualitative histopathology only and were not displayed in the figures (Caroleo et al. 1996; Li et al. 2015).

Secondary Effects in Mammals

Effects that were classified as secondary effects included indirect measures of dopaminergic neurons, modifications of α-synuclein levels, mitochondrial dysfunction, and general measures of oxidative stress (Figure 4 and Figure 5). Of the 11 studies in rats and mice that administered paraquat via exposure routes relevant to human exposures (dermal, oral, inhalation, and intranasal), 9 also assessed relevant secondary animal effects. An additional 5 studies using relevant exposure routes evaluated secondary animal effects only and are included in Figure 4 for a total of 14 studies. Oxidative stress parameters were examined in rats and mice, along with changes in levels of dopamine, dopamine metabolites, and other neurotransmitters. Glial or astrocyte activity, as well as alpha-synuclein and expression of glial fibrillary acidic protein, were also described in mice. Other endpoints evaluated included mitochondrial dysfunction and lipid peroxidation.

Studies using exposure routes less relevant to humans also evaluated a wide variety of secondary endpoints in various mammalian models (Figure 5). Rats and mice were the most-studied species with the majority of rodent studies focused on effects on dopamine, gene expression, and oxidative stress. Other more general mechanisms such as oxidative stress and changes in genes or protein levels have also been evaluated following paraquat exposure. However, as was observed with the primary effects, the route of exposure for most of these studies was injection (interactive Figure 5 (NTP, 2019b)).

Alternative Model Organisms

Several nonmammalian organisms have also been used as models to investigate paraquat exposures to primary outcomes (Figure 6) and secondary outcomes (Figure F-5), modeling some aspects of Parkinson's disease. Similar to the rodent studies discussed earlier, the specific endpoints used to measure paraquat effects in these studies vary between species and studies, but the most-often-studied primary endpoint category was locomotor activity (Figure 6). With 20 studies describing the primary effects of paraquat on *Drosophila*, the species has been used as a model for Parkinson's disease. These studies often investigated genetic changes reported to be associated with Parkinson's disease with climbing being the primary measured effect on locomotor activity. Ten studies evaluated primary effects in other nonmammalian species, including zebrafish and *Caenorhabditis elegans*. The main primary endpoint category in these models was also locomotor activity (Figure 6).

Effect	Species: Rat	Species: Mouse	Grand Total
Dopamine (DA and metabolite levels, DAT and receptor expression, TH immunoreactivity)	1	5	6
Alpha synuclein, tau phosphorylation, tubulin		1	1
Other neurotransmitters (levels, receptors)	1	2	3
General mRNA, protein, or gene expression	1	1	2
Microglial activation and/or glial response		1	1
Mitochondrial effects		1	1
Other (apoptosis, etc.)	2	5	7
Oxidative stress	2	4	6
Grand Total	4	10	14

Figure 4. Number of Studies That Evaluated Secondary Animal Effects Following Oral, Dermal, or Inhalation Paraquat Exposures in Mammalian Models

Numbers indicate the counts of studies that have investigated the identified endpoints; no indication of direction or significance of effect is provided. Some studies might have characterized multiple health effects or species and therefore could be represented multiple times. Row and column grand totals represent counts of distinct references.
Interactive figure and additional study details in Tableau (NTP, 2019b).

As with primary effects, *Drosophila* were used in a number of secondary effects studies (n = 28) to evaluate different mechanistic aspects of paraquat, including modification effects of different genes known to play a role in human familial and sporadic Parkinson's disease (e.g., *DJ-1* [parkin] and *LRKK2* [leucine-rich repeat kinase 2]). Most of these studies evaluated dopamine levels or some other measure to address changes in dopamine (e.g., dopamine metabolites, density of TH immunoreactivity) (Figure F-5).

Effect	Rat	Mouse	Squirrel monkey	Grand Total
	Species			
Dopamine (DA and metabolite levels, DAT and receptor expression, TH immunoreactivity)	19	40	1	60
Alpha synuclein, tau phosphorylation, tubulin	3	15		18
Other neurotransmitters (levels, receptors)	2	5	1	8
General mRNA, protein, or gene expression	7	29		36
Microglial activation and/or glial response	4	14		18
Mitochondrial effects	4	6		10
Other (apoptosis, etc.)	13	23		36
Oxidative stress	18	27		45
Survival (whole animal)	2	3		5
Grand Total	44	81	1	126

Figure 5. Number of Studies That Evaluated Secondary Animal Effects Following Paraquat Exposures via Other Routes in Mammalian Models

Numbers indicate the counts of studies that have investigated the identified endpoints; no indication of direction or significance of effect is provided. Some studies might have characterized multiple health effects or species and therefore could be represented multiple times. Row and column grand totals represent counts of distinct references.
Interactive figure and additional study details in Tableau (NTP, 2019b).

Effect	Drosophila	Frog	Zebrafish	Nematode	Grand Total
	Species				
Dopaminergic neurons	3		1		4
Behavior - aggression			2		2
Behavior - anxiety			2		2
Behavior - exploratory activity			2		2
Behavior - learning and memory			1		1
Behavior - locomotor activity	19	2	7	1	29
Behavior - social			2		2
Sensation disorders				1	1
Grand Total	20	2	7	1	30

Figure 6. Number of Studies That Evaluated Primary Animal Effects Following Paraquat Exposures in Nonmammalian Models

Numbers indicate the counts of studies that have investigated the identified endpoints; no indication of direction or significance of effect is provided. Some studies might have characterized multiple health effects or species and therefore could be represented multiple times. Row and column grand totals represent counts of distinct references. The endpoints Behavior – exploratory activity and Behavior – locomotor activity are interlinked and sometimes measured using the same open field test. However, exploratory behavior is used for endpoints that measured a specific behavior that reflected more than simple locomotor movement. This may include specific patterns of movement or other designations of exploration given by study authors. Interactive figure and additional study details in Tableau (NTP, 2019b).

In Vitro Studies

Two hundred and forty-four studies were identified to have in vitro data potentially relevant to mechanistic links between paraquat exposure and Parkinson's disease either specifically or to the nervous system in general (Figure 1); 68 of these studies only used paraquat as a positive control to induce oxidative stress and are not further characterized in this report. The most-studied outcome categories included oxidative stress, cell viability, mitochondrial effects, and changes in gene expression, which are the same categories that were most reported in the animal in vivo secondary effects (Figure 7). These most-studied categories are also general effects, whereas the endpoints that might provide more specific mechanistic information for Parkinson's disease (e.g., TH+ neurons/dopamine and metabolite levels, α-synuclein) were less studied with a total of 16 studies each of dopaminergic neuron counts (TH+ neurons) and protein aggregation (mainly α-synuclein). The vast majority of human in vitro studies reported use of tumor cell lines including mostly SH-SY5Y, a neuroblastoma cell line originally derived from a bone marrow metastasis (48 of 80 total human in vitro studies), and the parent line of SH-SY5Y, SK-N-SH (seven studies). Only one study used primary human brain cells (HA1800 astrocytes), whereas three used Parkinson's disease patient-derived primary fibroblasts. Similarly, very few human in vitro studies used stem cells, including neural progenitor cells (n = 6), iPSC astrocytes (n = 1), and transformed neuroblasts (n = 1). The number of studies reporting rat in vitro models were second to human models with a total of 74 studies using a variety of rat models, including the tumor cell line PC12 (n = 20), a cell line isolated from an adrenal gland tumor of embryonic origin composed partially of neuroblasts that can be differentiated into neurons with some dopaminergic characteristics (Malagelada and Greene 2008). PC12 cells were most often used to study general categories, such as oxidative stress and cell viability. Other commonly reported in vitro models derived from rat or mouse included mesencephalic models, such as the transformed rat cell line N27 (n = 17), and primary cultures of neurons and mixed cell types. Other rodent in vitro models included ex vivo studies of brain tissue cultures and brain slices, and subcellular fractionations of organelles, such as brain mitochondria and synaptosomes.

	Species					
Effect	**Human**	**Mouse**	**Rat**	**Rat x Mouse**	**Cow**	**Grand Total**
DA (TH+) neurons	2	9	8			16
Dopamine (DA and metabolite levels, DAT and receptor expression, TH immunoreactivity)	4	1	6	1		11
Alpha synuclein, tau phosphorylation, tubulin	11	2	4			16
Proteasome (parkin, proteasomal activity)	10		3			13
Mitochondrial effects	22	2	13			37
Other (general expression changes, etc.)	39	13	28			77
Oxidative stress	40	12	39	2		88
Cell viability (LDH levels, apoptosis, total cell number)	64	18	60	2	1	135
Grand Total	80	29	74	2	1	176

Figure 7. Number of Studies That Evaluated In Vitro Effects Evaluated Following Paraquat Exposures

Numbers indicate the counts of studies that have investigated the identified endpoints; no indication of direction or significance of effect is provided. Some studies might have characterized multiple health effects or species and therefore could be represented multiple times. Row and column grand totals represent counts of distinct references. The "Rat × Mouse" column includes studies using either a hybrid cell line or a combination of rat and mouse cells.
Interactive figure and additional study details in Tableau (NTP, 2019b).

Discussion

Using systematic review methodologies, this scoping review of peer-reviewed, published scientific literature identified a sizable body of evidence comprising 458 studies that provide information about the association between exposure to paraquat and potential development of Parkinson’s disease (Figure 1). Interactive evidence maps were developed to allow readers to sort and explore the published scientific literature by study type, exposure scenarios, and measured endpoints. These maps include eight Tableau figures with qualitative summaries of the characteristics of each line of evidence, as well as three HAWC figures with quantitative summaries of the epidemiological evidence. All or part of this evidence base could be followed and updated over time to monitor the field and scientific advances.

A total of 24 human studies investigating the association between paraquat exposure and primary effects of Parkinson’s disease were identified, with the majority being case-control studies (Figure F-1). The largest studies focused on occupational exposures including the Agricultural Health Study (AHS), a large prospective cohort of agricultural workers in the United States, and the nested case-control studies in the Farming and Movement Evaluation (FAME) cohort, which reported significant associations between paraquat exposures and prevalence of Parkinson’s disease (Furlong et al. 2015; Goldman et al. 2012; Kamel et al. 2014; Kamel et al. 2007; Tanner et al. 2011). In these studies, paraquat exposures and co-exposures to other pesticides were captured by questionnaires. Although no formal study quality assessment was performed, some characteristics of the overall evidence base were noted. For example, most epidemiological studies reported few cases of Parkinson’s disease and were conducted in locations with higher environmental exposures (e.g., residences or workplaces near agricultural fields); few studies with exposures representative of the general population were identified.

Whereas human studies evaluated self-reported or clinician-confirmed cases of Parkinson’s disease or symptoms of parkinsonism, evidence in experimental animals and in vitro model systems comprised models of parkinsonism symptoms or known/suspected mechanisms leading to Parkinson’s disease in humans. To develop the inclusion criteria for these studies, the National Toxicology Program (NTP) worked closely with the U.S. Environmental Protection Agency (EPA) Office of Pesticide Programs (OPP) to identify primary outcomes that were most directly related to human Parkinson’s disease, such as loss of dopaminergic neurons and neuromuscular deficits, as well as secondary outcomes that were more mechanistic in nature, such as decreases in dopamine and other biochemical changes associated with Parkinson’s disease, and more general responses including changes in gene expression and oxidative stress levels.

A total of 143 experimental animal studies reported primary endpoints with 113 studies reporting effects observed in mammals (Figure 2) and 30 studies in nonmammalian models (Figure 6). The experimental designs across these studies differed with a variety of dosing regimens and measured health endpoints with some specifically designed to model some component of Parkinson’s disease and others that were not. The most commonly reported outcome categories were neuromuscular effects, including effects on locomotor activity, as well as dopaminergic neuron degeneration. In most of these studies, paraquat was administered via injection, whereas humans are mainly exposed via dermal, inhalation, or oral routes and 11 studies in rats and mice reported the use of these more human-relevant exposure routes (Figure 3). *Drosophila*, zebrafish, and *C. elegans* were the primary nonmammalian species used to investigate mechanistic aspects of Parkinson's disease, including consequences of genetic changes and α-synuclein accumulation. As was noted with primary endpoint studies in mammals, studies on these nonmammalian species mostly evaluated locomotor activity (Figure 6). Secondary effects studies in these species might provide key mechanistic information on the potential development of Parkinson's disease after exposures to paraquat (Figure F-2) but require follow-up studies in mammals or humans to verify relevance.

In addition to alternative whole organism models, various in vitro model systems were used to investigate the mechanisms of paraquat exposures on endpoints potentially relevant to the development of Parkinson's disease (Figure 7). Overall, 244 in vitro studies were included at the full-text level with 68 of these studies describing the use of paraquat as a positive control used to induce oxidative stress. Of the remaining 176 studies that were investigating paraquat's effects on cells, the general effects of cell death, oxidative stress, and mitochondrial stress were among the most measured. These studies might provide important information about how oxidative stress could contribute to Parkinson's disease. More recently, a variety of in vitro models have been reported, including primary cell cultures and stem cells, which might include mixed cell types or genotypes from Parkinson's disease patients and could allow for chronic exposures and more relevant endpoint measurements, such as neurite outgrowth versus cytotoxicity.

Limitations of the Evidence Base

Key information gaps and scientific challenges were identified in the corpus of available scientific literature that describe associations between paraquat exposures and development of Parkinson's disease. However, it should be noted that individual study quality assessment was not included in this scoping review.

Gaps and challenges identified in the human evidence include:

- Most epidemiological studies were small case-control studies with very few cases of paraquat-exposed participants, and even fewer reported or confirmed cases of Parkinson's disease; this is particularly true for studies that might be more representative of the general population in the United States.
- Most cases of Parkinson's disease are self-reported, prevalent cases (i.e., participants report prior diagnosis or symptoms) rather than clinician-confirmed incident cases (i.e., newly diagnosed cases). Incidence might be difficult to measure due to the progressive nature of Parkinson's disease such that initial symptoms might go unnoticed or unreported (e.g., disrupted sleep, slight tremor).
- Females were not included in most epidemiological studies, except in the few that included spouses of agricultural workers, namely those associated with the AHS. Thus, the vast majority of reported cases were male and even population-based studies did not include female cases.
- Occupational studies included co-exposures to other pesticides and reported significant associations for one or more, including rotenone, although adjustment for co-exposures was often lacking (Furlong et al. 2015; Kamel et al. 2014; Tanner et al. 2011). Pouchieu et al. (2018) observed a significant association between paraquat and Parkinson's disease, but this study was eliminated when the authors adjusted for co-exposure between active ingredients. Studies of environmental exposure based on the

PEG cohort also had potential co-exposures to other pesticides. Studies that adjusted for exposure to other pesticides or included subjects only exposed to paraquat in the analysis did not observe an association between paraquat exposure and Parkinson's disease.

- Exposure was mainly self-reported via questionnaires. Participants in environmental and general population studies might not be aware of paraquat exposures, and cases in retrospective studies might be prone to recall bias.

Gaps and challenges identified in the animal and in vitro evidence include:

- Animal models do not specifically develop Parkinson's disease. Instead, deficits in dopaminergic neurons and associated neuromuscular and neurobehavioral deficits after exposures to paraquat are used to model parkinsonism.
- The paraquat exposure regimes and measured health effects endpoints varied widely across the animal and in vitro data.
- The majority of mammalian studies reported exposure to paraquat via injection, whereas humans are exposed to paraquat via dermal, oral, and inhalation routes.
- Exposure scenarios in animals might have been sufficiently high and acute, such that the effects on activity or muscle coordination might be more indicative of general toxicity than of Parkinson's disease-like behaviors.
- Despite the challenges noted above, it is important to note that acute exposures to some compounds such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) via injections lead to parkinsonism in animals, including humans; thus, these studies might provide mechanistic information about paraquat's potential effects and the effects of oxidative stress on dopaminergic neurons in general.
- Most in vitro studies reported the use of tumor-derived cell lines to study general stress responses.

Limitations of the Scoping Review

Case reports or case series were not included in this review because they do not include non-exposed comparators and most describe high, acute exposures to paraquat, such as those in accidental poisonings with unclear connections to Parkinson's disease. Although not included here, case reports might be useful for determining mechanistic insight as long as the limitations noted above are considered. For example, a case series in China reported acute exposures of subjects to paraquat mainly after suicide attempts (Wu et al. 2012). Results included significant abnormalities in the MRI scans of brains from two surviving patients with neurological symptoms, with some results still abnormal a year later.

A total of 45 reports were excluded at the full-text level because they were published in a language other than English. These reports might contain additional useful data that could contribute to a full systematic review.

It should be noted that this scoping review was limited to data from the published scientific literature. Inclusion of proprietary pesticide literature and unpublished studies were beyond the scope of this review but would potentially increase the knowledge base of any future health hazard evaluations.

Summary

In summary, a relatively large body of evidence was identified that collectively describes the potential association between paraquat exposure and Parkinson's disease. Several recommendations can be drawn from this evidence to inform future research. Future epidemiological studies could include biomonitoring of specific pesticide exposures to separate paraquat's effects from those of other chemicals and mixtures. Inclusion of higher numbers of paraquat-exposed and incident Parkinson's disease cases from the general population (including women exposed to paraquat and/or with symptoms of Parkinson's disease) would allow findings to be further generalized beyond occupational settings. To increase the direct relevance of experimental animal studies to human Parkinson's disease, future laboratory animal studies could include administration of paraquat via a route that is more relevant to the general human population (oral or inhalation) and include measurement of neuromuscular or neurobehavioral endpoints and direct counts of dopaminergic neurons. Investigating the effects of longer-term paraquat exposures in vitro on endpoints with clear linkages to Parkinson's disease (such as loss in neuron numbers and accumulation of α-synuclein) in primary human cell models might provide critical mechanistic information linking these exposures to neurological deficits observed in humans and animals.

This scoping review along with associated online interactive figures and visualizations were used to support an ongoing systematic review of paraquat and Parkinson's disease as part of a registration review of paraquat dichloride by EPA OPP (Docket ID EPA-HQ-OPP-2011-0855).

References

Ahmed H, Abushouk AI, Gabr M, Negida A, Abdel-Daim MM. 2017. Parkinson's disease and pesticides: A meta-analysis of disease connection and genetic alterations. Biomed Pharmacother. 90:638-649. http://dx.doi.org/10.1016/j.biopha.2017.03.100

Baltazar MT, Dinis-Oliveira RJ, de Lourdes Bastos M, Tsatsakis AM, Duarte JA, Carvalho F. 2014. Pesticides exposure as etiological factors of Parkinson's disease and other neurodegenerative diseases--a mechanistic approach. Toxicol Lett. 230(2):85-103. http://dx.doi.org/10.1016/j.toxlet.2014.01.039

Bromilow RH. 2004. Paraquat and sustainable agriculture. Pest Manag Sci. 60(4):340-349. http://dx.doi.org/10.1002/ps.823

Brouwer M, Huss A, van der Mark M, Nijssen PCG, Mulleners WM, Sas AMG, van Laar T, de Snoo GR, Kromhout H, Vermeulen RCH. 2017. Environmental exposure to pesticides and the risk of Parkinson's disease in the Netherlands. Environ Int. 107:100-110. http://dx.doi.org/10.1016/j.envint.2017.07.001

Caroleo MC, Rispoli V, Arbitrio M, Strongoli C, Rainaldi G, Rotiroti D, Nistico G. 1996. Chronic administration of paraquat produces immunosuppression of T lymphocytes and astrocytosis in rats. Tox Subst Mech. 15(3):183-194.

Chen Q, Niu Y, Zhang R, Guo H, Gao Y, Li Y, Liu R. 2010. The toxic influence of paraquat on hippocampus of mice: Involvement of oxidative stress. Neurotoxicology. 31(3):310-316. http://dx.doi.org/10.1016/j.neuro.2010.02.006

Choi J, Polcher A, Joas A. 2016. Systematic literature review on Parkinson's disease and Childhood Leukaemia and mode of actions for pesticides. EFSA J. 13(1):955E. http://dx.doi.org/10.2903/sp.efsa.2016.EN-955

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(8):919-926. http://dx.doi.org/10.1093/aje/kwp006

Dhillon AS, Tarbutton GL, Levin JL, Plotkin GM, Lowry LK, Nalbone JT, Shepherd S. 2008. Pesticide/environmental exposures and Parkinson's disease in East Texas. J Agromedicine. 13(1):37-48. http://dx.doi.org/10.1080/10599240801986215

Dinis-Oliveira RJ, Duarte JA, Sanchez-Navarro A, Remiao F, Bastos ML, Carvalho F. 2008. Paraquat poisonings: Mechanisms of lung toxicity, clinical features, and treatment. Crit Rev Toxicol. 38(1):13-71. http://dx.doi.org/10.1080/10408440701669959

Engel LS, Checkoway H, Keifer MC, Seixas NS, Longstreth WT, Jr., Scott KC, Hudnell K, Anger WK, Camicioli R. 2001. Parkinsonism and occupational exposure to pesticides. Occup Environ Med. 58(9):582-589. http://dx.doi.org/10.1136/oem.58.9.582

Firestone JA, Lundin JI, Powers KM, Smith-Weller T, Franklin GM, Swanson PD, Longstreth WT, Jr., Checkoway H. 2010. Occupational factors and risk of Parkinson's disease: A population-based case-control study. Am J Ind Med. 53(3):217-223. http://dx.doi.org/10.1002/ajim.20788

Firestone JA, Smith-Weller T, Franklin G, Swanson P, Longstreth WT, Jr., Checkoway H. 2005. Pesticides and risk of Parkinson disease: A population-based case-control study. Arch Neurol. 62(1):91-95. http://dx.doi.org/10.1001/archneur.62.1.91

Fredriksson A, Fredriksson M, Eriksson P. 1993. Neonatal exposure to paraquat or MPTP induces permanent changes in striatum dopamine and behavior in adult mice. Toxicol Appl Pharmacol. 122(2):258-264. http://dx.doi.org/10.1006/taap.1993.1194

Furlong M, Tanner CM, Goldman SM, Bhudhikanok GS, Blair A, Chade A, Comyns K, Hoppin JA, Kasten M, Korell M et al. 2015. Protective glove use and hygiene habits modify the associations of specific pesticides with Parkinson's disease. Environ Int. 75:144-150. http://dx.doi.org/10.1016/j.envint.2014.11.002

Gatto NM, Cockburn M, Bronstein J, Manthripragada AD, Ritz B. 2009. Well-water consumption and Parkinson's disease in rural California. Environ Health Perspect. 117(12):1912-1918. http://dx.doi.org/10.1289/ehp.0900852

Gatto NM, Rhodes SL, Manthripragada AD, Bronstein J, Cockburn M, Farrer M, Ritz B. 2010. alpha-Synuclein gene may interact with environmental factors in increasing risk of Parkinson's disease. Neuroepidemiology. 35(3):191-195. http://dx.doi.org/10.1159/000315157

Goldman SM, Kamel F, Ross GW, Bhudhikanok GS, Hoppin JA, Korell M, Marras C, Meng C, Umbach DM, Kasten M et al. 2012. Genetic modification of the association of paraquat and Parkinson's disease. Mov Disord. 27(13):1652-1658. http://dx.doi.org/10.1002/mds.25216

Hertzman C, Wiens M, Bowering D, Snow B, Calne D. 1990. Parkinson's disease: A case-control study of occupational and environmental risk factors. Am J Ind Med. 17(3):349-355. http://dx.doi.org/10.1002/ajim.4700170307

Hertzman C, Wiens M, Snow B, Kelly S, Calne D. 1994. A case-control study of Parkinson's disease in a horticultural region of British Columbia. Mov Disord. 9(1):69-75. http://dx.doi.org/10.1002/mds.870090111

Higgins JPT, Green S. 2011. Cochrane handbook for systematic reviews of interventions. John Wiley & Sons.

Kamel F, Goldman SM, Umbach DM, Chen H, Richardson G, Barber MR, Meng C, Marras C, Korell M, Kasten M et al. 2014. Dietary fat intake, pesticide use, and Parkinson's disease. Parkinsonism Relat Disord. 20(1):82-87. http://dx.doi.org/10.1016/j.parkreldis.2013.09.023

Kamel F, Tanner CM, Umbach DM, Hoppin JA, Alavanja MCR, Blair A, Comyns K, Goldman SM, Korell M, Langston JW et al. 2007. Pesticide exposure and self-reported Parkinson's disease in the agricultural health study. American Journal of Epidemiology. 165(4):364-374. 10.1093/aje/kwk024

Kang GA, Bronstein JM, Masterman DL, Redelings M, Crum JA, Ritz B. 2005. Clinical characteristics in early Parkinson's disease in a central California population-based study. Mov Disord. 20(9):1133-1142. http://dx.doi.org/10.1002/mds.20513

Lee PC, Bordelon Y, Bronstein J, Ritz B. 2012. Traumatic brain injury, paraquat exposure, and their relationship to Parkinson disease. Neurology. 79(20):2061-2066. http://dx.doi.org/10.1212/WNL.0b013e3182749f28

Li HF, Zhao SX, Xing BP, Sun ML. 2015. Ulinastatin suppresses endoplasmic reticulum stress and apoptosis in the hippocampus of rats with acute paraquat poisoning. Neural Regen Res. 10(3):467-472. http://dx.doi.org/10.4103/1673-5374.153698

Liou HH, Tsai MC, Chen CJ, Jeng JS, Chang YC, Chen SY, Chen RC. 1997. Environmental risk factors and Parkinson's disease: A case-control study in Taiwan. Neurology. 48(6):1583-1588. http://dx.doi.org/10.1212/WNL.48.6.1583

Lou D, Wang Q, Huang M, Zhou Z. 2016. Does age matter? Comparison of neurobehavioral effects of paraquat exposure on postnatal and adult C57BL/6 mice. Toxicol Mech Methods. 26(9):667-673. http://dx.doi.org/10.1080/15376516.2016.1223241

Luty S, Lutaszyńska J, Halliop J, Tochman A, Obuchowska D, Korczak B, Przylepa E, Bychawski E. 1997. Dermal toxicity of paraquat. Ann Agric Environ Med. 4(2):217-227.

Malagelada C, Greene LA. 2008. Chapter 29 - PC12 Cells as a model for parkinson's disease research. In: Nass R, Przedborski S, editors. Parkinson's Disease: Molecular and Therapeutic Insights From Model Systems. San Diego: Academic Press. p. 375-387.

Minnema DJ, Travis KZ, Breckenridge CB, Sturgess NC, Butt M, Wolf JC, Zadory D, Beck MJ, Mathews JM, Tisdel MO et al. 2014. Dietary administration of paraquat for 13 weeks does not result in a loss of dopaminergic neurons in the substantia nigra of C57BL/6J mice. Regul Toxicol Pharmacol. 68(2):250-258. http://dx.doi.org/10.1016/j.yrtph.2013.12.010

Moher D, Liberati A, Tetzlaff J, Altman DG. 2009. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med. 6(7):e1000097. http://dx.doi.org/10.1371/journal.pmed.1000097

National Institutes of Health (NIH). 2018. ChemIDplus. U.S. Department of Health & Human Services, National Institutes of Health, National Toxicology Program.https://chem.nlm.nih.gov/chemidplus/. [Accessed: May 24, 2018]

National Toxicology Program (NTP). 2015. Handbook for conducting a literature-based health assessment using ohat approach for systematic review and evidence integration. Research Triangle Park, NC: National Institute of Environmental Health Sciences, Office of Health Assessment and Translation, Division of the National Toxicology Program. http://ntp.niehs.nih.gov/go/38673.

National Toxicology Program (NTP). 2019a. Health Assessment Workspace Collaborative (HAWC) page on paraquat and Parkinson's disease. https://hawcproject.org/assessment/475/.

National Toxicology Program (NTP). 2019b. Tableau page on the scoping review of paraquat dichloride and Parkinson's disease. https://doi.org/10.22427/NTP-DATA-RR-16

Naudet N, Antier E, Gaillard D, Morignat E, Lakhdar L, Baron T, Bencsik A. 2017. Oral exposure to paraquat triggers earlier expression of phosphorylated alpha-synuclein in the enteric nervous system of A53T mutant human alpha-synuclein transgenic mice. J Neuropathol Exp Neurol. 76(12):1046-1057. http://dx.doi.org/10.1093/jnen/nlx092

Peled-Kamar M, Lotem J, Wirguin I, Weiner L, Hermalin A, Groner Y. 1997. Oxidative stress mediates impairment of muscle function in transgenic mice with elevated level of wild-type Cu/Zn superoxide dismutase. Proc Natl Acad Sci U S A. 94(8):3883-3887. http://dx.doi.org/10.1073/pnas.94.8.3883

Pouchieu C, Piel C, Carles C, Gruber A, Helmer C, Tual S, Marcotullio E, Lebailly P, Baldi I. 2018. Pesticide use in agriculture and Parkinson's disease in the AGRICAN cohort study. Int J Epidemiol. 47(1):299-310. http://dx.doi.org/10.1093/ije/dyx225

Ranjbar A, Pasalar P, Sedighi A, Abdollahi M. 2002. Induction of oxidative stress in paraquat formulating workers. Toxicol Lett. 131(3):191-194. http://dx.doi.org/10.1016/S0378-4274(02)00033-4

Ren JP, Zhao YW, Sun XJ. 2009. Toxic influence of chronic oral administration of paraquat on nigrostriatal dopaminergic neurons in C57BL/6 mice. Chin Med J (Engl). 122(19):2366-2371. http://dx.doi.org/10.1016/S0161-813X(03)00057-3

Rojo AI, Cavada C, de Sagarra MR, Cuadrado A. 2007. Chronic inhalation of rotenone or paraquat does not induce Parkinson's disease symptoms in mice or rats. Exp Neurol. 208(1):120-126. http://dx.doi.org/10.1016/j.expneurol.2007.07.022

Rooney AA, Boyles AL, Wolfe MS, Bucher JR, Thayer KA. 2014. Systematic review and evidence integration for literature-based environmental health science assessments. Environ Health Perspect. 122(7):711-718. http://dx.doi.org/10.1289/ehp.1307972

Sanders LH, Paul KC, Howlett EH, Lawal H, Boppana S, Bronstein JM, Ritz B, Greenamyre JT. 2017. Editor's highlight: Base excision repair variants and pesticide exposure increase Parkinson's disease risk. Toxicol Sci. 158(1):188-198. http://dx.doi.org/10.1093/toxsci/kfx086

Satpute RM, Pawar PP, Puttewar S, Sawale SD, Ambhore PD. 2017. Effect of resveratrol and tetracycline on the subacute paraquat toxicity in mice. Hum Exp Toxicol. 36(12):1303-1314. http://dx.doi.org/10.1177/0960327116688070

Tanner CM, Kamel F, Ross GW, Hoppin JA, Goldman SM, Korell M, Marras C, Bhudhikanok GS, Kasten M, Chade AR et al. 2011. Rotenone, paraquat, and Parkinson's disease. Environ Health Perspect. 119(6):866-872. http://dx.doi.org/10.1289/ehp.1002839

Tanner CM, Ross GW, Jewell SA, Hauser RA, Jankovic J, Factor SA, Bressman S, Deligtisch A, Marras C, Lyons KE et al. 2009. Occupation and risk of Parkinsonism a multicenter case-control study. Arch Neurol. 66(9):1106-1113. http://dx.doi.org/10.1001/archneurol.2009.195

Tomenson JA, Campbell C. 2011. Mortality from Parkinson's disease and other causes among a workforce manufacturing paraquat: A retrospective cohort study. BMJ Open. 1(2):e000283. http://dx.doi.org/10.1136/bmjopen-2011-000283

U.S. Environmental Protection Agency (US EPA). 1976. The effects of pesticide exposure on the life span of a selected segment of the population: Work Unit E-31 Final Report. Washington, DC: U. S. Environmental Protection Agency, ESP, Human Effects Monitoring Branch, Technical Services Division.

U.S. Environmental Protection Agency (US EPA). 1997. Reregistration eligibility decision document: Paraquat dichloride. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticide Programs, Special Review and Reregistration Division. EPA-738-F-96-018

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

van der Mark M, Vermeulen R, Nijssen PC, Mulleners WM, Sas AM, 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(11):757-764. http://dx.doi.org/10.1136/oemed-2014-102170

Wan N, Lin G. 2016. Parkinson's disease and pesticides exposure: New findings from a comprehensive study in Nebraska, USA. J Rural Health. 32(3):303-313. http://dx.doi.org/10.1111/jrh.12154

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(7):547-555. http://dx.doi.org/10.1007/s10654-011-9574-5

Widdowson PS, Farnworth MJ, Upton R, Simpson MG. 1996. No changes in behaviour, nigro-striatal system neurochemistry or neuronal cell death following toxic multiple oral paraquat administration to rats. Hum Exp Toxicol. 15(7):583-591. http://dx.doi.org/10.1177/096032719601500706

Wu B, Song B, Tian S, Huo S, Cui C, Guo Y, Liu H. 2012. Central nervous system damage due to acute paraquat poisoning: A neuroimaging study with 3.0 T MRI. Neurotoxicology. 33(5):1330-1337. http://dx.doi.org/10.1016/j.neuro.2012.08.007

Zhang XF, Thompson M, Xu YH. 2016. Multifactorial theory applied to the neurotoxicity of paraquat and paraquat-induced mechanisms of developing Parkinson's disease. Lab Invest. 96(5):496-507. http://dx.doi.org/10.1038/labinvest.2015.161

Appendix A. Literature Search Strategy

Table A-1. Literature Search Strategy

Database	Search Parameters
Embase Date of original search: April 6, 2017; 107 results Date of search update: May 24, 2018; 242 results	**Limits; original search:** None **Limits; search update:** 2017 to present OR added since April 1, 2017; Embase or Embase Classic; no automatic term mapping **Search Terms:** (paraquat OR 1910-42-5 OR gramoxone OR methyl-viologen OR paragreen-A) AND (alpha-synuclein OR apoptosis OR astrocyte OR astrocytes OR ataxia OR autophagy OR axon OR axonal OR axons OR bradykinesia OR brain OR central-nervous OR dendrite OR dendrites OR dentritic OR dj-1 OR dopamine OR dopaminergic OR gait OR ganglia OR glial OR gliosis OR glutamate OR glutamates OR Glutamic Acids OR glutathione OR Lewy bodies OR lewy body OR locomotion OR locomotor-activity OR lrrk2 OR Mesencephalon OR Mesencephalons OR microglia OR microglial OR microglials OR midbrain OR mitochondria OR Mitochondrial OR Mitochondrion OR motor-activity OR mpp OR mptp OR NADPH-oxidase OR nerve OR nerves OR nervous OR neural OR neurobehavior OR neurobehavioral OR neurobehaviour OR neurobehavioural OR neuroblastoma OR neurodegeneration OR neurodegenerative OR neuroglia OR neurological OR neuromotor OR neuron OR neuronal OR neuronopathy OR neurons OR neuropathies OR neuropathology OR neuropathy OR neurotoxic OR neurotoxicity OR neurotransmitter OR neurotransmitters OR nigral OR nigrostriatal OR nitric-oxide OR nitrosative-stress OR oxidative-stress OR paralysis-agitans OR parkin OR parkinson OR parkinsons OR parkinsonian OR parkinsonism OR pink1 OR reactive-oxygen-species OR rigidity OR snpc OR striatal OR striatum OR substantia-nigra OR synapse OR synapses OR synaptic OR synuclein OR synucleins OR tau OR tauopathies OR tauopathology OR tauopathy OR Thioredoxin-Disulfide OR thioredoxin-reductase OR tremor OR tremors OR Tyrosine 3-Monooxygenase OR tyrosine-hydroxylase OR ubiquitin)

Database	Search Parameters
PubMed Date of original search: April 6, 2017; 3,501 results Date of search update: May 24, 2018; 307 results	**Limits; original search:** None **Limits; search update:** (2017/4/1:3000[mhda] OR 2017/4/1:3000 [crdt] OR 2017/4/1:3000 [edat] OR 2017/4/1[PDAT]:3000[PDAT]) **Search Terms:** (paraquat[tiab] OR paraquat[mh] OR gramoxone[tiab] OR methyl-viologen[tiab] OR paragreen-A[tiab]) AND (alpha-synuclein[tiab] OR alpha-synuclein[mh] OR apoptosis[tiab] OR apoptosis[mh] OR astrocyte[tiab] OR astrocytes[tiab] OR astrocytes[mh] OR ataxia[tiab] OR autophagy[tiab] OR autophagy[mh] OR axon[tiab] OR axonal[tiab] OR axons[tiab] OR axons[mh] OR bradykinesia[tiab] OR brain[tiab] OR central-nervous[tiab] OR dendrite[tiab] OR dendrites[tiab] OR dentritic[tiab] OR dj-1[tiab] OR dopamine[mh] OR dopamine[tiab] OR Dopamine Plasma Membrane Transport Proteins[mh] OR dopaminergic[tiab] OR gait[tiab] OR gait[mh] OR ganglia[tiab] OR glial[tiab] OR gliosis[tiab] OR gliosis[mh] OR glutamate[tiab] OR glutamates[mh] OR glutamates[tiab] OR Glutamic Acids[tiab] OR glutathione[tiab] OR glutathione[mh] OR Lewy bodies[tiab] OR lewy body[tiab] OR locomotion[mh] OR locomotion[tiab] OR locomotor-activity[tiab] OR lrrk2[tiab] OR Mesencephalon[tiab] OR Mesencephalons[tiab] OR microglia[tiab] OR microglial[tiab] OR microglials[tiab] OR midbrain[tiab] OR mitochondria[tiab] OR mitochondria[mh] OR Mitochondrial[tiab] OR Mitochondrion[tiab] OR motor-activity[tiab] OR motor-activity[mh] OR mpp[tiab] OR mptp[tiab] OR NADPH-oxidase[mh] OR NADPH-oxidase[tiab] OR nerve[tiab] OR nerves[tiab] OR nervous[tiab] OR nervous-system[mh] OR nervous-system-diseases[mh] OR nervous-system-physiological-processes[mh] OR neural[tiab] OR neurobehavior[tiab] OR neurobehavioral[tiab] OR neurobehaviour[tiab] OR neurobehavioural[tiab] OR neuroblastoma[tiab] OR neuroblastoma[mh] OR neurodegeneration[tiab] OR neurodegenerative[tiab] OR neuroglia[tiab] OR neurological[tiab] OR neuromotor[tiab] OR neuron[tiab] OR neuronal[tiab] OR neuronopathy[tiab] OR neurons[tiab] OR neuropathies[tiab] OR neuropathology[tiab] OR neuropathy[tiab] OR neurotoxic[tiab] OR neurotoxicity[tiab] OR neurotransmitter[tiab] OR neurotransmitter agents[mh] OR neurotransmitter agents[Pharmacological Action] OR neurotransmitters[tiab] OR nigral[tiab] OR nigrostriatal[tiab] OR nitric-oxide[tiab] OR nitric-oxide[mh] OR nitric-oxide-synthase[mh] OR nitrosative-stress[tiab] OR oxidative-stress[tiab] OR paralysis-agitans[tiab] OR parkin[tiab] OR parkin protein[supplementary concept] OR parkinson[tiab] OR parkinsons[tiab] OR parkinson's[tiab] OR parkinsonian[tiab] OR parkinsonism[tiab] OR pink1[tiab] OR reactive-oxygen-species[tiab] OR reactive-oxygen-species[mh] OR rigidity[tiab] OR snpc[tiab] OR striatal[tiab] OR striatum[tiab] OR substantia-nigra[tiab] OR synapse[tiab] OR synapses[tiab] OR synaptic[tiab] OR synuclein[tiab] OR synucleins[tiab] OR synucleins[mh] OR tau[tiab] OR tau proteins[mh] OR tauopathies[tiab] OR tauopathology[tiab] OR tauopathy[tiab] OR Thioredoxin-Disulfide[tiab] OR Thioredoxin-Disulfide Reductase[mh] OR thioredoxin-reductase[tiab] OR tremor[tiab] OR tremors[tiab] OR Tyrosine 3-Monooxygenase[mh] OR Tyrosine 3-Monooxygenase[tiab] OR tyrosine-hydroxylase[tiab] OR ubiquitin[tiab] OR ubiquitin[mh])

Database	Search Parameters
Web of Science Date of original search: April 6, 2017; 3,551 results Date of search update: May 24, 2018; 252 results	**Original search and search update parameters:** All terms searched in Title, Abstract, or Keywords; Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC; Timespan=All years **Search Terms:** (paraquat OR 1,1'-Dimethyl-4,4'-bipyridinium-dichloride OR 1910-42-5 OR gramoxone OR methyl-viologen OR paragreen-A) AND (alpha-synuclein OR apoptosis OR astrocyte OR astrocytes OR ataxia OR autophagy OR axon OR axonal OR axons OR bradykinesia OR brain OR central-nervous OR dendrite OR dendrites OR dentritic OR dj-1 OR dopamine OR dopaminergic OR gait OR ganglia OR glial OR gliosis OR glutamate OR glutamates OR Glutamic Acids OR glutathione OR Lewy bodies OR lewy body OR locomotion OR locomotor-activity OR lrrk2 OR Mesencephalon OR Mesencephalons OR microglia OR microglial OR microglials OR midbrain OR mitochondria OR Mitochondrial OR Mitochondrion OR motor-activity OR mpp OR mptp OR NADPH-oxidase OR nerve OR nerves OR nervous OR neural OR neurobehavior OR neurobehavioral OR neurobehaviour OR neurobehavioural OR neuroblastoma OR neurodegeneration OR neurodegenerative OR neuroglia OR neurological OR neuromotor OR neuron OR neuronal OR neuronopathy OR neurons OR neuropathies OR neuropathology OR neuropathy OR neurotoxic OR neurotoxicity OR neurotransmitter OR neurotransmitters OR nigral OR nigrostriatal OR nitric-oxide OR nitrosative-stress OR oxidative-stress OR paralysis-agitans OR parkin OR parkinson OR parkinsons OR parkinson's OR parkinsonian OR parkinsonism OR pink1 OR reactive-oxygen-species OR rigidity OR snpc OR striatal OR striatum OR substantia-nigra OR synapse OR synapses OR synaptic OR synuclein OR synucleins OR tau OR tauopathies OR tauopathology OR tauopathy OR Thioredoxin-Disulfide OR thioredoxin-reductase OR tremor OR tremors OR Tyrosine 3-Monooxygenase OR tyrosine-hydroxylase OR ubiquitin)

Database	Search Parameters
SCOPUS Date of original search: April 6, 2017; 128 results Date of search update: May 24, 2018; 0 results	**Original search and search update parameters:** All terms searched in Title, Abstract, or Keywords; Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC; Timespan=All years **Search Terms; original search:** (paraquat OR 1,1'-Dimethyl-4,4'-bipyridinium-dichloride OR 1910-42-5 OR gramoxone OR methyl-viologen OR paragreen-A) **Search Terms; search update:** (paraquat OR 1,1'-Dimethyl-4,4'-bipyridinium-dichloride OR 1910-42-5 OR gramoxone OR methyl-viologen OR paragreen-A) AND (alpha-synuclein OR apoptosis OR astrocyte OR astrocytes OR ataxia OR autophagy OR axon OR axonal OR axons OR bradykinesia OR brain OR central-nervous OR dendrite OR dendrites OR dentritic OR dj-1 OR dopamine OR dopaminergic OR gait OR ganglia OR glial OR gliosis OR glutamate OR glutamates OR Glutamic Acids OR glutathione OR Lewy bodies OR lewy body OR locomotion OR locomotor-activity OR lrrk2 OR Mesencephalon OR Mesencephalons OR microglia OR microglial OR microglials OR midbrain OR mitochondria OR Mitochondrial OR Mitochondrion OR motor-activity OR mpp OR mptp OR NADPH-oxidase OR nerve OR nerves OR nervous OR neural OR neurobehavior OR neurobehavioral OR neurobehaviour OR neurobehavioural OR neuroblastoma OR neurodegeneration OR neurodegenerative OR neuroglia OR neurological OR neuromotor OR neuron OR neuronal OR neuronopathy OR neurons OR neuropathies OR neuropathology OR neuropathy OR neurotoxic OR neurotoxicity OR neurotransmitter OR neurotransmitters OR nigral OR nigrostriatal OR nitric-oxide OR nitrosative-stress OR oxidative-stress OR paralysis-agitans OR parkin OR parkinson OR parkinsons OR parkinson's OR parkinsonian OR parkinsonism OR pink1 OR reactive-oxygen-species OR rigidity OR snpc OR striatal OR striatum OR substantia-nigra OR synapse OR synapses OR synaptic OR synuclein OR synucleins OR tau OR tauopathies OR tauopathology OR tauopathy OR Thioredoxin-Disulfide OR thioredoxin-reductase OR tremor OR tremors OR Tyrosine 3-Monooxygenase OR tyrosine-hydroxylase OR ubiquitin)

Database	Search Parameters
TOXLINE Date of original search: April 6, 2017; 1,089 results Date of search update: May 24, 2018; 0 results	**Original search and search update parameters:** All terms searched in Title, Abstract, or Keywords; **Limits; original search:** Exclude PubMed Records; Search exact words **Limits; search update:** Exclude PubMed Records; Do NOT add chemical synonyms and CASRNs to search; Search exact words **Search Terms:** (paraquat OR 1,1'-Dimethyl-4,4'-bipyridinium-dichloride OR 1910-42-5 OR gramoxone OR methyl-viologen OR paragreen-A) AND (alpha-synuclein OR apoptosis OR astrocyte OR astrocytes OR ataxia OR autophagy OR axon OR axonal OR axons OR bradykinesia OR brain OR central-nervous OR dendrite OR dendrites OR dentritic OR dj-1 OR dopamine OR dopaminergic OR gait OR ganglia OR glial OR gliosis OR glutamate OR glutamates OR Glutamic Acids OR glutathione OR Lewy bodies OR lewy body OR locomotion OR locomotor-activity OR lrrk2 OR Mesencephalon OR Mesencephalons OR microglia OR microglial OR microglials OR midbrain OR mitochondria OR Mitochondrial OR Mitochondrion OR motor-activity OR mpp OR mptp OR NADPH-oxidase OR nerve OR nerves OR nervous OR neural OR neurobehavior OR neurobehavioral OR neurobehaviour OR neurobehavioural OR neuroblastoma OR neurodegeneration OR neurodegenerative OR neuroglia OR neurological OR neuromotor OR neuron OR neuronal OR neuronopathy OR neurons OR neuropathies OR neuropathology OR neuropathy OR neurotoxic OR neurotoxicity OR neurotransmitter OR neurotransmitters OR nigral OR nigrostriatal OR nitric-oxide OR nitrosative-stress OR oxidative-stress OR paralysis-agitans OR parkin OR parkinson OR parkinsons OR parkinson's OR parkinsonian OR parkinsonism OR pink1 OR reactive-oxygen-species OR rigidity OR snpc OR striatal OR striatum OR substantia-nigra OR synapse OR synapses OR synaptic OR synuclein OR synucleins OR tau OR tauopathies OR tauopathology OR tauopathy OR Thioredoxin-Disulfide OR thioredoxin-reductase OR tremor OR tremors OR Tyrosine 3-Monooxygenase OR tyrosine-hydroxylase OR ubiquitin)

Appendix B. Detailed Inclusion/Exclusion Criteria

Table B-1. Detailed Inclusion and Exclusion Criteria to Determine Study Eligibility[a]

Evidence Stream	Inclusion Criteria	Exclusion Criteria (or Blank if None)
Participants/Population (Human Studies or Experimental Model Systems)		
Human	No restrictions on sex, age, life stage (including in utero exposure) at time of exposure or outcome assessment No restrictions on country of residence/origin, lifestyle, race/ethnicity, or occupation	
Animal	No restrictions on sex, age, species (including *Drosophila* and *C. elegans*), or life stage at exposure or outcome assessment	Studies in non-animal organisms (e.g., plants, fungi, protists, bacteria)
In Vitro	Studies involving an in vitro exposure system and neurological measures directed at cellular, biochemical, and molecular mechanisms that might explain how exposure to paraquat leads to Parkinson's disease	
Exposure		
Human	Exposure to paraquat dichloride (CASRN 1910-42-5) based on administered dose or concentration, biomonitoring data (e.g., urine, blood, or other specimens), environmental measures (e.g., air, water levels), or indirect measures (e.g., job title)	
Animal	Exposure to paraquat dichloride based on administered dose or concentration or biomonitoring data (e.g., urine, blood, or other specimens) No restrictions on route of administration	
In Vitro	Exposure to paraquat dichloride based on administered dose or concentration	
Comparators		
Human	Humans exposed to lower levels (or no exposure/exposure below detection levels) of paraquat dichloride	
Animal	Study must include vehicle or untreated control group	
In Vitro	Study must include vehicle or untreated control group	

Evidence Stream	Inclusion Criteria	Exclusion Criteria (or Blank if None)
Outcomes		
Human	**<u>Primary outcomes</u> (following in vivo exposure to paraquat dichloride):** Diagnosis of Parkinson's disease and/or clinical observations, neurobehavioral, or neuropathological outcomes typically associated with Parkinson's disease following in vivo exposure; focusing on tissue level and functional abnormalities, descriptive and/or functional assessment of the central nervous system, including the nigrostriatal (dopamine) system; examples of relevant neurobehavioral outcomes include tremor, bradykinesia, rigidity, and postural instability **<u>Secondary outcomes</u> (following in vivo exposure to paraquat dichloride):** Targeted molecular assays that investigate proposed cellular, biochemical, and/or molecular pathways for the etiology of Parkinson's disease following in vivo exposure	Studies reporting on toxicity in organs or tissues not associated with the central or peripheral nervous system
Animal	**<u>Primary outcomes</u> (following in vivo exposure to paraquat dichloride):** Neurobehavioral or neuropathological outcomes, focusing on whole body and tissue level abnormalities typically associated with Parkinson's disease following in vivo exposure; endpoints might include motor activity and coordination, sensorimotor reflexes, effects on cognitive function, quantitative or qualitative assessment of dopaminergic neuron counts in the substantia nigra and dopaminergic neuron terminals in the striatum, and other descriptive and/or functional assessments of the central nervous system, including the nigrostriatal (dopamine) system, which are considered hallmarks of Parkinson's disease (e.g., detection of intracytoplasmic Lewy bodies) **<u>Secondary outcomes</u> (following in vivo exposure to paraquat dichloride):** Targeted molecular assays that investigate proposed cellular, biochemical, and/or molecular pathways for the etiology of Parkinson's disease following in vivo exposure, including measures of oxidative stress, inflammation, mitochondrial and/or proteasomal dysfunction, dopamine and metabolite levels in the nigrostriatal pathway, or other key molecular initiating events related to parkinsonism	Studies reporting on toxicity in organs or tissues not associated with the central or peripheral nervous system

Evidence Stream	Inclusion Criteria	Exclusion Criteria (or Blank if None)
In Vitro	**Following <u>in vitro exposure</u> to paraquat dichloride:** In vitro assays investigating either cellular responses commonly attributed to Parkinson's disease (e.g., assessment of functionality, integrity, and viability for nerve cells critical to the nigrostriatal [dopamine] system) or generic cellular responses commonly attributed to paraquat exposure but are not unique to Parkinson's disease (e.g., measures of oxidative stress and mitochondria dysfunction in nerve cells, epigenetic changes) Mechanistic assays investigating proposed pathways for the etiology of Parkinson's disease (e.g., enzyme interactions, cell signaling)	Studies reporting on toxicity unrelated to the central or peripheral nervous system
Publications (e.g., Language Restrictions, Use of Conference Abstracts)		
Human, Animal, In Vitro	Study must contain original data Studies published in a language other than English will be collected and categorized by health effect or mechanism to the extent they can be categorized without full translation as extensive translation and level of effort are beyond the goals of this scoping review	Articles with no original data (e.g., editorial or review[b]) Studies published in abstract form only (grant awards, conference abstracts) Retracted articles Non-English language articles that cannot be categorized based on English abstract

[a]These criteria were developed from the PECO statement outlined in Table 1.
[b]Relevant reviews are used as background and for reference scanning.

Appendix C. Data Extraction Elements for Human Studies

Table C-1. Data Extraction Elements for Human Studies

Element Type	Element
Funding	Funding source(s)
	Reporting of conflict of interest by authors and/or translators (*reporting bias)
Subjects	Study population name/description
	Dates of study and sampling timeframe
	Geography (country, region, state, etc.)
	Demographics (sex, race/ethnicity, age or life stage and exposure and outcome assessment)
	Number of subjects (target, enrolled, n per group in analysis, and participation/follow-up rates) (*missing data bias)
	Inclusion/exclusion criteria/recruitment strategy (*selection bias)
	Description of reference group (*selection bias)
Methods	Study design (e.g., prospective or retrospective cohort, nested case-control study, cross-sectional, population-based case-control study, intervention, case report)
	Length of follow-up (*information bias)
	Health outcome category, e.g., neurodevelopment
	Health outcome, e.g., memory (*reporting bias)
	Diagnostic or methods used to measure health outcome (*information bias)
	Confounders or modifying factors and how considered in analysis (e.g., included in final model, considered for inclusion but determined not needed (*confounding bias)
	Substance name and CASRN
	Exposure assessment (e.g., blood, urine, hair, air, drinking water, job classification, residence, administered treatment in controlled study) (*information bias)
	Methodological details for exposure assessment (e.g., high-performance liquid chromatography-mass spectrometry/mass spectrometry, limit of detection) (*information bias)
	Statistical methods (*information bias)
Results	Exposure levels (e.g., mean, median, measures of variance as presented in paper, such as standard deviation, standard error of the mean, 75th/90th/95th percentile, minimum/maximum); range of exposure levels, number of exposed cases
	Statistical findings (e.g., adjusted β, standardized mean difference, adjusted odds ratio, standardized mortality ratio, relative risk) or description of qualitative results. When possible, OHAT will convert measures of effect to a common metric with associated 95% confidence intervals. Most often, measures of effect for continuous data are expressed as mean difference, standardized mean difference, and percent control response. Categorical data are typically expressed as odds ratio, relative risk (also called risk ratio), or β values, depending on what metric is most commonly reported in the included studies and on OHAT's ability to obtain information for effect conversions from the study or through author query.

Element Type	Element
	If not presented in the study, statistical power can be assessed during data extraction using an approach that can detect a 10% to 20% change from response by control or referent group for continuous data, or a risk ratio or odds ratio of 1.5 to 2 for categorical data, using the prevalence of exposure or prevalence of outcome in the control or referent group to determine sample size. For categorical data where the sample sizes of exposed and control or referent groups differ, the sample size of the exposed group will be used to determine the relative power category. Recommended sample sizes to achieve 80% power for a given effect size (i.e., 10% or 20% change from control) will be compared with sample sizes used in the study to categorize statistical power as "appears to be adequately powered" (sample size for 80% power met), "somewhat underpowered" (sample size is 75% to <100% of number required for 80% power), "underpowered" (sample size is 50% to <75% of number required for 80% power), or "severely underpowered" (sample size is <50% of number required for 80% power). Observations on dose response (e.g., trend analysis, description of whether dose-response shape appears to be monotonic, non-monotonic)
Other	Documentation of author queries, use of digital rulers to estimate data values from figures, exposure unit, and statistical result conversions, etc.

Appendix D. Data Extraction Elements for Animal Studies

Table D-1. Data Extraction Elements for Animal Studies

Element Type	Element
Funding	Funding source(s)
	Reporting of conflict of interest by authors and/or translators (*reporting bias)
Animal Model	Sex
	Species
	Strain
Treatment	Chemical name and CASRN
	Source of chemical
	Purity of chemical (*information bias)
	Dose levels or concentration (as presented and converted to mg/kg bw/d when possible)
	Other dose-related details, such as whether administered dose level was verified by measurement, information on internal dosimetry (*information bias)
	Vehicle used for exposed animals
	Route of administration (e.g., oral, inhalation, dermal, injection)
	Age or life stage at start of dosing and at health outcome assessment
	Duration and frequency of dosing (e.g., hours, days, weeks when administration was ended, days per week)
Methods	Study design (e.g., single treatment, acute, subchronic (e.g., 90 days in a rodent), chronic, multigenerational, developmental, other)
	Guideline compliance (i.e., use of EPA, OECD, NTP or another guideline for study design, conducted under good laboratory practice (GLP) guideline conditions, non-GLP but consistent with guideline study, non-GLP peer-reviewed publication)
	Number of animals per group (and dams per group in developmental studies) (*missing data bias)
	Randomization procedure, allocation concealment, blinding during outcome assessment (*selection bias)
	Method to control for litter effects in developmental studies (*information bias)
	Use of negative controls and whether controls were untreated, vehicle-treated, or both
	Endpoint health category (e.g., reproductive)
	Endpoint (e.g., infertility)
	Diagnostic or method to measure endpoint (*information bias)
	Statistical methods (*information bias)
Results	Measures of effect at each dose or concentration level (e.g., mean, median, frequency, measures of precision or variance) or description of qualitative results. When possible, OHAT will convert measures of effect to a common metric with associated 95% confidence intervals. Most often, measures of effect for continuous data will be expressed as percent control response, mean difference, or standardized mean difference. Categorical data will be expressed as relative risk (also called risk ratio).

Element Type	Element
	No-observed-effect level (NOEL), lowest-observed-effect level (LOEL), benchmark dose (BMD) analysis, statistical significance of other dose levels, or other estimates of effect presented in paper. **Note:** The NOEL and LOEL are highly influenced by study design, give no quantitative information about the relationship between dose and response, and can be subject to author's interpretation (e.g., a statistically significant effect might not be considered biologically important). Also, a NOEL does not necessarily mean zero response. Ideally, the response rate or effect size at specific dose levels is used as the primary measure to characterize the response. If not presented in the study, statistical power can be assessed during data extraction using an approach that assesses the ability to detect a 10% to 20% change from control group's response for continuous data, or a relative risk or odds ratio of 1.5–2 for categorical data, using the outcome frequency in the control group to determine sample size. Recommended sample sizes to achieve 80% power for a given effect size, i.e., 10% or 20% change from control, will be compared with sample sizes used in the study to categorize statistical power. Studies will be considered adequately powered when sample size for 80% power is met. Observations on dose response (e.g., trend analysis, description of whether dose-response shape appears to be monotonic, non-monotonic). Data on internal concentration, toxicokinetics, or toxicodynamics (when reported).
Other	Documentation of author queries, use of digital rulers to estimate data values from figures, exposure unit, statistical result conversions, etc.

Appendix E. List of Included Studies

Table of Contents

E.1. Human Studies: Primary Endpoints

Certain studies in this list are also included in the Animal Studies: Secondary Endpoints list and in the In Vitro Studies list if they contained data relating to those endpoints in addition to human primary endpoints.

Brouwer M, Huss A, van der Mark M, Nijssen PCG, Mulleners WM, Sas AMG, van Laar T, de Snoo GR, Kromhout H, Vermeulen RCH. 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

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(8):919-926. https://doi.org/10.1093/aje/kwp006

Dhillon AS, Tarbutton GL, Levin JL, Plotkin GM, Lowry LK, Nalbone JT, Shepherd S. 2008. Pesticide/environmental exposures and Parkinson's disease in East Texas. J Agromed. 13(1):37-48. https://doi.org/10.1080/10599240801986215

Engel L, Checkoway H, Keifer M, Seixas N, Longstreth W, Scott K, Hudnell K, Anger W, Camicioli R. 2001. Parkinsonism and occupational exposure to pesticides. Occup Environ Med. 58(9):582-589.

Firestone JA, Lundin JI, Powers KM, Smith-Weller T, Franklin GM, Swanson PD, Longstreth Jr W, Checkoway H. 2010. Occupational factors and risk of Parkinson's disease: A population-based case-control study. Am J Ind Med. 53(3):217-223.

Firestone JA, Smith-Weller T, Franklin G, Swanson P, Longstreth WT, Jr., Checkoway H. 2005. Pesticides and risk of Parkinson disease: A population-based case-control study. Arch Neurol. 62(1):91-95. https://doi.org/10.1001/archneur.62.1.91

Furlong M, Tanner CM, Goldman SM, Bhudhikanok GS, Blair A, Chade A, Comyns K, Hoppin JA, Kasten M, Korell M et al. 2015. Protective glove use and hygiene habits modify the associations of specific pesticides with Parkinson's disease. Environ Int. 75:144-150. https://doi.org/10.1016/j.envint.2014.11.002

Gatto NM, Cockburn M, Bronstein J, Manthripragada AD, Ritz B. 2009. Well-water consumption and Parkinson's disease in rural California. Environ Health Perspect. 117(12):1912-1918. https://doi.org/10.1289/ehp.0900852

Gatto NM, Rhodes SL, Manthripragada AD, Bronstein J, Cockburn M, Farrer M, Ritz B. 2010. alpha-Synuclein gene may interact with environmental factors in increasing risk of Parkinson's disease. Neuroepidemiology. 35(3):191-195. https://doi.org/10.1159/000315157

Goldman SM, Kamel F, Ross GW, Bhudhikanok GS, Hoppin JA, Korell M, Marras C, Meng C, Umbach DM, Kasten M et al. 2012. Genetic modification of the association of paraquat and Parkinson's disease. Mov Disord. 27(13):1652-1658. https://doi.org/10.1002/mds.25216

Hertzman C, Wiens M, Bowering D, Snow B, Calne D. 1990. Parkinson's disease: A case-control study of occupational and environmental risk factors. Am J Ind Med. 17(3):349-355.

Hertzman C, Wiens M, Snow B, Kelly S, Calne D. 1994. A case-control study of Parkinson's disease in a horticultural region of British Columbia. Mov Disord. 9(1):69-75.

Kamel F, Goldman SM, Umbach DM, Chen H, Richardson G, Barber MR, Meng C, Marras C, Korell M, Kasten M et al. 2014. Dietary fat intake, pesticide use, and Parkinson's disease. Parkinsonism Relat Disord. 20(1):82-87. https://doi.org/10.1016/j.parkreldis.2013.09.023

Kamel F, Tanner CM, Umbach DM, Hoppin JA, Alavanja MCR, Blair A, Comyns K, Goldman SM, Korell M, Langston JW et al. 2007. Pesticide exposure and self-reported Parkinson's disease in the agricultural health study. Am J Epidemiol. 165(4):364-374. https://doi.org/10.1093/aje/kwk024

Lee PC, Bordelon Y, Bronstein J, Ritz B. 2012. Traumatic brain injury, paraquat exposure, and their relationship to Parkinson disease. Neurology. 79(20):2061-2066. https://doi.org/10.1212/WNL.0b013e3182749f28

Liou HH, Tsai MC, Chen CJ, Jeng JS, Chang YC, Chen SY, Chen RC. 1997. Environmental risk factors and Parkinson's disease: A case-control study in Taiwan. Neurology. 48(6):1583-1588. https://doi.org/10.1212/wnl.48.6.1583

Pouchieu C, Piel C, Carles C, Gruber A, Helmer C, Tual S, Marcotullio E, Lebailly P, Baldi I. 2018. Pesticide use in agriculture and Parkinson's disease in the AGRICAN cohort study. Int J Epidemiol. 47(1):299-310. https://doi.org/10.1093/ije/dyx225

Sanders LH, Paul KC, Howlett EH, Lawal H, Boppana S, Bronstein JM, Ritz B, Greenamyre JT. 2017. Editor's highlight: Base excision repair variants and pesticide exposure increase Parkinson's disease risk. Toxicol Sci. 158(1):188-198. https://doi.org/10.1093/toxsci/kfx086

Tanner CM, Kamel F, Ross GW, Hoppin JA, Goldman SM, Korell M, Marras C, Bhudhikanok GS, Kasten M, Chade AR et al. 2011. Rotenone, paraquat, and Parkinson's disease. Environ Health Perspect. 119(6):866-872. https://doi.org/10.1289/ehp.1002839

Tanner CM, Ross GW, Jewell SA, Hauser RA, Jankovic J, Factor SA, Bressman S, Deligtisch A, Marras C, Lyons KE et al. 2009. Occupation and risk of parkinsonism a multicenter case-control study. Arch Neurol. 66(9):1106-1113.

Tomenson JA, Campbell C. 2011. Mortality from Parkinson's disease and other causes among a workforce manufacturing paraquat: A retrospective cohort study. BMJ open. 1(2):e000283. https://doi.org/10.1136/bmjopen-2011-000283

van der Mark M, Vermeulen R, Nijssen PC, Mulleners WM, Sas AM, 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(11):757-764.

Wan N, Lin G. 2016. Parkinson's disease and pesticides exposure: New findings from a comprehensive study in Nebraska, USA. J Rural Health. 32(3):303-313. https://doi.org/10.1111/jrh.12154

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(7):547-555. https://doi.org/10.1007/s10654-011-9574-5

E.2. Human Studies: Secondary Endpoints

Ranjbar A, Pasalar P, Sedighi A, Abdollahi M. 2002. Induction of oxidative stress in paraquat formulating workers. Toxicol Lett. 131(3):191-194.

E.3. Animal Studies: Primary Endpoints

Certain studies in this list are also included in the Animal Studies: Secondary Endpoints list and in the In Vitro Studies list if they contained data relating to those endpoints in addition to animal primary endpoints.

Ait-Bali Y, Ba-M'hamed S, Bennis M. 2016. Prenatal paraquat exposure induces neurobehavioral and cognitive changes in mice offspring. Environ Toxicol Pharmacol. 48:53-62. https://doi.org/10.1016/j.etap.2016.10.008

Anselmi L, Toti L, Bove C, Hampton J, Travagli RA. 2017. A nigro-vagal pathway controls gastric motility and is affected in a rat model of Parkinsonism. Gastroenterology. 153(6):1581-1593. https://doi.org/10.1053/j.gastro.2017.08.069

Attia HN, Maklad YA. 2018. Neuroprotective effects of coenzyme Q10 on paraquat-induced Parkinson's disease in experimental animals. Behav Pharmacol. 29(1):79-86. https://doi.org/10.1097/fbp.0000000000000342

Bagetta G, Corasaniti MT, Iannone M, Nistico G, Stephenson JD. 1992. Production of limbic motor seizures and brain damage by systemic and intracerebral injections of paraquat in rats. Pharmacol Toxicol. 71(6):443-448.

Bajo-Graneras R, Ganfornina MD, Martin-Tejedor E, Sanchez D. 2011. Apolipoprotein D mediates autocrine protection of astrocytes and controls their reactivity level, contributing to the functional maintenance of paraquat-challenged dopaminergic systems. Glia. 59(10):1551-1566. https://doi.org/10.1002/glia.21200

Barbeau A, Dallaire L, Buu NT, Poirier J, Rucinska E. 1985. Comparative behavioral, biochemical and pigmentary effects of MPTP, MPP+ and paraquat in Rana pipiens. Life Sci. 37(16):1529-1538. https://doi.org/10.1016/0024-3205(85)90185-7

Barlow BK, Richfield EK, Cory-Slechta DA, Thiruchelvam M. 2004. A fetal risk factor for Parkinson's disease. Dev Neurosci. 26(1):11-23. https://doi.org/10.1159/000080707

Bingol B, Tea JS, Phu L, Reichelt M, Bakalarski CE, Song Q, Foreman O, Kirkpatrick DS, Sheng M. 2014. The mitochondrial deubiquitinase USP30 opposes parkin-mediated mitophagy. Nature. 510(7505):370-375. https://doi.org/10.1038/nature13418

Bobyn J, Mangano EN, Gandhi A, Nelson E, Moloney K, Clarke M, Hayley S. 2012. Viral-toxin interactions and Parkinson's disease: poly I:C priming enhanced the neurodegenerative effects of paraquat. J Neuroinflammation. 9:86. https://doi.org/10.1186/1742-2094-9-86

Bortolotto JW, Cognato GP, Christoff RR, Roesler LN, Leite CE, Kist LW, Bogo MR, Vianna MR, Bonan CD. 2014. Long-term exposure to paraquat alters behavioral parameters and dopamine levels in adult zebrafish (Danio rerio). Zebrafish. 11(2):142-153. https://doi.org/10.1089/zeb.2013.0923

Breckenridge CB, Sturgess NC, Butt M, Wolf JC, Zadory D, Beck M, Mathews JM, Tisdel MO, Minnema D, Travis KZ et al. 2013. Pharmacokinetic, neurochemical, stereological and neuropathological studies on the potential effects of paraquat in the substantia nigra pars compacta and striatum of male C57BL/6J mice. Neurotoxicology. 37:1-14. https://doi.org/10.1016/j.neuro.2013.03.005

Bretaud S, Lee S, Guo S. 2004. Sensitivity of zebrafish to environmental toxins implicated in Parkinson's disease. Neurotoxicol Teratol. 26(6):857-864. https://doi.org/10.1016/j.ntt.2004.06.014

Brooks AI, Chadwick CA, Gelbard HA, Cory-Slechta DA, Federoff HJ. 1999. Paraquat elicited neurobehavioral syndrome caused by dopaminergic neuron loss. Brain Res. 823(1-2):1-10. https://doi.org/10.1016/s0006-8993(98)01192-5

Calo M, Iannone M, Passafaro M, Nistico G. 1990. Selective vulnerability of hippocampal CA3 neurones after microinfusion of paraquat into the rat substantia nigra or into the ventral tegmental area. J Comp Pathol. 103(1):73-78. https://doi.org/10.1016/s0021-9975(08)80136-3

Campos FL, Carvalho MM, Cristovao AC, Je G, Baltazar G, Salgado AJ, Kim YS, Sousa N. 2013. Rodent models of Parkinson's disease: Beyond the motor symptomatology. Front Behav Neurosci. 7:175. https://doi.org/10.3389/fnbeh.2013.00175

Caroleo MC, Rispoli V, Arbitrio M, Strongoli C, Rainaldi G, Rotiroti D, Nistico G. 1996. Chronic administration of paraquat produces immunosuppression of T lymphocytes and astrocytosis in rats. Toxic Subst Mech. 15(3):183-194.

Chanyachukul T, Yoovathaworn K, Thongsaard W, Chongthammakun S, Navasumrit P, Satayavivad J. 2004. Attenuation of paraquat-induced motor behavior and neurochemical disturbances by L-valine in vivo. Toxicol Lett. 150(3):259-269. https://doi.org/10.1016/j.toxlet.2004.02.007

Chaudhuri A, Bowling K, Funderburk C, Lawal H, Inamdar A, Wang Z, O'Donnell JM. 2007. Interaction of genetic and environmental factors in a Drosophila parkinsonism model. J Neurosci. 27(10):2457-2467. https://doi.org/10.1523/jneurosci.4239-06.2007

Chen AY, Tully T. 2018. A stress-enhanced model for discovery of disease-modifying gene: Ece1-suppresses the toxicity of alpha-synuclein A30P. Neurobiol Dis. 114:153-163. https://doi.org/10.1016/j.nbd.2018.03.003

Chen LJ, Yoo SE, Na R, Liu YH, Ran QT. 2012. Cognitive impairment and increased A beta levels induced by paraquat exposure are attenuated by enhanced removal of mitochondrial H2O2. Neurobiol Aging. 33(2). https://doi.org/10.1016/j.neurobiolaging.2011.01.008

Chen P, Chen Z, Li A, Lou XC, Wu XK, Zhao CJ, Wang SL, Liang LP. 2008. Catalytic metalloporphyrin protects against paraquat neurotoxicity in vivo. Biomed Environ Sci. 21(3):233-238. https://doi.org/10.1016/s0895-3988(08)60035-5

Chen Q, Niu Y, Zhang R, Guo H, Gao Y, Li Y, Liu R. 2010. The toxic influence of paraquat on hippocampus of mice: Involvement of oxidative stress. Neurotoxicology. 31(3):310-316. https://doi.org/10.1016/j.neuro.2010.02.006

Chinta SJ, Woods G, Demaria M, Rane A, Zou Y, McQuade A, Rajagopalan S, Limbad C, Madden DT, Campisi J et al. 2018. Cellular senescence is induced by the environmental neurotoxin paraquat and contributes to neuropathology linked to Parkinson's disease. Cell Rep. 22(4):930-940. https://doi.org/10.1016/j.celrep.2017.12.092

Choi HS, An JJ, Kim SY, Lee SH, Kim DW, Yoo KY, Won MH, Kang TC, Kwon HJ, Kang JH et al. 2006. PEP-1-SOD fusion protein efficiently protects against paraquat-induced dopaminergic neuron damage in a Parkinson disease mouse model. Free Radic Biol Med. 41(7):1058-1068. https://doi.org/10.1016/j.freeradbiomed.2006.06.006

Choi WS, Abel G, Klintworth H, Flavell RA, Xia Z. 2010. JNK3 mediates paraquat- and rotenone-induced dopaminergic neuron death. J Neuropathol Exp Neurol. 69(5):511-520. https://doi.org/10.1097/NEN.0b013e3181db8100

Cicchetti F, Lapointe N, Roberge-Tremblay A, Saint-Pierre M, Jimenez L, Ficke BW, Gross RE. 2005. Systemic exposure to paraquat and maneb models early Parkinson's disease in young adult rats. Neurobiol Dis. 20(2):360-371. https://doi.org/10.1016/j.nbd.2005.03.018

Corasaniti MT, Bagetta G, Rodino P, Gratteri S, Nistico G. 1992. Neurotoxic effects induced by intracerebral and systemic injection of paraquat in rats. Hum Exp Toxicol. 11(6):535-539. https://doi.org/10.1177/096032719201100616

Costa KM, Maciel IS, Kist LW, Campos MM, Bogo MR. 2014. Pharmacological inhibition of CXCR2 chemokine receptors modulates paraquat-induced intoxication in rats. PLoS One. 9(8):e105740. https://doi.org/10.1371/journal.pone.0105740

Coughlan C, Walker DI, Lohr KM, Richardson JR, Saba LM, Caudle WM, Fritz KS, Roede JR. 2015. Comparative proteomic analysis of carbonylated proteins from the striatum and cortex of pesticide-treated mice. Parkinsons Dis. 2015:812532. https://doi.org/10.1155/2015/812532

Cristovao AC, Choi DH, Baltazar G, Beal MF, Kim YS. 2009. The role of NADPH oxidase 1-derived reactive oxygen species in paraquat-mediated dopaminergic cell death. Antioxid Redox Signal. 11(9):2105-2118. https://doi.org/10.1089/ars.2009.2459

Cristovao AC, Guhathakurta S, Bok E, Je G, Yoo SD, Choi DH, Kim YS. 2012. NADPH oxidase 1 mediates alpha-synucleinopathy in Parkinson's disease. J Neurosci. 32(42):14465-14477. https://doi.org/10.1523/jneurosci.2246-12.2012

Czerniczyniec A, Karadayian AG, Bustamante J, Cutrera RA, Lores-Arnaiz S. 2011. Paraquat induces behavioral changes and cortical and striatal mitochondrial dysfunction. Free Radic Biol Med. 51(7):1428-1436. https://doi.org/10.1016/j.freeradbiomed.2011.06.034

de Oliveira Souza A, Couto-Lima CA, Rosa Machado MC, Espreafico EM, Pinheiro Ramos RG, Alberici LC. 2017. Protective action of Omega-3 on paraquat intoxication in Drosophila melanogaster. J Toxicol Environ Health A. 80(19-21):1050-1063. https://doi.org/10.1080/15287394.2017.1357345

Degori N, Froio F, Strongoli MC, Defrancesco A, Calo M, Nistico G. 1988. Behavioural and electrocortical changes induced by paraquat after injection in specific areas of the brain of the rat. Neuropharmacology. 27(2):201-207. https://doi.org/10.1016/0028-3908(88)90171-2

Ellwanger JH, Molz P, Dallemole DR, Pereira dos Santos A, Müller TE, Cappelletti L, Goncalves da Silva M, Franke SI, Pra D, Pegas Henriques JA. 2015. Selenium reduces bradykinesia and DNA damage in a rat model of Parkinson's disease. Nutrition. 31(2):359-365. https://doi.org/10.1016/j.nut.2014.07.004

Fahim MA, Shehab S, Nemmar A, Adem A, Dhanasekaran S, Hasan MY. 2013. Daily subacute paraquat exposure decreases muscle function and substantia nigra dopamine level. Physiol Res. 62(3):313-321.

Fernagut PO, Hutson CB, Fleming SM, Tetreaut NA, Salcedo J, Masliah E, Chesselet MF. 2007. Behavioral and histopathological consequences of paraquat intoxication in mice: Effects of alpha-synuclein over-expression. Synapse. 61(12):991-1001. https://doi.org/10.1002/syn.20456

Fredriksson A, Fredriksson M, Eriksson P. 1993. Neonatal exposure to paraquat or MPTP induces permanent changes in striatum dopamine and behavior in adult mice. Toxicol Appl Pharmacol. 122(2):258-264. https://doi.org/10.1006/taap.1993.1194

Gollamudi S, Johri A, Calingasan NY, Yang L, Elemento O, Beal MF. 2012. Concordant signaling pathways produced by pesticide exposure in mice correspond to pathways identified in human Parkinson's disease. PLoS One. 7(5):e36191. https://doi.org/10.1371/journal.pone.0036191

Goncalves C, Dos Santos DB, Portilho SS, Lopes MW, Ghizoni H, de Souza V, Mack JM, Naime AA, Dafre AL, de Souza Brocardo P et al. 2018. Lipopolysaccharide-induced striatal nitrosative stress and impaired social recognition memory are not magnified by paraquat coexposure. Neurochem Res. 43(3):745-759. https://doi.org/10.1007/s11064-018-2477-z

Gourgou E, Chronis N. 2016. Chemically induced oxidative stress affects ASH neuronal function and behavior in C-elegans. Sci Rep. 6. https://doi.org/10.1038/srep38147

Hara S, Iwata N, Kuriiwa F, Kano S, Kawaguchi N, Endo T. 1993. Involvement of opioid receptors in shaking behaviour induced by paraquat in rats. Pharmacol Toxicol. 73(3):146-149.

Heredia L, Belles M, Llovet MI, Domingo JL, Linares V. 2015. Neurobehavioral effects of concurrent exposure to cesium-137 and paraquat during neonatal development in mice. Toxicology. 329:73-79. https://doi.org/10.1016/j.tox.2015.01.012

Hutson CB, Lazo CR, Mortazavi F, Giza CC, Hovda D, Chesselet MF. 2011. Traumatic brain injury in adult rats causes progressive nigrostriatal dopaminergic cell loss and enhanced vulnerability to the pesticide paraquat. J Neurotrauma. 28(9):1783-1801. https://doi.org/10.1089/neu.2010.1723

Iannone M, Calo M, Rispoli V, Sancesario G, Nistico G. 1988. Neuropathological lesions after microinfusion of paraquat and MPP+ into different areas of the rat brain. Acta Neurol (Napoli). 10(6):313-321.

Inamdar AA, Chaudhuri A, O'Donnell J. 2012. The protective effect of minocycline in a paraquat-induced Parkinson's disease model in Drosophila is modified in altered genetic backgrounds. Parkinsons Dis. 2012:938528. https://doi.org/10.1155/2012/938528

Jahromi SR, Haddadi M, Shivanandappa T, Ramesh SR. 2015. Attenuation of neuromotor deficits by natural antioxidants of Decalepis hamiltonii in transgenic Drosophila model of Parkinson's disease. Neuroscience. 293:136-150. https://doi.org/10.1016/j.neuroscience.2015.02.048

Janda E, Parafati M, Aprigliano S, Carresi C, Visalli V, Sacco I, Ventrice D, Mega T, Vadala N, Rinaldi S et al. 2013. The antidote effect of quinone oxidoreductase 2 inhibitor against paraquat-induced toxicity in vitro and in vivo. Br J Pharmacol. 168(1):46-59. https://doi.org/10.1111/j.1476-5381.2012.01870.x

Jhonsa DJ, Badgujar LB, Sutariya BK, Saraf MN. 2016. Neuroprotective effect of flavonoids against paraquat induced oxidative stress and neurotoxicity in Drosophila melanogaster. Current Topics in Nutraceutical Research. 14(4):283-294.

Jiao Y, Lu L, Williams RW, Smeyne RJ. 2012. Genetic dissection of strain dependent paraquat-induced neurodegeneration in the substantia nigra pars compacta. PLoS One. 7(1):e29447. https://doi.org/10.1371/journal.pone.0029447

Kang MJ, Gil SJ, Koh HC. 2009. Paraquat induces alternation of the dopamine catabolic pathways and glutathione levels in the substantia nigra of mice. Toxicol Lett. 188(2):148-152. https://doi.org/10.1016/j.toxlet.2009.03.026

Kang MJ, Gil SJ, Lee JE, Koh HC. 2010. Selective vulnerability of the striatal subregions of C57BL/6 mice to paraquat. Toxicol Lett. 195(2-3):127-134. https://doi.org/10.1016/j.toxlet.2010.03.011

Khwaja M, McCormack A, McIntosh JM, Di Monte DA, Quik M. 2007. Nicotine partially protects against paraquat-induced nigrostriatal damage in mice; link to α6β2* nAChRs. J Neurochem. 100(1):180-190. https://doi.org/10.1111/j.1471-4159.2006.04177.x

Kumar A, Ahmad I, Shukla S, Singh BK, Patel DK, Pandey HP, Singh C. 2010. Effect of zinc and paraquat co-exposure on neurodegeneration: Modulation of oxidative stress and expression of metallothioneins, toxicant responsive and transporter genes in rats. Free Radic Res. 44(8):950-965. https://doi.org/10.3109/10715762.2010.492832

Kumar A, Christian PK, Panchal K, Guruprasad BR, Tiwari AK. 2017. Supplementation of spirulina (Arthrospira platensis) improves lifespan and locomotor activity in paraquat-sensitive DJ-1beta(Delta93) flies, a Parkinson's disease model in Drosophila melanogaster. J Diet Suppl. 14(5):573-588. https://doi.org/10.1080/19390211.2016.1275917

Kumar A, Singh BK, Ahmad I, Shukla S, Patel DK, Srivastava G, Kumar V, Pandey HP, Singh C. 2012. Involvement of NADPH oxidase and glutathione in zinc-induced dopaminergic neurodegeneration in rats: Similarity with paraquat neurotoxicity. Brain Res. 1438:48-64. https://doi.org/10.1016/j.brainres.2011.12.028

Kuter K, Smialowska M, Wieronska J, Zieba B, Wardas J, Pietraszek M, Nowak P, Biedka I, Roczniak W, Konieczny J et al. 2007. Toxic influence of subchronic paraquat administration on dopaminergic neurons in rats. Brain Res. 1155:196-207. https://doi.org/10.1016/j.brainres.2007.04.018

Lawal HO, Chang HY, Terrell AN, Brooks ES, Pulido D, Simon AF, Krantz DE. 2010. The Drosophila vesicular monoamine transporter reduces pesticide-induced loss of dopaminergic neurons. Neurobiol Dis. 40(1):102-112. https://doi.org/10.1016/j.nbd.2010.05.008

Li H, Wu S, Wang Z, Lin W, Zhang C, Huang B. 2012. Neuroprotective effects of tert-butylhydroquinone on paraquat-induced dopaminergic cell degeneration in C57BL/6 mice and in PC12 cells. Arch Toxicol. 86(11):1729-1740. https://doi.org/10.1007/s00204-012-0935-y

Li HF, Zhao SX, Xing BP, Sun ML. 2015. Ulinastatin suppresses endoplasmic reticulum stress and apoptosis in the hippocampus of rats with acute paraquat poisoning. Neural Regen Res. 10(3):467-472. https://doi.org/10.4103/1673-5374.153698

Li K, Cheng X, Jiang J, Wang J, Xie J, Hu X, Huang Y, Song L, Liu M, Cai L et al. 2017. The toxic influence of paraquat on hippocampal neurogenesis in adult mice. Food Chem Toxicol. 106(Pt A):356-366. https://doi.org/10.1016/j.fct.2017.05.067

Li X, Yin J, Cheng CM, Sun JL, Li Z, Wu YL. 2005. Paraquat induces selective dopaminergic nigrostriatal degeneration in aging C57BL/6 mice. Chin Med J. 118(16):1357-1361.

Liou HH, Chen RC, Chen TH, Tsai YF, Tsai MC. 2001. Attenuation of paraquat-induced dopaminergic toxicity on the substantia nigra by (-)-deprenyl in vivo. Toxicol Appl Pharmacol. 172(1):37-43. https://doi.org/10.1006/taap.2001.9130

Liou HH, Chen RC, Tsai YF, Chen WP, Chang YC, Tsai MC. 1996. Effects of paraquat on the substantia nigra of the wistar rats: Neurochemical, histological, and behavioral studies. Toxicol Appl Pharmacol. 137(1):34-41. https://doi.org/10.1006/taap.1996.0054

Litteljohn D, Mangano E, Shukla N, Hayley S. 2009. Interferon-gamma deficiency modifies the motor and co-morbid behavioral pathology and neurochemical changes provoked by the pesticide paraquat. Neuroscience. 164(4):1894-1906. https://doi.org/10.1016/j.neuroscience.2009.09.025

Litteljohn D, Mangano EN, Hayley S. 2008. Cyclooxygenase-2 deficiency modifies the neurochemical effects, motor impairment and co-morbid anxiety provoked by paraquat administration in mice. Eur J Neurosci. 28(4):707-716. https://doi.org/10.1111/j.1460-9568.2008.06371.x

Litteljohn D, Nelson E, Bethune C, Hayley S. 2011. The effects of paraquat on regional brain neurotransmitter activity, hippocampal BDNF and behavioural function in female mice. Neurosci Lett. 502(3):186-191. https://doi.org/10.1016/j.neulet.2011.07.041

Lou D, Wang Q, Huang M, Zhou Z. 2016. Does age matter? Comparison of neurobehavioral effects of paraquat exposure on postnatal and adult C57BL/6 mice. Toxicol Mech Methods. 26(9):667-673. https://doi.org/10.1080/15376516.2016.1223241

Luty S, Latuszynska J, Halliop J, Tochman A, Obuchowska D, Korczak B, Przylepa E, Bychawski E. 1997. Dermal toxicity of paraquat. Ann Agric Environ Med. 4:217-228.

Mangano EN, Hayley S. 2009. Inflammatory priming of the substantia nigra influences the impact of later paraquat exposure: Neuroimmune sensitization of neurodegeneration. Neurobiol Aging. 30(9):1361-1378. https://doi.org/10.1016/j.neurobiolaging.2007.11.020

Mangano EN, Litteljohn D, So R, Nelson E, Peters S, Bethune C, Bobyn J, Hayley S. 2012. Interferon-gamma plays a role in paraquat-induced neurodegeneration involving oxidative and proinflammatory pathways. Neurobiol Aging. 33(7):1411-1426. https://doi.org/10.1016/j.neurobiolaging.2011.02.016

Mangano EN, Peters S, Litteljohn D, So R, Bethune C, Bobyn J, Clarke M, Hayley S. 2011. Granulocyte macrophage-colony stimulating factor protects against substantia nigra dopaminergic cell loss in an environmental toxin model of Parkinson's disease. Neurobiol Dis. 43(1):99-112. https://doi.org/10.1016/j.nbd.2011.02.011

Manning-Bog AB, McCormack AL, Purisai MG, Bolin LM, Di Monte DA. 2003. Alpha-synuclein overexpression protects against paraquat-induced neurodegeneration. J Neurosci. 23(8):3095-3099.

Martin CA, Barajas A, Lawless G, Lawal HO, Assani K, Lumintang YP, Nunez V, Krantz DE. 2014. Synergistic effects on dopamine cell death in a Drosophila model of chronic toxin exposure. Neurotoxicology. 44:344-351. https://doi.org/10.1016/j.neuro.2014.08.005

Martinez-Perez DA, Jimenez-Del-Rio M, Velez-Pardo C. 2018. Epigallocatechin-3-gallate protects and prevents paraquat-induced oxidative stress and neurodegeneration in knockdown dj-1-beta Drosophila melanogaster. Neurotox Res. 34(3):401-416. https://doi.org/10.1007/s12640-018-9899-x

McCormack AL, Atienza JG, Johnston LC, Andersen JK, Vu S, Di Monte DA. 2005. Role of oxidative stress in paraquat-induced dopaminergic cell degeneration. J Neurochem. 93(4):1030-1037. https://doi.org/10.1111/j.1471-4159.2005.03088.x

McCormack AL, Atienza JG, Langston JW, Di Monte DA. 2006. Decreased susceptibility to oxidative stress underlies the resistance of specific dopaminergic cell populations to paraquat-induced degeneration. Neuroscience. 141(2):929-937. https://doi.org/10.1016/j.neuroscience.2006.03.069

McCormack AL, Di Monte DA. 2003. Effects of L-dopa and other amino acids against paraquat-induced nigrostriatal degeneration. J Neurochem. 85(1):82-86. https://doi.org/10.1046/j.1471-4159.2003.01621.x

McCormack AL, Thiruchelvam M, Manning-Bog AB, Thiffault C, Langston JW, Cory-Slechta DA, Di Monte DA. 2002. Environmental risk factors and Parkinson's disease: Selective degeneration of nigral dopaminergic neurons caused by the herbicide paraquat. Neurobiol Dis. 10(2):119-127.

Minnema DJ, Travis KZ, Breckenridge CB, Sturgess NC, Butt M, Wolf JC, Zadory D, Beck MJ, Mathews JM, Tisdel MO et al. 2014. Dietary administration of paraquat for 13 weeks does not result in a loss of dopaminergic neurons in the substantia nigra of C57BL/6J mice. Regul Toxicol Pharm. 68(2):250-258. https://doi.org/10.1016/j.yrtph.2013.12.010

Miranda-Contreras L, Davila-Ovalles R, Benitez-Diaz P, Pena-Contreras Z, Palacios-Pru E. 2005. Effects of prenatal paraquat and mancozeb exposure on amino acid synaptic transmission in developing mouse cerebellar cortex. Brain Res Dev Brain Res. 160(1):19-27. https://doi.org/10.1016/j.devbrainres.2005.08.001

Mitra S, Chakrabarti N, Bhattacharyya A. 2011. Differential regional expression patterns of alpha-synuclein, TNF-alpha, and IL-1beta; and variable status of dopaminergic neurotoxicity in mouse brain after paraquat treatment. J Neuroinflammation. 8:163. https://doi.org/10.1186/1742-2094-8-163

Mollace V, Iannone M, Muscoli C, Palma E, Granato T, Rispoli V, Nistico R, Rotiroti D, Salvemini D. 2003. The role of oxidative stress in paraquat-induced neurotoxicity in rats: Protection by non peptidyl superoxide dismutase mimetic. Neurosci Lett. 335(3):163-166. https://doi.org/10.1016/s0304-3940(02)01168-0

Müller TE, Nunes ME, Menezes CC, Marins AT, Leitemperger J, Gressler ACL, Carvalho FB, de Freitas CM, Quadros VA, Fachinetto R. 2018. Sodium selenite prevents paraquat-induced neurotoxicity in zebrafish. Mol Neurobiol. 55(3):1928-1941.

Muthukumaran K, Leahy S, Harrison K, Sikorska M, Sandhu JK, Cohen J, Keshan C, Lopatin D, Miller H, Borowy-Borowski H et al. 2014. Orally delivered water soluble Coenzyme Q10 (Ubisol-Q10) blocks on-going neurodegeneration in rats exposed to paraquat: Potential for therapeutic application in Parkinson's disease. BMC Neurosci. 15:21. https://doi.org/10.1186/1471-2202-15-21

Naudet N, Antier E, Gaillard D, Morignat E, Lakhdar L, Baron T, Bencsik A. 2017. Oral exposure to paraquat triggers earlier expression of phosphorylated alpha-synuclein in the enteric nervous system of A53T mutant human alpha-synuclein transgenic mice. J Neuropathol Exp Neurol. 76(12):1046-1057. https://doi.org/10.1093/jnen/nlx092

Nellore J, Nandita P. 2015. Paraquat exposure induces behavioral deficits in larval zebrafish during the window of dopamine neurogenesis. Toxicol Rep. 2:950-956.

Nellore J, Shajan A, Antony D, Cynthia PP, Karthick R, Namasivayam S. 2015. Proteinaceous compounds from fragaria ananassa fruit attenuates paraquat induced Parkinson like locomotor and mitochondrial alterations in Zebrafish. Int J Pharm Pharm Sci. 7:246-251.

Niveditha S, Ramesh SR, Shivanandappa T. 2017. Paraquat-induced movement disorder in relation to oxidative stress-mediated neurodegeneration in the brain of Drosophila melanogaster. Neurochem Res. 42(11):3310-3320. https://doi.org/10.1007/s11064-017-2373-y

Nixon AM, Meadowcroft MD, Neely EB, Snyder AM, Purnell CJ, Wright J, Lamendella R, Nandar W, Huang X, Connor JR. 2018. HFE genotype restricts the response to paraquat in a mouse model of neurotoxicity. J Neurochem. 145(4):299-311. https://doi.org/10.1111/jnc.14299

Nuber S, Tadros D, Fields J, Overk CR, Ettle B, Kosberg K, Mante M, Rockenstein E, Trejo M, Masliah E. 2014. Environmental neurotoxic challenge of conditional alpha-synuclein transgenic mice predicts a dopaminergic olfactory-striatal interplay in early PD. Acta Neuropathol. 127(4):477-494. https://doi.org/10.1007/s00401-014-1255-5

Nunes ME, Müller TE, Braga MM, Fontana BD, Quadros VA, Marins A, Rodrigues C, Menezes C, Rosemberg DB, Loro VL. 2017. Chronic treatment with paraquat induces brain injury, changes in antioxidant defenses system, and modulates behavioral functions in zebrafish. Mol Neurobiol. 54(6):3925-3934. https://doi.org/10.1007/s12035-016-9919-x

Ortega-Arellano HF, Jimenez-Del-Rio M, Velez-Pardo C. 2011. Life span and locomotor activity modification by glucose and polyphenols in Drosophila melanogaster chronically exposed to oxidative stress-stimuli: Implications in Parkinson's disease. Neurochem Res. 36(6):1073-1086.

Ossowska K, Smialowska M, Kuter K, Wieronska J, Zieba B, Wardas J, Nowak P, Dabrowska J, Bortel A, Biedka I et al. 2006. Degeneration of dopaminergic mesocortical neurons and activation of compensatory processes induced by a long-term paraquat administration in rats: Implications for Parkinson's disease. Neuroscience. 141(4):2155-2165. https://doi.org/10.1016/j.neuroscience.2006.05.039

Ossowska K, Wardas J, Smialowska M, Kuter K, Lenda T, Wieronska JM, Zieba B, Nowak P, Dabrowska J, Bortel A et al. 2005. A slowly developing dysfunction of dopaminergic nigrostriatal neurons induced by long-term paraquat administration in rats: An animal model of preclinical stages of Parkinson's disease? Eur J Neurosci. 22(6):1294-1304. https://doi.org/10.1111/j.1460-9568.2005.04301.x

Park J, Kim SY, Cha GH, Lee SB, Kim S, Chung J. 2005. Drosophila DJ-1 mutants show oxidative stress-sensitive locomotive dysfunction. Gene. 361:133-139. https://doi.org/10.1016/j.gene.2005.06.040

Peled-Kamar M, Lotem J, Wirguin I, Weiner L, Hermalin A, Groner Y. 1997. Oxidative stress mediates impairment of muscle function in transgenic mice with elevated level of wild-type Cu/Zn superoxide dismutase. Proc Natl Acad Sci U S A. 94(8):3883-3887. https://doi.org/10.1073/pnas.94.8.3883

Peng J, Mao XO, Stevenson FF, Hsu M, Andersen JK. 2004. The herbicide paraquat induces dopaminergic nigral apoptosis through sustained activation of the JNK pathway. J Biol Chem. 279(31):32626-32632. https://doi.org/10.1074/jbc.M404596200

Peng J, Oo ML, Andersen JK. 2010. Synergistic effects of environmental risk factors and gene mutations in Parkinson's disease accelerate age-related neurodegeneration. J Neurochem. 115(6):1363-1373. https://doi.org/10.1111/j.1471-4159.2010.07036.x

Peng J, Peng L, Stevenson FF, Doctrow SR, Andersen JK. 2007. Iron and paraquat as synergistic environmental risk factors in sporadic Parkinson's disease accelerate age-related neurodegeneration. J Neurosci. 27(26):6914-6922. https://doi.org/10.1523/jneurosci.1569-07.2007

Phom L, Achumi B, Alone DP, Muralidhara, Yenisetti SC. 2014. Curcumin's neuroprotective efficacy in Drosophila model of idiopathic Parkinson's disease is phase specific: Implication of its therapeutic effectiveness. Rejuvenation Res. 17(6):481-489. https://doi.org/10.1089/rej.2014.1591

Prasad K, Tarasewicz E, Mathew J, Strickland PA, Buckley B, Richardson JR, Richfield EK. 2009. Toxicokinetics and toxicodynamics of paraquat accumulation in mouse brain. Exp Neurol. 215(2):358-367. https://doi.org/10.1016/j.expneurol.2008.11.003

Purisai MG, McCormack AL, Cumine S, Li J, Isla MZ, Di Monte DA. 2007. Microglial activation as a priming event leading to paraquat-induced dopaminergic cell degeneration. Neurobiol Dis. 25(2):392-400. https://doi.org/10.1016/j.nbd.2006.10.008

Qin X, Wu Q, Lin L, Sun A, Liu S, Li X, Cao X, Gao T, Luo P, Zhu X et al. 2015. Soluble epoxide hydrolase deficiency or inhibition attenuates MPTP-induced Parkinsonism. Mol Neurobiol. 52(1):187-195. https://doi.org/10.1007/s12035-014-8833-3

Quintero-Espinosa D, Jimenez-Del-Rio M, Velez-Pardo C. 2017. Knockdown transgenic Lrrk Drosophila resists paraquat-induced locomotor impairment and neurodegeneration: A therapeutic strategy for Parkinson's disease. Brain Res. 1657:253-261. https://doi.org/10.1016/j.brainres.2016.12.023

Rappold PM, Cui M, Chesser AS, Tibbett J, Grima JC, Duan L, Sen N, Javitch JA, Tieu K. 2011. Paraquat neurotoxicity is mediated by the dopamine transporter and organic cation transporter-3. Proc Natl Acad Sci U S A. 108(51):20766-20771. https://doi.org/10.1073/pnas.1115141108

Reeves R, Thiruchelvam M, Baggs RB, Cory-Slechta DA. 2003. Interactions of paraquat and triadimefon: Behavioral and neurochemical effects. Neurotoxicology. 24(6):839-850. https://doi.org/10.1016/s0161-813x(03)00057-3

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

Rodriguez-Rocha H, Garcia Garcia A, Zavala-Flores L, Li S, Madayiputhiya N, Franco R. 2012. Glutaredoxin 1 protects dopaminergic cells by increased protein glutathionylation in experimental Parkinson's disease. Antioxid Redox Signal. 17(12):1676-1693. https://doi.org/10.1089/ars.2011.4474

Rojo AI, Cavada C, de Sagarra MR, Cuadrado A. 2007. Chronic inhalation of rotenone or paraquat does not induce Parkinson's disease symptoms in mice or rats. Exp Neurol. 208(1):120-126. https://doi.org/10.1016/j.expneurol.2007.07.022

Rudyk CA, McNeill J, Prowse N, Dwyer Z, Farmer K, Litteljohn D, Caldwell W, Hayley S. 2017. Age and chronicity of administration dramatically influenced the impact of low dose paraquat exposure on behavior and hypothalamic-pituitary-adrenal activity. Front Aging Neurosci. 9:222. https://doi.org/10.3389/fnagi.2017.00222

S N, Shivanandappa T. 2018. Neuroprotective action of 4-Hydroxyisophthalic acid against paraquat-induced motor impairment involves amelioration of mitochondrial damage and neurodegeneration in Drosophila. Neurotoxicology. 66:160-169. https://doi.org/10.1016/j.neuro.2018.04.006

Satayavivad J, Sirapat W, Thiantanawat A. 1997. Neurological effects of chronic exposure to low doses of paraquat in rats. Res Commun Pharmacol Toxicol. 2:269-282.

Satpute RM, Pawar PP, Puttewar S, Sawale SD, Ambhore PD. 2017. Effect of resveratrol and tetracycline on the subacute paraquat toxicity in mice. Hum Exp Toxicol. 36(12):1303-1314. https://doi.org/10.1177/0960327116688070

Shaikh KT, Yang A, Youshin E, Schmid S. 2015. Transgenic LRRK2 (R1441G) rats-a model for Parkinson disease? PeerJ. 3:e945. https://doi.org/10.7717/peerj.945

Shepherd KR, Lee ES, Schmued L, Jiao Y, Ali SF, Oriaku ET, Lamango NS, Soliman KF, Charlton CG. 2006. The potentiating effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) on paraquat-induced neurochemical and behavioral changes in mice. Pharmacol Biochem Behav. 83(3):349-359. https://doi.org/10.1016/j.pbb.2006.02.013

Shukla AK, Pragya P, Chaouhan HS, Patel DK, Abdin MZ, Kar Chowdhuri D. 2014. Mutation in Drosophila methuselah resists paraquat induced Parkinson-like phenotypes. Neurobiol Aging. 35(10):2419.e2411-2419.e2416. https://doi.org/10.1016/j.neurobiolaging.2014.04.008

Shukla AK, Pragya P, Chaouhan HS, Tiwari AK, Patel DK, Abdin MZ, Chowdhuri DK. 2014. Heat shock protein-70 (Hsp-70) suppresses paraquat-induced neurodegeneration by inhibiting JNK and caspase-3 activation in Drosophila model of Parkinson's disease. PLoS One. 9(6):e98886. https://doi.org/10.1371/journal.pone.0098886

Sidlauskaite E, Gibson JW, Megson IL, Whitfield PD, Tovmasyan A, Batinic-Haberle I, Murphy MP, Moult PR, Cobley JN. 2018. Mitochondrial ROS cause motor deficits induced by synaptic inactivity: Implications for synapse pruning. Redox Biol. 16:344-351. https://doi.org/10.1016/j.redox.2018.03.012

Smeyne RJ, Breckenridge CB, Beck M, Jiao Y, Butt MT, Wolf JC, Zadory D, Minnema DJ, Sturgess NC, Travis KZ et al. 2016. Assessment of the effects of MPTP and paraquat on dopaminergic neurons and microglia in the substantia nigra pars compacta of C57BL/6 mice. PLoS One. 11(10):e0164094. https://doi.org/10.1371/journal.pone.0164094

Soares JJ, Rodrigues DT, Goncalves MB, Lemos MC, Gallarreta MS, Bianchini MC, Gayer MC, Puntel RL, Roehrs R, Denardin ELG. 2017. Paraquat exposure-induced Parkinson's disease-like symptoms and oxidative stress in Drosophila melanogaster: Neuroprotective effect of Bougainvillea glabra Choisy. Biomed Pharmacother. 95:245-251. https://doi.org/10.1016/j.biopha.2017.08.073

Somayajulu-Nitu M, Sandhu JK, Cohen J, Sikorska M, Sridhar TS, Matei A, Borowy-Borowski H, Pandey S. 2009. Paraquat induces oxidative stress, neuronal loss in substantia nigra region and parkinsonism in adult rats: Neuroprotection and amelioration of symptoms by water-soluble formulation of coenzyme Q10. BMC Neurosci. 10:88. https://doi.org/10.1186/1471-2202-10-88

Songin M, Strosznajder JB, Fital M, Kuter K, Kolasiewicz W, Nowak P, Ossowska K. 2011. Glycogen synthase kinase 3beta and its phosphorylated form (Y216) in the paraquat-induced model of parkinsonism. Neurotox Res. 19(1):162-171. https://doi.org/10.1007/s12640-010-9153-7

Su C, Niu P. 2015. Low doses of single or combined agrichemicals induces alpha-synuclein aggregation in nigrostriatal system of mice through inhibition of proteasomal and autophagic pathways. Int J Clin Exp Med. 8(11):20508-20515.

Tang SP, Salam SKN, Jaafar H, Gan SH, Muzaimi M, Sulaiman SA. 2017. Tualang honey protects the rat midbrain and lung against repeated paraquat exposure. Oxid Med Cell Longev. https://doi.org/10.1155/2017/4605782

Thiruchelvam M, Brockel BJ, Richfield EK, Baggs RB, Cory-Slechta DA. 2000. Potentiated and preferential effects of combined paraquat and maneb on nigrostriatal dopamine systems: Environmental risk factors for Parkinson's disease? Brain Res. 873(2):225-234. https://doi.org/10.1016/s0006-8993(00)02496-3

Thiruchelvam M, McCormack A, Richfield EK, Baggs RB, Tank AW, Di Monte DA, Cory-Slechta DA. 2003. Age-related irreversible progressive nigrostriatal dopaminergic neurotoxicity in the paraquat and maneb model of the Parkinson's disease phenotype. Eur J Neurosci. 18(3):589-600.

Thiruchelvam M, Richfield EK, Baggs RB, Tank AW, Cory-Slechta DA. 2000. The nigrostriatal dopaminergic system as a preferential target of repeated exposures to combined paraquat and maneb: Implications for Parkinson's disease. J Neurosci. 20(24):9207-9214.

Thiruchelvam M, Richfield EK, Goodman BM, Baggs RB, Cory-Slechta DA. 2002. Developmental exposure to the pesticides paraquat and maneb and the Parkinson's disease phenotype. Neurotoxicology. 23(4-5):621-633.

Wang Q, Ren N, Cai Z, Lin Q, Wang Z, Zhang Q, Wu S, Li H. 2017. Paraquat and MPTP induce neurodegeneration and alteration in the expression profile of microRNAs: The role of transcription factor Nrf2. NPJ Parkinson’s Dis. 3:31. https://doi.org/10.1038/s41531-017-0033-1

Wang R, Zhao X, Xu J, Wen Y, Li A, Lu M, Zhou J. 2018. Astrocytic JWA deletion exacerbates dopaminergic neurodegeneration by decreasing glutamate transporters in mice. Cell Death Dis. 9(3):352. https://doi.org/10.1038/s41419-018-0381-8

Wang XH, Souders CL, 2nd, Zhao YH, Martyniuk CJ. 2018. Paraquat affects mitochondrial bioenergetics, dopamine system expression, and locomotor activity in zebrafish (Danio rerio). Chemosphere. 191:106-117. https://doi.org/10.1016/j.chemosphere.2017.10.032

Watson MB, Nobuta H, Abad C, Lee SK, Bala N, Zhu C, Richter F, Chesselet MF, Waschek JA. 2013. PACAP deficiency sensitizes nigrostriatal dopaminergic neurons to paraquat-induced damage and modulates central and peripheral inflammatory activation in mice. Neuroscience. 240:277-286. https://doi.org/10.1016/j.neuroscience.2013.03.002

Widdowson PS, Farnworth MJ, Upton R, Simpson MG. 1996. No changes in behaviour, nigro-striatal system neurochemistry or neuronal cell death following toxic multiple oral paraquat administration to rats. Hum Exp Toxicol. 15(7):583-591. https://doi.org/10.1177/096032719601500706

Willis GL, Moore C, Armstrong SM. 2014. Parkinson's disease, lights and melanocytes: Looking beyond the retina. Sci Rep. 4:3921. https://doi.org/10.1038/srep03921

Woolley DE, Gietzen DW, Gee SJ, Magdalou J, Hammock BD. 1989. Does paraquat (PQ) mimic MPP+ toxicity? Proc West Pharmacol Soc. 32:191-193.

Yadav SK, Prakash J, Chouhan S, Singh SP. 2013. Mucuna pruriens seed extract reduces oxidative stress in nigrostriatal tissue and improves neurobehavioral activity in paraquat-induced Parkinsonian mouse model. Neurochem Int. 62(8):1039-1047. https://doi.org/10.1016/j.neuint.2013.03.015

Yadav SK, Rai SN, Singh SP. 2017. Mucuna pruriens reduces inducible nitric oxide synthase expression in Parkinsonian mice model. J Chem Neuroanat. 80:1-10. https://doi.org/10.1016/j.jchemneu.2016.11.009

Yang W, Chen L, Ding Y, Zhuang X, Kang UJ. 2007. Paraquat induces dopaminergic dysfunction and proteasome impairment in DJ-1-deficient mice. Hum Mol Genet. 16(23):2900-2910. https://doi.org/10.1093/hmg/ddm249

Yin L, Lu L, Prasad K, Richfield EK, Unger EL, Xu J, Jones BC. 2011. Genetic-based, differential susceptibility to paraquat neurotoxicity in mice. Neurotoxicol Teratol. 33(3):415-421. https://doi.org/10.1016/j.ntt.2011.02.012

Zhao F, Wang W, Wang C, Siedlak SL, Fujioka H, Tang B, Zhu X. 2017. Mfn2 protects dopaminergic neurons exposed to paraquat both in vitro and in vivo: Implications for idiopathic Parkinson's disease. Biochim Biophys Acta. 1863(6):1359-1370. https://doi.org/10.1016/j.bbadis.2017.02.016

Zhao X, Wang R, Xiong J, Yan D, Li A, Wang S, Xu J, Zhou J. 2017. JWA antagonizes paraquat-induced neurotoxicity via activation of Nrf2. Toxicol Lett. 277:32-40. https://doi.org/10.1016/j.toxlet.2017.04.011

Zhou H, Huang C, Tong J, Xia XG. 2011. Early exposure to paraquat sensitizes dopaminergic neurons to subsequent silencing of PINK1 gene expression in mice. Int J Biol Sci. 7(8):1180-1187. https://doi.org/10.7150/ijbs.7.1180

E.4. Animal Studies: Secondary Endpoints

Certain studies in this list are also included in the Human Studies: Primary Endpoints list, the Animal Studies: Primary Endpoints list, and the In Vitro Studies list if they contained data relating to those endpoints in addition to animal secondary endpoints.

Ait-Bali Y, Ba-M'hamed S, Bennis M. 2016. Prenatal paraquat exposure induces neurobehavioral and cognitive changes in mice offspring. Environ Toxicol Pharmacol. 48:53-62. https://doi.org/10.1016/j.etap.2016.10.008

Ajjuri RR, O'Donnell JM. 2013. Novel whole-tissue quantitative assay of nitric oxide levels in Drosophila neuroinflammatory response. J Vis Exp. (82):50892. https://doi.org/10.3791/50892

Anselmi L, Toti L, Bove C, Hampton J, Travagli RA. 2017. A nigro-vagal pathway controls gastric motility and is affected in a rat model of Parkinsonism. Gastroenterology. 153(6):1581-1593. https://doi.org/10.1053/j.gastro.2017.08.069

Attia HN, Maklad YA. 2018. Neuroprotective effects of coenzyme Q10 on paraquat-induced Parkinson's disease in experimental animals. Behav Pharmacol. 29(1):79-86. https://doi.org/10.1097/fbp.0000000000000342

Bagetta G, Iannone M, Vecchio I, Rispoli V, Rotiroti D, Nistico G. 1994. Neurodegeneration produced by intrahippocampal injection of paraquat is reduced by systemic administration of the 21-aminosteroid U74389F in rats. Free Radic Res. 21(2):85-93.

Bajo-Graneras R, Ganfornina MD, Martin-Tejedor E, Sanchez D. 2011. Apolipoprotein D mediates autocrine protection of astrocytes and controls their reactivity level, contributing to the functional maintenance of paraquat-challenged dopaminergic systems. Glia. 59(10):1551-1566. https://doi.org/10.1002/glia.21200

Bajo-Graneras R, Sanchez D, Gutierrez G, Gonzalez C, Do Carmo S, Rassart E, Ganfornina MD. 2011. Apolipoprotein D alters the early transcriptional response to oxidative stress in the adult cerebellum. J Neurochem. 117(6):949-960. https://doi.org/10.1111/j.1471-4159.2011.07266.x

Barbeau A, Dallaire L, Buu NT, Poirier J, Rucinska E. 1985. Comparative behavioral, biochemical and pigmentary effects of MPTP, MPP+ and paraquat in Rana pipiens. Life Sci. 37(16):1529-1538. https://doi.org/10.1016/0024-3205(85)90185-7

Barlow BK, Richfield EK, Cory-Slechta DA, Thiruchelvam M. 2004. A fetal risk factor for Parkinson's disease. Dev Neurosci. 26(1):11-23. https://doi.org/10.1159/000080707

Benzi G, Marzatico F, Pastoris O, Villa RF. 1990. Influence of oxidative stress on the age-linked alterations of the cerebral glutathione system. J Neurosci Res. 26(1):120-128. https://doi.org/10.1002/jnr.490260116

Bobyn J, Mangano EN, Gandhi A, Nelson E, Moloney K, Clarke M, Hayley S. 2012. Viral-toxin interactions and Parkinson's disease: Poly I:C priming enhanced the neurodegenerative effects of paraquat. J Neuroinflammation. 9:86. https://doi.org/10.1186/1742-2094-9-86

Bortolotto JW, Cognato GP, Christoff RR, Roesler LN, Leite CE, Kist LW, Bogo MR, Vianna MR, Bonan CD. 2014. Long-term exposure to paraquat alters behavioral parameters and dopamine levels in adult zebrafish (Danio rerio). Zebrafish. 11(2):142-153. https://doi.org/10.1089/zeb.2013.0923

Breckenridge CB, Sturgess NC, Butt M, Wolf JC, Zadory D, Beck M, Mathews JM, Tisdel MO, Minnema D, Travis KZ et al. 2013. Pharmacokinetic, neurochemical, stereological and neuropathological studies on the potential effects of paraquat in the substantia nigra pars compacta and striatum of male C57BL/6J mice. Neurotoxicology. 37:1-14. https://doi.org/10.1016/j.neuro.2013.03.005

Brooks AI, Chadwick CA, Gelbard HA, Cory-Slechta DA, Federoff HJ. 1999. Paraquat elicited neurobehavioral syndrome caused by dopaminergic neuron loss. Brain Res. 823(1-2):1-10. https://doi.org/10.1016/s0006-8993(98)01192-5

Chanyachukul T, Yoovathaworn K, Thongsaard W, Chongthammakun S, Navasumrit P, Satayavivad J. 2004. Attenuation of paraquat-induced motor behavior and neurochemical disturbances by L-valine in vivo. Toxicol Lett. 150(3):259-269. https://doi.org/10.1016/j.toxlet.2004.02.007

Chaudhuri A, Bowling K, Funderburk C, Lawal H, Inamdar A, Wang Z, O'Donnell JM. 2007. Interaction of genetic and environmental factors in a Drosophila parkinsonism model. J Neurosci. 27(10):2457-2467. https://doi.org/10.1523/jneurosci.4239-06.2007

Chen AY, Tully T. 2018. A stress-enhanced model for discovery of disease-modifying gene: Ece1-suppresses the toxicity of alpha-synuclein A30P. Neurobiol Dis. 114:153-163. https://doi.org/10.1016/j.nbd.2018.03.003

Chen LJ, Yoo SE, Na R, Liu YH, Ran QT. 2012. Cognitive impairment and increased Aβ levels induced by paraquat exposure are attenuated by enhanced removal of mitochondrial H2O2. Neurobiol Aging. 33(2). https://doi.org/10.1016/j.neurobiolaging.2011.01.008

Chen P, Chen Z, Li A, Lou XC, Wu XK, Zhao CJ, Wang SL, Liang LP. 2008. Catalytic metalloporphyrin protects against paraquat neurotoxicity in vivo. Biomed Environ Sci. 21(3):233-238. https://doi.org/10.1016/s0895-3988(08)60035-5

Chen Q, Niu Y, Zhang R, Guo H, Gao Y, Li Y, Liu R. 2010. The toxic influence of paraquat on hippocampus of mice: Involvement of oxidative stress. Neurotoxicology. 31(3):310-316. https://doi.org/10.1016/j.neuro.2010.02.006

Chinta SJ, Woods G, Demaria M, Rane A, Zou Y, McQuade A, Rajagopalan S, Limbad C, Madden DT, Campisi J et al. 2018. Cellular senescence is induced by the environmental neurotoxin paraquat and contributes to neuropathology linked to Parkinson's disease. Cell Rep. 22(4):930-940. https://doi.org/10.1016/j.celrep.2017.12.092

Choi HS, An JJ, Kim SY, Lee SH, Kim DW, Yoo KY, Won MH, Kang TC, Kwon HJ, Kang JH et al. 2006. PEP-1-SOD fusion protein efficiently protects against paraquat-induced dopaminergic neuron damage in a Parkinson disease mouse model. Free Radic Biol Med. 41(7):1058-1068. https://doi.org/10.1016/j.freeradbiomed.2006.06.006

Cicchetti F, Lapointe N, Roberge-Tremblay A, Saint-Pierre M, Jimenez L, Ficke BW, Gross RE. 2005. Systemic exposure to paraquat and maneb models early Parkinson's disease in young adult rats. Neurobiol Dis. 20(2):360-371. https://doi.org/10.1016/j.nbd.2005.03.018

Cosenza M, Bidanset J, Johnson D. 1994. Effects of paraquat on the midbrain micromass cell culture system. In Vitro Toxicol. 7(4):313-320.

Costa KM, Maciel IS, Kist LW, Campos MM, Bogo MR. 2014. Pharmacological inhibition of CXCR2 chemokine receptors modulates paraquat-induced intoxication in rats. PLoS One. 9(8):e105740. https://doi.org/10.1371/journal.pone.0105740

Coughlan C, Walker DI, Lohr KM, Richardson JR, Saba LM, Caudle WM, Fritz KS, Roede JR. 2015. Comparative proteomic analysis of carbonylated proteins from the striatum and cortex of pesticide-treated mice. Parkinsons Dis. 2015:812532. https://doi.org/10.1155/2015/812532

Cristovao AC, Choi DH, Baltazar G, Beal MF, Kim YS. 2009. The role of NADPH oxidase 1-derived reactive oxygen species in paraquat-mediated dopaminergic cell death. Antioxid Redox Signal. 11(9):2105-2118. https://doi.org/10.1089/ars.2009.2459

Cristovao AC, Guhathakurta S, Bok E, Je G, Yoo SD, Choi DH, Kim YS. 2012. NADPH oxidase 1 mediates alpha-synucleinopathy in Parkinson's disease. J Neurosci. 32(42):14465-14477. https://doi.org/10.1523/jneurosci.2246-12.2012

Czerniczyniec A, Karadayian AG, Bustamante J, Cutrera RA, Lores-Arnaiz S. 2011. Paraquat induces behavioral changes and cortical and striatal mitochondrial dysfunction. Free Radic Biol Med. 51(7):1428-1436. https://doi.org/10.1016/j.freeradbiomed.2011.06.034

Czerniczyniec A, Lanza EM, Karadayian AG, Bustamante J, Lores-Arnaiz S. 2015. Impairment of striatal mitochondrial function by acute paraquat poisoning. J Bioenerg Biomembr. 47(5):395-408. https://doi.org/10.1007/s10863-015-9624-x

Czerniczyniec A, Lores-Arnaiz S, Bustamante J. 2013. Mitochondrial susceptibility in a model of paraquat neurotoxicity. Free Radic Res. 47(8):614-623. https://doi.org/10.3109/10715762.2013.806797

de Oliveira Souza A, Couto-Lima CA, Rosa Machado MC, Espreafico EM, Pinheiro Ramos RG, Alberici LC. 2017. Protective action of Omega-3 on paraquat intoxication in Drosophila melanogaster. J Toxicol Environ Health A. 80(19-21):1050-1063. https://doi.org/10.1080/15287394.2017.1357345

Degori N, Froio F, Strongoli MC, Defrancesco A, Calo M, Nistico G. 1988. Behavioral and electrocortical changes induced by paraquat after injection in specific areas of the brain of the rat. Neuropharmacology. 27(2):201-207. https://doi.org/10.1016/0028-3908(88)90171-2

Djukic M, Jovanovic MC, Ninkovic M, Vasiljevic I, Jovanovic M. 2007. The role of nitric oxide in paraquat-induced oxidative stress in rat striatum. Ann Agric Environ Med. 14(2):247-252.

Djukic MM, Jovanovic MD, Ninkovic M, Stevanovic I, Ilic K, Curcic M, Vekic J. 2012. Protective role of glutathione reductase in paraquat induced neurotoxicity. Chem Biol Interact. 199(2):74-86. https://doi.org/10.1016/j.cbi.2012.05.008

Ellwanger JH, Molz P, Dallemole DR, Pereira dos Santos A, Müller TE, Cappelletti L, Goncalves da Silva M, Franke SI, Pra D, Pegas Henriques JA. 2015. Selenium reduces bradykinesia and DNA damage in a rat model of Parkinson's disease. Nutrition. 31(2):359-365. https://doi.org/10.1016/j.nut.2014.07.004

Endo T, Hara S, Kano S, Kuriwa F. 1988. Effects of a paraquat-containing herbicide, gramoxon®, on the central monoamines and acetylcholine in mice. Res Commun Psychol Psychiatr Behav. 13(4):261-270.

Fahim MA, Shehab S, Nemmar A, Adem A, Dhanasekaran S, Hasan MY. 2013. Daily subacute paraquat exposure decreases muscle function and substantia nigra dopamine level. Physiol Res. 62(3):313-321.

Faro LR, Alfonso M, Cervantes R, Duran R. 2009. Comparative effects of pesticides on in vivo dopamine release in freely moving rats. Basic Clin Pharmacol Toxicol. 105(6):395-400. https://doi.org/10.1111/j.1742-7843.2009.00468.x

Fernagut PO, Hutson CB, Fleming SM, Tetreaut NA, Salcedo J, Masliah E, Chesselet MF. 2007. Behavioral and histopathological consequences of paraquat intoxication in mice: Effects of alpha-synuclein over-expression. Synapse. 61(12):991-1001. https://doi.org/10.1002/syn.20456

Filograna R, Godena VK, Sanchez-Martinez A, Ferrari E, Casella L, Beltramini M, Bubacco L, Whitworth AJ, Bisaglia M. 2016. Uperoxide dismutase (SOD)-mimetic M40403 is protective in cell and fly models of paraquat toxicity: Implications for Parkinson disease. J Biol Chem. 291(17):9257-9267. https://doi.org/10.1074/jbc.M115.708057

Finnerty NJ, O'Riordan SL, Lowry JP, Cloutier M, Wellstead P. 2013. Continuous real-time in vivo measurement of cerebral nitric oxide supports theoretical predictions of an irreversible switching in cerebral ROS after sufficient exposure to external toxins. J Parkinsons Dis. 3(3):351-362. https://doi.org/10.3233/jpd-130198

Fredriksson A, Fredriksson M, Eriksson P. 1993. Neonatal exposure to paraquat or MPTP induces permanent changes in striatum dopamine and behavior in adult mice. Toxicol Appl Pharmacol. 122(2):258-264. https://doi.org/10.1006/taap.1993.1194

Goers J, Manning-Bog AB, McCormack AL, Millett IS, Doniach S, Di Monte DA, Uversky VN, Fink AL. 2003. Nuclear localization of alpha-synuclein and its interaction with histones. Biochemistry. 42(28):8465-8471. https://doi.org/10.1021/bi0341152

Gollamudi S, Johri A, Calingasan NY, Yang L, Elemento O, Beal MF. 2012. Concordant signaling pathways produced by pesticide exposure in mice correspond to pathways identified in human Parkinson's disease. PLoS One. 7(5):e36191. https://doi.org/10.1371/journal.pone.0036191

Goncalves C, Dos Santos DB, Portilho SS, Lopes MW, Ghizoni H, de Souza V, Mack JM, Naime AA, Dafre AL, de Souza Brocardo P et al. 2018. Lipopolysaccharide-induced striatal nitrosative stress and impaired social recognition memory are not magnified by paraquat coexposure. Neurochem Res. 43(3):745-759. https://doi.org/10.1007/s11064-018-2477-z

Gonzalez-Hunt CP, Leung MC, Bodhicharla RK, McKeever MG, Arrant AE, Margillo KM, Ryde IT, Cyr DD, Kosmaczewski SG, Hammarlund M et al. 2014. Exposure to mitochondrial genotoxins and dopaminergic neurodegeneration in Caenorhabditis elegans. PLoS One. 9(12):e114459. https://doi.org/10.1371/journal.pone.0114459

Gorkin V, Amanov K, Mamadiev M, Medvedev A, Khuzhamberdiev M. 1994. The biochemical-mechanisms of the toxic effects of some pyridine-derivatives .1. Study on the deamination of biogenic-amines and other nitrogenous compounds in paraquat intoxication. Arch Environ Contam Toxicol. 26(4):534-539. https://doi.org/10.1007/bf00214158

Gourgou E, Chronis N. 2016. Chemically induced oxidative stress affects ASH neuronal function and behavior in C-elegans. Sci Rep. 6. https://doi.org/10.1038/srep38147

Hosamani R, Krishna G, Muralidhara. 2016. Standardized Bacopa monnieri extract ameliorates acute paraquat-induced oxidative stress, and neurotoxicity in prepubertal mice brain. Nutr Neurosci. 19(10):434-446. https://doi.org/10.1179/1476830514y.0000000149

Hutson CB, Lazo CR, Mortazavi F, Giza CC, Hovda D, Chesselet MF. 2011. Traumatic brain injury in adult rats causes progressive nigrostriatal dopaminergic cell loss and enhanced vulnerability to the pesticide paraquat. J Neurotrauma. 28(9):1783-1801. https://doi.org/10.1089/neu.2010.1723

Iannone M, Ciriolo MR, Rotilio G, Nistico G. 1991. Intra-nigral infusion of Cu-free superoxide dismutase prevents paraquat-induced behavioural stimulation and ECoG epileptogenic discharges in rats. Neuropharmacology. 30(8):893-898.

Inamdar AA, Chaudhuri A, O'Donnell J. 2012. The protective effect of minocycline in a paraquat-induced Parkinson's disease model in drosophila is modified in altered genetic backgrounds. Parkinsons Dis. 2012:938528. https://doi.org/10.1155/2012/938528

Jadiya P, Nazir A. 2012. Environmental toxicants as extrinsic epigenetic factors for parkinsonism: Studies employing transgenic C. elegans model. CNS Neurol Disord Drug Targets. 11(8):976-983.

Janda E, Parafati M, Aprigliano S, Carresi C, Visalli V, Sacco I, Ventrice D, Mega T, Vadala N, Rinaldi S et al. 2013. The antidote effect of quinone oxidoreductase 2 inhibitor against paraquat-induced toxicity in vitro and in vivo. Br J Pharmacol. 168(1):46-59. https://doi.org/10.1111/j.1476-5381.2012.01870.x

Jhonsa DJ, Badgujar LB, Sutariya BK, Saraf MN. 2016. Neuroprotective effect of flavonoids against paraquat induced oxidative stress and neurotoxicity in Drosophila melanogaster. Curr Top Nutraceutical Res. 14(4):283-294.

Kang MJ, Gil SJ, Koh HC. 2009. Paraquat induces alternation of the dopamine catabolic pathways and glutathione levels in the substantia nigra of mice. Toxicol Lett. 188(2):148-152. https://doi.org/10.1016/j.toxlet.2009.03.026

Kang MJ, Gil SJ, Lee JE, Koh HC. 2010. Selective vulnerability of the striatal subregions of C57BL/6 mice to paraquat. Toxicol Lett. 195(2-3):127-134. https://doi.org/10.1016/j.toxlet.2010.03.011

Khwaja M, McCormack A, McIntosh JM, Di Monte DA, Quik M. 2007. Nicotine partially protects against paraquat-induced nigrostriatal damage in mice; link to $\alpha 6\beta 2^*$ nAChRs. J Neurochem. 100(1):180-190. https://doi.org/10.1111/j.1471-4159.2006.04177.x

Krucek T, Korandova M, Sery M, Frydrychova RC, Krucek T, Korandova M, Szakosova K. 2015. Effect of low doses of herbicide paraquat on antioxidant defense in Drosophila. Arch Insect Biochem Physiol. 88(4):235-248. https://doi.org/10.1002/arch.21222

Kubo S, Tokunaga I, Yamamoto A, Morita K. 1999. Immunohistochemical studies on paraquat-induced damage to neuronal and glial cells in rat hippocampus. Acta Histochem Cytochem. 32(4):373-376. https://doi.org/10.1267/ahc.32.373

Kumar A, Ahmad I, Shukla S, Singh BK, Patel DK, Pandey HP, Singh C. 2010. Effect of zinc and paraquat co-exposure on neurodegeneration: Modulation of oxidative stress and expression of metallothioneins, toxicant responsive and transporter genes in rats. Free Radic Res. 44(8):950-965. https://doi.org/10.3109/10715762.2010.492832

Kumar A, Christian PK, Panchal K, Guruprasad BR, Tiwari AK. 2017. Supplementation of spirulina (Arthrospira platensis) improves lifespan and locomotor activity in paraquat-sensitive DJ-1beta(delta93) flies, a Parkinson's disease model in Drosophila melanogaster. J Diet Suppl. 14(5):573-588. https://doi.org/10.1080/19390211.2016.1275917

Kumar A, Singh BK, Ahmad I, Shukla S, Patel DK, Srivastava G, Kumar V, Pandey HP, Singh C. 2012. Involvement of NADPH oxidase and glutathione in zinc-induced dopaminergic neurodegeneration in rats: Similarity with paraquat neurotoxicity. Brain Res. 1438:48-64. https://doi.org/10.1016/j.brainres.2011.12.028

Kuter K, Nowak P, Golembiowska K, Ossowska K. 2010. Increased reactive oxygen species production in the brain after repeated low-dose pesticide paraquat exposure in rats. A comparison with peripheral tissues. Neurochem Res. 35(8):1121-1130. https://doi.org/10.1007/s11064-010-0163-x

Kuter K, Smialowska M, Wieronska J, Zieba B, Wardas J, Pietraszek M, Nowak P, Biedka I, Roczniak W, Konieczny J et al. 2007. Toxic influence of subchronic paraquat administration on dopaminergic neurons in rats. Brain Res. 1155:196-207. https://doi.org/10.1016/j.brainres.2007.04.018

Lavara-Culebras E, Paricio N. 2007. Drosophila DJ-1 mutants are sensitive to oxidative stress and show reduced lifespan and motor deficits. Gene. 400(1-2):158-165. https://doi.org/10.1016/j.gene.2007.06.013

Lawal HO, Chang HY, Terrell AN, Brooks ES, Pulido D, Simon AF, Krantz DE. 2010. The Drosophila vesicular monoamine transporter reduces pesticide-induced loss of dopaminergic neurons. Neurobiol Dis. 40(1):102-112. https://doi.org/10.1016/j.nbd.2010.05.008

Li H, Wu S, Wang Z, Lin W, Zhang C, Huang B. 2012. Neuroprotective effects of tert-butylhydroquinone on paraquat-induced dopaminergic cell degeneration in C57BL/6 mice and in PC12 cells. Arch Toxicol. 86(11):1729-1740. https://doi.org/10.1007/s00204-012-0935-y

Li HF, Zhao SX, Xing BP, Sun ML. 2015. Ulinastatin suppresses endoplasmic reticulum stress and apoptosis in the hippocampus of rats with acute paraquat poisoning. Neural Regen Res. 10(3):467-472. https://doi.org/10.4103/1673-5374.153698

Li X, Yin J, Cheng CM, Sun JL, Li Z, Wu YL. 2005. Paraquat induces selective dopaminergic nigrostriatal degeneration in aging C57BL/6 mice. Chin Med J. 118(16):1357-1361.

Liang LP, Kavanagh TJ, Patel M. 2013. Glutathione deficiency in Gclm null mice results in complex I inhibition and dopamine depletion following paraquat administration. Toxicol Sci. 134(2):366-373. https://doi.org/10.1093/toxsci/kft112

Ling LB, Chang Y, Liu CW, Lai PL, Hsu T. 2017. Oxidative stress intensity-related effects of cadmium (Cd) and paraquat (PQ) on UV-damaged-DNA binding and excision repair activities in zebrafish (Danio rerio) embryos. Chemosphere. 167:10-18. https://doi.org/10.1016/j.chemosphere.2016.09.068

Liou HH, Chen RC, Chen TH, Tsai YF, Tsai MC. 2001. Attenuation of paraquat-induced dopaminergic toxicity on the substantia nigra by (-)-deprenyl in vivo. Toxicol Appl Pharmacol. 172(1):37-43. https://doi.org/10.1006/taap.2001.9130

Liou HH, Chen RC, Tsai YF, Chen WP, Chang YC, Tsai MC. 1996. Effects of paraquat on the substantia nigra of the wistar rats: Neurochemical, histological, and behavioral studies. Toxicol Appl Pharmacol. 137(1):34-41. https://doi.org/10.1006/taap.1996.0054

Litteljohn D, Mangano E, Shukla N, Hayley S. 2009. Interferon-gamma deficiency modifies the motor and co-morbid behavioral pathology and neurochemical changes provoked by the pesticide paraquat. Neuroscience. 164(4):1894-1906. https://doi.org/10.1016/j.neuroscience.2009.09.025

Litteljohn D, Mangano EN, Hayley S. 2008. Cyclooxygenase-2 deficiency modifies the neurochemical effects, motor impairment and co-morbid anxiety provoked by paraquat administration in mice. Eur J Neurosci. 28(4):707-716. https://doi.org/10.1111/j.1460-9568.2008.06371.x

Litteljohn D, Nelson E, Bethune C, Hayley S. 2011. The effects of paraquat on regional brain neurotransmitter activity, hippocampal BDNF and behavioural function in female mice. Neurosci Lett. 502(3):186-191. https://doi.org/10.1016/j.neulet.2011.07.041

Liu D, Yang J, Li L, McAdoo DJ. 1995. Paraquat--a superoxide generator--kills neurons in the rat spinal cord. Free Radic Biol Med. 18(5):861-867.

Mak SK, McCormack AL, Manning-Bog AB, Cuervo AM, Di Monte DA. 2010. Lysosomal degradation of alpha-synuclein in vivo. J Biol Chem. 285(18):13621-13629. https://doi.org/10.1074/jbc.M109.074617

Mangano EN, Hayley S. 2009. Inflammatory priming of the substantia nigra influences the impact of later paraquat exposure: Neuroimmune sensitization of neurodegeneration. Neurobiol Aging. 30(9):1361-1378. https://doi.org/10.1016/j.neurobiolaging.2007.11.020

Mangano EN, Litteljohn D, So R, Nelson E, Peters S, Bethune C, Bobyn J, Hayley S. 2012. Interferon-gamma plays a role in paraquat-induced neurodegeneration involving oxidative and proinflammatory pathways. Neurobiol Aging. 33(7):1411-1426. https://doi.org/10.1016/j.neurobiolaging.2011.02.016

Mangano EN, Peters S, Litteljohn D, So R, Bethune C, Bobyn J, Clarke M, Hayley S. 2011. Granulocyte macrophage-colony stimulating factor protects against substantia nigra dopaminergic cell loss in an environmental toxin model of Parkinson's disease. Neurobiol Dis. 43(1):99-112. https://doi.org/10.1016/j.nbd.2011.02.011

Manning-Bog AB, McCormack AL, Li J, Uversky VN, Fink AL, Di Monte DA. 2002. The herbicide paraquat causes up-regulation and aggregation of alpha-synuclein in mice: Paraquat and alpha-synuclein. J Biol Chem. 277(3):1641-1644. https://doi.org/10.1074/jbc.C100560200

Manning-Bog AB, McCormack AL, Purisai MG, Bolin LM, Di Monte DA. 2003. Alpha-synuclein overexpression protects against paraquat-induced neurodegeneration. J Neurosci. 23(8):3095-3099.

Martin CA, Barajas A, Lawless G, Lawal HO, Assani K, Lumintang YP, Nunez V, Krantz DE. 2014. Synergistic effects on dopamine cell death in a Drosophila model of chronic toxin exposure. Neurotoxicology. 44:344-351. https://doi.org/10.1016/j.neuro.2014.08.005

Martinez-Perez DA, Jimenez-Del-Rio M, Velez-Pardo C. 2018. Epigallocatechin-3-gallate protects and prevents paraquat-induced oxidative stress and neurodegeneration in knockdown DJ-1-beta Drosophila melanogaster. Neurotox Res. 34(3):401-416. https://doi.org/10.1007/s12640-018-9899-x

McCormack AL, Atienza JG, Johnston LC, Andersen JK, Vu S, Di Monte DA. 2005. Role of oxidative stress in paraquat-induced dopaminergic cell degeneration. J Neurochem. 93(4):1030-1037. https://doi.org/10.1111/j.1471-4159.2005.03088.x

McCormack AL, Atienza JG, Langston JW, Di Monte DA. 2006. Decreased susceptibility to oxidative stress underlies the resistance of specific dopaminergic cell populations to paraquat-induced degeneration. Neuroscience. 141(2):929-937. https://doi.org/10.1016/j.neuroscience.2006.03.069

McCormack AL, Di Monte DA. 2003. Effects of L-dopa and other amino acids against paraquat-induced nigrostriatal degeneration. J Neurochem. 85(1):82-86. https://doi.org/10.1046/j.1471-4159.2003.01621.x

McCormack AL, Thiruchelvam M, Manning-Bog AB, Thiffault C, Langston JW, Cory-Slechta DA, Di Monte DA. 2002. Environmental risk factors and Parkinson's disease: Selective degeneration of nigral dopaminergic neurons caused by the herbicide paraquat. Neurobiol Dis. 10(2):119-127.

Melchiorri D, Del Duca C, Piccirilli S, Trombetta G, Bagetta G, Nistico G. 1998. Intrahippocampal injection of paraquat produces apoptotic cell death which is prevented by the lazaroid U74389G, in rats. Life Sci. 62(21):1927-1932. https://doi.org/10.1016/s0024-3205(98)00161-1

Menzies FM, Yenisetti SC, Min KT. 2005. Roles of Drosophila DJ-1 in survival of dopaminergic neurons and oxidative stress. Curr Biol. 15(17):1578-1582. https://doi.org/10.1016/j.cub.2005.07.036

Meulener M, Whitworth AJ, Armstrong-Gold CE, Rizzu P, Heutink P, Wes PD, Pallanck LJ, Bonini NM. 2005. Drosophila DJ-1 mutants are selectively sensitive to environmental toxins associated with Parkinson's disease. Curr Biol. 15(17):1572-1577. https://doi.org/10.1016/j.cub.2005.07.064

Minnema DJ, Travis KZ, Breckenridge CB, Sturgess NC, Butt M, Wolf JC, Zadory D, Beck MJ, Mathews JM, Tisdel MO et al. 2014. Dietary administration of paraquat for 13 weeks does not result in a loss of dopaminergic neurons in the substantia nigra of C57BL/6J mice. Regul Toxicol Pharm. 68(2):250-258. https://doi.org/10.1016/j.yrtph.2013.12.010

Miranda-Contreras L, Davila-Ovalles R, Benitez-Diaz P, Pena-Contreras Z, Palacios-Pru E. 2005. Effects of prenatal paraquat and mancozeb exposure on amino acid synaptic transmission in developing mouse cerebellar cortex. Brain Res Dev Brain Res. 160(1):19-27. https://doi.org/10.1016/j.devbrainres.2005.08.001

Mitra S, Chakrabarti N, Bhattacharyya A. 2011. Differential regional expression patterns of alpha-synuclein, TNF-alpha, and IL-1beta; and variable status of dopaminergic neurotoxicity in mouse brain after Paraquat treatment. J Neuroinflammation. 8:163. https://doi.org/10.1186/1742-2094-8-163

Mollace V, Iannone M, Muscoli C, Palma E, Granato T, Rispoli V, Nistico R, Rotiroti D, Salvemini D. 2003. The role of oxidative stress in paraquat-induced neurotoxicity in rats: Protection by non peptidyl superoxide dismutase mimetic. Neurosci Lett. 335(3):163-166. https://doi.org/10.1016/s0304-3940(02)01168-0

Müller TE, Nunes ME, Menezes CC, Marins AT, Leitemperger J, Gressler ACL, Carvalho FB, de Freitas CM, Quadros VA, Fachinetto R. 2018. Sodium selenite prevents paraquat-induced neurotoxicity in zebrafish. Mol Neurobiol. 55(3):1928-1941.

Naudet N, Antier E, Gaillard D, Morignat E, Lakhdar L, Baron T, Bencsik A. 2017. Oral exposure to paraquat triggers earlier expression of phosphorylated alpha-synuclein in the enteric nervous system of A53T mutant human alpha-synuclein transgenic mice. J Neuropathol Exp Neurol. 76(12):1046-1057. https://doi.org/10.1093/jnen/nlx092

Navarro JA, Hessner S, Yenisetti SC, Bayersdorfer F, Zhang L, Voigt A, Schneuwly S, Botella JA. 2014. Analysis of dopaminergic neuronal dysfunction in genetic and toxin-induced models of Parkinson's disease in Drosophila. J Neurochem. 131(3):369-382. https://doi.org/10.1111/jnc.12818

Navarro-Yepes J, Anandhan A, Bradley E, Bohovych I, Yarabe B, de Jong A, Ovaa H, Zhou Y, Khalimonchuk O, Quintanilla-Vega B et al. 2016. Inhibition of protein ubiquitination by paraquat and 1-methyl-4-phenylpyridinium impairs ubiquitin-dependent protein degradation pathways. Mol Neurobiol. 53(8):5229-5251. https://doi.org/10.1007/s12035-015-9414-9

Nellore J, Nandita P. 2015. Paraquat exposure induces behavioral deficits in larval zebrafish during the window of dopamine neurogenesis. Toxicol Rep. 2:950-956.

Nellore J, Shajan A, Antony D, Cynthia PP, Karthick RNS. 2015. Proteinaceous compounds from fragaria ananassa fruit attenuates paraquat induced Parkinson like locomotor and mitochondrial alterations in Zebrafish. Int J Pharm Pharm Sci. 7:246-251.

Niveditha S, Ramesh SR, Shivanandappa T. 2017. Paraquat-induced movement disorder in relation to oxidative stress-mediated neurodegeneration in the brain of Drosophila melanogaster. Neurochem Res. 42(11):3310-3320. https://doi.org/10.1007/s11064-017-2373-y

Nixon AM, Meadowcroft MD, Neely EB, Snyder AM, Purnell CJ, Wright J, Lamendella R, Nandar W, Huang X, Connor JR. 2018. HFE genotype restricts the response to paraquat in a mouse model of neurotoxicity. J Neurochem. 145(4):299-311. https://doi.org/10.1111/jnc.14299

Norris EH, Uryu K, Leight S, Giasson BI, Trojanowski JQ, Lee VM. 2007. Pesticide exposure exacerbates alpha-synucleinopathy in an A53T transgenic mouse model. Am J Pathol. 170(2):658-666. https://doi.org/10.2353/ajpath.2007.060359

Nuber S, Tadros D, Fields J, Overk CR, Ettle B, Kosberg K, Mante M, Rockenstein E, Trejo M, Masliah E. 2014. Environmental neurotoxic challenge of conditional alpha-synuclein transgenic mice predicts a dopaminergic olfactory-striatal interplay in early PD. Acta Neuropathol. 127(4):477-494. https://doi.org/10.1007/s00401-014-1255-5

Nunes ME, Müller TE, Braga MM, Fontana BD, Quadros VA, Marins A, Rodrigues C, Menezes C, Rosemberg DB, Loro VL. 2017. Chronic treatment with paraquat induces brain injury, changes in antioxidant defenses system, and modulates behavioral functions in zebrafish. Mol Neurobiol. 54(6):3925-3934. https://doi.org/10.1007/s12035-016-9919-x

Oeda T, Shimohama S, Kitagawa N, Kohno R, Imura T, Shibasaki H, Ishii N. 2001. Oxidative stress causes abnormal accumulation of familial amyotrophic lateral sclerosis-related mutant SOD1 in transgenic Caenorhabditis elegans. Hum Mol Genet. 10(19):2013-2023. https://doi.org/10.1093/hmg/10.19.2013

Offenburger SL, Ho XY, Tachie-Menson T, Coakley S, Hilliard MA, Gartner A. 2018. 6-OHDA-induced dopaminergic neurodegeneration in Caenorhabditis elegans is promoted by the engulfment pathway and inhibited by the transthyretin-related protein TTR-33. PLoS Genet. 14(1):e1007125. https://doi.org/10.1371/journal.pgen.1007125

Offenburger SL, Jongsma E, Gartner A. 2018. Mutations in Caenorhabditis elegans neuroligin-like glit-1, the apoptosis pathway and the calcium chaperone crt-1 increase dopaminergic neurodegeneration after 6-OHDA treatment. PLoS Genet. 14(1):e1007106. https://doi.org/10.1371/journal.pgen.1007106

O'Leary KT, Parameswaran N, Johnston LC, McIntosh JM, Di Monte DA, Quik M. 2008. Paraquat exposure reduces nicotinic receptor-evoked dopamine release in monkey striatum. J Pharmacol Exp Ther. 327(1):124-129. https://doi.org/10.1124/jpet.108.141861

Ossowska K, Smialowska M, Kuter K, Wieronska J, Zieba B, Wardas J, Nowak P, Dabrowska J, Bortel A, Biedka I et al. 2006. Degeneration of dopaminergic mesocortical neurons and activation of compensatory processes induced by a long-term paraquat administration in rats: Implications for Parkinson's disease. Neuroscience. 141(4):2155-2165. https://doi.org/10.1016/j.neuroscience.2006.05.039

Ossowska K, Wardas J, Kuter K, Nowak P, Dabrowska J, Bortel A, Labus L, Kwiecinski A, Krygowska-Wajs A, Wolfarth S. 2005. Influence of paraquat on dopaminergic transporter in the rat brain. Pharmacol Rep. 57(3):330-335.

Ossowska K, Wardas J, Smialowska M, Kuter K, Lenda T, Wieronska JM, Zieba B, Nowak P, Dabrowska J, Bortel A et al. 2005. A slowly developing dysfunction of dopaminergic nigrostriatal neurons induced by long-term paraquat administration in rats: An animal model of preclinical stages of Parkinson's disease? Eur J Neurosci. 22(6):1294-1304. https://doi.org/10.1111/j.1460-9568.2005.04301.x

Pangestiningsih TW, Wendo WD, Selan YN, Amalo FA, Ndaong NA, Lenda V. 2014. Histological features of Catecholaminergic neuron in substantia nigra induced by paraquat dichloride (1, 1-dimethyl-4, 4 bipyridinium) in wistar rat as a model of Parkinson disease. Indones J Biotechnol. 19(1):91-98.

Patel S, Singh V, Kumar A, Gupta YK, Singh MP. 2006. Status of antioxidant defense system and expression of toxicant responsive genes in striatum of maneb- and paraquat-induced

Parkinson's disease phenotype in mouse: Mechanism of neurodegeneration. Brain Res. 1081(1):9-18. https://doi.org/10.1016/j.brainres.2006.01.060

Pattarini R, Rong Y, Shepherd KR, Jiao Y, Qu C, Smeyne RJ, Morgan JI. 2012. Long-lasting transcriptional refractoriness triggered by a single exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyrimidine. Neuroscience. 214:84-105. https://doi.org/10.1016/j.neuroscience.2012.03.047

Peled-Kamar M, Lotem J, Wirguin I, Weiner L, Hermalin A, Groner Y. 1997. Oxidative stress mediates impairment of muscle function in transgenic mice with elevated level of wild-type Cu/Zn superoxide dismutase. Proc Natl Acad Sci U S A. 94(8):3883-3887. https://doi.org/10.1073/pnas.94.8.3883

Peng J, Mao XO, Stevenson FF, Hsu M, Andersen JK. 2004. The herbicide paraquat induces dopaminergic nigral apoptosis through sustained activation of the JNK pathway. J Biol Chem. 279(31):32626-32632. https://doi.org/10.1074/jbc.M404596200

Peng J, Oo ML, Andersen JK. 2010. Synergistic effects of environmental risk factors and gene mutations in Parkinson's disease accelerate age-related neurodegeneration. J Neurochem. 115(6):1363-1373. https://doi.org/10.1111/j.1471-4159.2010.07036.x

Peng J, Peng L, Stevenson FF, Doctrow SR, Andersen JK. 2007. Iron and paraquat as synergistic environmental risk factors in sporadic Parkinson's disease accelerate age-related neurodegeneration. J Neurosci. 27(26):6914-6922. https://doi.org/10.1523/jneurosci.1569-07.2007

Peng J, Stevenson FF, Oo ML, Andersen JK. 2009. Iron-enhanced paraquat-mediated dopaminergic cell death due to increased oxidative stress as a consequence of microglial activation. Free Radic Biol Med. 46(2):312-320. https://doi.org/10.1016/j.freeradbiomed.2008.10.045

Perry TL, Yong VW, Wall RA, Jones K. 1986. Paraquat and two endogenous analogues of the neurotoxic substance N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine do not damage dopaminergic nigrostriatal neurons in the mouse. Neurosci Lett. 69(3):285-289. https://doi.org/10.1016/0304-3940(86)90495-7

Pesah Y, Pham T, Burgess H, Middlebrooks B, Verstreken P, Zhou Y, Harding M, Bellen H, Mardon G. 2004. Drosophila parkin mutants have decreased mass and cell size and increased sensitivity to oxygen radical stress. Development. 131(9):2183-2194. https://doi.org/10.1242/dev.01095

Phom L, Achumi B, Alone DP, Muralidhara, Yenisetti SC. 2014. Curcumin's neuroprotective efficacy in Drosophila model of idiopathic Parkinson's disease is phase specific: Implication of its therapeutic effectiveness. Rejuvenation Res. 17(6):481-489. https://doi.org/10.1089/rej.2014.1591

Pomatto LCD, Carney C, Shen B, Wong S, Halaszynski K, Salomon MP, Davies KJA, Tower J. 2017. The mitochondrial lon protease is required for age-specific and sex-specific adaptation to oxidative stress. Curr Biol. 27(1):1-15. https://doi.org/10.1016/j.cub.2016.10.044

Prasad K, Tarasewicz E, Mathew J, Strickland PA, Buckley B, Richardson JR, Richfield EK. 2009. Toxicokinetics and toxicodynamics of paraquat accumulation in mouse brain. Exp Neurol. 215(2):358-367. https://doi.org/10.1016/j.expneurol.2008.11.003

Prasad K, Winnik B, Thiruchelvam MJ, Buckley B, Mirochnitchenko O, Richfield EK. 2007. Prolonged toxicokinetics and toxicodynamics of paraquat in mouse brain. Environ Health Perspect. 115(10):1448-1453. https://doi.org/10.1289/ehp.9932

Purisai MG, McCormack AL, Cumine S, Li J, Isla MZ, Di Monte DA. 2007. Microglial activation as a priming event leading to paraquat-induced dopaminergic cell degeneration. Neurobiol Dis. 25(2):392-400. https://doi.org/10.1016/j.nbd.2006.10.008

Quintero-Espinosa D, Jimenez-Del-Rio M, Velez-Pardo C. 2017. Knockdown transgenic Lrrk Drosophila resists paraquat-induced locomotor impairment and neurodegeneration: A therapeutic strategy for Parkinson's disease. Brain Res. 1657:253-261. https://doi.org/10.1016/j.brainres.2016.12.023

Rappold PM, Cui M, Chesser AS, Tibbett J, Grima JC, Duan L, Sen N, Javitch JA, Tieu K. 2011. Paraquat neurotoxicity is mediated by the dopamine transporter and organic cation transporter-3. Proc Natl Acad Sci U S A. 108(51):20766-20771. https://doi.org/10.1073/pnas.1115141108

Reeves R, Thiruchelvam M, Baggs RB, Cory-Slechta DA. 2003. Interactions of paraquat and triadimefon: Behavioral and neurochemical effects. Neurotoxicology. 24(6):839-850. https://doi.org/10.1016/s0161-813x(03)00057-3

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

Rizzo M, Ventrice D, Giannetto F, Cirinna S, Santagati NA, Procopio A, Mollace V, Muscoli C. 2017. Antioxidant activity of oleuropein and semisynthetic acetyl-derivatives determined by measuring malondialdehyde in rat brain. J Pharm Pharmacol. 69(11):1502-1512. https://doi.org/10.1111/jphp.12807

Rodriguez-Rocha H, Garcia Garcia A, Zavala-Flores L, Li S, Madayiputhiya N, Franco R. 2012. Glutaredoxin 1 protects dopaminergic cells by increased protein glutathionylation in experimental Parkinson's disease. Antioxid Redox Signal. 17(12):1676-1693. https://doi.org/10.1089/ars.2011.4474

Rojo AI, Cavada C, de Sagarra MR, Cuadrado A. 2007. Chronic inhalation of rotenone or paraquat does not induce Parkinson's disease symptoms in mice or rats. Exp Neurol. 208(1):120-126. https://doi.org/10.1016/j.expneurol.2007.07.022

Rudyk C, Litteljohn D, Syed S, Dwyer Z, Hayley S. 2015. Paraquat and psychological stressor interactions as pertains to Parkinsonian co-morbidity. Neurobiol Stress. 2:85-93. https://doi.org/10.1016/j.ynstr.2015.09.001

Rudyk CA, McNeill J, Prowse N, Dwyer Z, Farmer K, Litteljohn D, Caldwell W, Hayley S. 2017. Age and chronicity of administration dramatically influenced the impact of low dose paraquat exposure on behavior and hypothalamic-pituitary-adrenal activity. Front Aging Neurosci. 9:222. https://doi.org/10.3389/fnagi.2017.00222

S N, Shivanandappa T. 2018. Neuroprotective action of 4-Hydroxyisophthalic acid against paraquat-induced motor impairment involves amelioration of mitochondrial damage and neurodegeneration in Drosophila. Neurotoxicology. 66:160-169. https://doi.org/10.1016/j.neuro.2018.04.006

Saha S, Guillily MD, Ferree A, Lanceta J, Chan D, Ghosh J, Hsu CH, Segal L, Raghavan K, Matsumoto K et al. 2009. LRRK2 modulates vulnerability to mitochondrial dysfunction in Caenorhabditis elegans. J Neurosci. 29(29):9210-9218. https://doi.org/10.1523/jneurosci.2281-09.2009

Samann J, Hegermann J, von Gromoff E, Eimer S, Baumeister R, Schmidt E. 2009. Caenorhabditits elegans LRK-1 and PINK-1 act antagonistically in stress response and neurite outgrowth. J Biol Chem. 284(24):16482-16491. https://doi.org/10.1074/jbc.M808255200

Sanders LH, Paul KC, Howlett EH, Lawal H, Boppana S, Bronstein JM, Ritz B, Greenamyre JT. 2017. Editor's highlight: Base excision repair variants and pesticide exposure increase Parkinson's disease risk. Toxicol Sci. 158(1):188-198. https://doi.org/10.1093/toxsci/kfx086

Satayavivad J, Sirapat W, Thiantanawat A. 1997. Neurological effects of chronic exposure to low doses of paraquat in rats. Res Commun Pharmacol Toxicol. 2:269-282.

Sato N, Fujii K, Yuge O, Morio M. 1992. Changes in lipid-peroxidation levels and lipid-composition in the lungs, livers, kidneys and brains of mice treated with paraquat. J Appl Toxicol. 12(5):365-368. https://doi.org/10.1002/jat.2550120513

Satpute RM, Pawar PP, Puttewar S, Sawale SD, Ambhore PD. 2017. Effect of resveratrol and tetracycline on the subacute paraquat toxicity in mice. Hum Exp Toxicol. 36(12):1303-1314. https://doi.org/10.1177/0960327116688070

Seo J, Singh NN, Ottesen EW, Sivanesan S, Shishimorova M, Singh RN. 2016. Oxidative stress triggers body-wide skipping of multiple exons of the spinal muscular atrophy gene. PLoS One. 11(4):e0154390. https://doi.org/10.1371/journal.pone.0154390

Shepherd KR, Lee ES, Schmued L, Jiao Y, Ali SF, Oriaku ET, Lamango NS, Soliman KF, Charlton CG. 2006. The potentiating effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) on paraquat-induced neurochemical and behavioral changes in mice. Pharmacol Biochem Behav. 83(3):349-359. https://doi.org/10.1016/j.pbb.2006.02.013

Shimizu K, Matsubara K, Ohtaki K, Fujimaru S, Saito O, Shiono H. 2003. Paraquat induces long-lasting dopamine overflow through the excitotoxic pathway in the striatum of freely moving rats. Brain Res. 976(2):243-252. https://doi.org/10.1016/s0006-8993(03)02750-1

Shimizu K, Ohtaki K, Matsubara K, Aoyama K, Uezono T, Saito O, Suno M, Ogawa K, Hayase N, Kimura K et al. 2001. Carrier-mediated processes in blood--brain barrier penetration and neural uptake of paraquat. Brain Res. 906(1-2):135-142. https://doi.org/10.1016/s0006-8993(01)02577-x

Shukla AK, Pragya P, Chaouhan HS, Patel DK, Abdin MZ, Kar Chowdhuri D. 2014. Mutation in Drosophila methuselah resists paraquat induced Parkinson-like phenotypes. Neurobiol Aging. 35(10):2419.e2411-2419.e2416. https://doi.org/10.1016/j.neurobiolaging.2014.04.008

Shukla AK, Pragya P, Chaouhan HS, Tiwari AK, Patel DK, Abdin MZ, Chowdhuri DK. 2014. Heat shock protein-70 (Hsp-70) suppresses paraquat-induced neurodegeneration by inhibiting JNK and caspase-3 activation in Drosophila model of Parkinson's disease. PLoS One. 9(6):e98886. https://doi.org/10.1371/journal.pone.0098886

Sidlauskaite E, Gibson JW, Megson IL, Whitfield PD, Tovmasyan A, Batinic-Haberle I, Murphy MP, Moult PR, Cobley JN. 2018. Mitochondrial ROS cause motor deficits induced by synaptic inactivity: Implications for synapse pruning. Redox Biol. 16:344-351. https://doi.org/10.1016/j.redox.2018.03.012

Singh S, Dimri U, Kataria M, Kumari P. 2011. Ameliorative activity of Withania somnifera root extract on paraquat-induced oxidative stress in mice. J Pharmacol Toxicol. 6(4):433-439.

Soares JJ, Rodrigues DT, Goncalves MB, Lemos MC, Gallarreta MS, Bianchini MC, Gayer MC, Puntel RL, Roehrs R, Denardin ELG. 2017. Paraquat exposure-induced Parkinson's disease-like symptoms and oxidative stress in Drosophila melanogaster: Neuroprotective effect of Bougainvillea glabra Choisy. Biomed Pharmacother. 95:245-251. https://doi.org/10.1016/j.biopha.2017.08.073

Somayajulu-Nitu M, Sandhu JK, Cohen J, Sikorska M, Sridhar TS, Matei A, Borowy-Borowski H, Pandey S. 2009. Paraquat induces oxidative stress, neuronal loss in substantia nigra region and parkinsonism in adult rats: Neuroprotection and amelioration of symptoms by water-soluble formulation of coenzyme Q10. BMC Neurosci. 10:88. https://doi.org/10.1186/1471-2202-10-88

Song L, He Y, Ou J, Zhao Y, Li R, Cheng J, Lin CH, Ho MS. 2017. Auxilin underlies progressive locomotor deficits and dopaminergic neuron loss in a Drosophila model of Parkinson's disease. Cell Rep. 18(5):1132-1143. https://doi.org/10.1016/j.celrep.2017.01.005

Songin M, Ossowska K, Kuter K, Strosznajder JB. 2011. Alteration of GSK-3beta in the hippocampus and other brain structures after chronic paraquat administration in rats. Folia Neuropathol. 49(4):319-327.

Songin M, Strosznajder JB, Fital M, Kuter K, Kolasiewicz W, Nowak P, Ossowska K. 2011. Glycogen synthase kinase 3beta and its phosphorylated form (Y216) in the paraquat-induced model of Parkinsonism. Neurotox Res. 19(1):162-171. https://doi.org/10.1007/s12640-010-9153-7

Soylemezoglu T. 2001. The effectiveness of n-acetylcysteine and cinnarizine on paraquat-induced neuro and hepato-toxicity in mice. J Fac Phann Gazi. 18(1):49-57.

Srivastava G, Dixit A, Yadav S, Patel DK, Prakash O, Singh MP. 2012. Resveratrol potentiates cytochrome P450 2 d22-mediated neuroprotection in maneb- and paraquat-induced parkinsonism in the mouse. Free Radic Biol Med. 52(8):1294-1306. https://doi.org/10.1016/j.freeradbiomed.2012.02.005

Su C, Niu P. 2015. Low doses of single or combined agrichemicals induces alpha-synuclein aggregation in nigrostriatal system of mice through inhibition of proteasomal and autophagic pathways. Int J Clin Exp Med. 8(11):20508-20515.

Tang SP, Salam SKN, Jaafar H, Gan SH, Muzaimi M, Sulaiman SA. 2017. Tualang honey protects the rat midbrain and lung against repeated paraquat exposure. Oxid Med Cell Longev. https://doi.org/10.1155/2017/4605782

Tawara T, Fukushima T, Hojo N, Isobe A, Shiwaku K, Setogawa T, Yamane Y. 1996. Effects of paraquat on mitochondrial electron transport system and catecholamine contents in rat brain. Arch Toxicol. 70(9):585-589.

Thiruchelvam M, Brockel BJ, Richfield EK, Baggs RB, Cory-Slechta DA. 2000. Potentiated and preferential effects of combined paraquat and maneb on nigrostriatal dopamine systems: Environmental risk factors for Parkinson's disease? Brain Res. 873(2):225-234. https://doi.org/10.1016/s0006-8993(00)02496-3

Thiruchelvam M, McCormack A, Richfield EK, Baggs RB, Tank AW, Di Monte DA, Cory-Slechta DA. 2003. Age-related irreversible progressive nigrostriatal dopaminergic neurotoxicity in the paraquat and maneb model of the Parkinson's disease phenotype. Eur J Neurosci. 18(3):589-600.

Thiruchelvam M, Richfield EK, Baggs RB, Tank AW, Cory-Slechta DA. 2000. The nigrostriatal dopaminergic system as a preferential target of repeated exposures to combined paraquat and maneb: Implications for Parkinson's disease. J Neurosci. 20(24):9207-9214.

Thiruchelvam M, Richfield EK, Goodman BM, Baggs RB, Cory-Slechta DA. 2002. Developmental exposure to the pesticides paraquat and maneb and the Parkinson's disease phenotype. Neurotoxicology. 23(4-5):621-633.

Ved R, Saha S, Westlund B, Perier C, Burnam L, Sluder A, Hoener M, Rodrigues CM, Alfonso A, Steer C et al. 2005. Similar patterns of mitochondrial vulnerability and rescue induced by genetic modification of alpha-synuclein, parkin, and DJ-1 in Caenorhabditis elegans. J Biol Chem. 280(52):42655-42668. https://doi.org/10.1074/jbc.M505910200

Voronkov DN, Khudoerkov RM, Dikalova YV, Sheloukhova LI. 2016. Quantitative evaluation of changes in the striatal astrocyte axons in simulated parkinsonism. Bull Exp Biol Med. 160(4):505-509. https://doi.org/10.1007/s10517-016-3208-6

Wang D, Tang B, Zhao G, Pan Q, Xia K, Bodmer R, Zhang Z. 2008. Dispensable role of Drosophila ortholog of LRRK2 kinase activity in survival of dopaminergic neurons. Mol Neurodegener. 3:3. https://doi.org/10.1186/1750-1326-3-3

Wang L, Yang H, Wang Q, Zhang Q, Wang Z, Zhang Q, Wu S, Li H. 2018. Paraquat and MPTP induce alteration in the expression profile of long noncoding RNAs in the substantia nigra of mice: Role of the transcription factor Nrf2. Toxicol Lett. 291:11-28. https://doi.org/10.1016/j.toxlet.2018.04.002

Wang Q, Liu S, Hu D, Wang Z, Wang L, Wu T, Wu Z, Mohan C, Peng A. 2016. Identification of apoptosis and macrophage migration events in paraquat-induced oxidative stress using a zebrafish model. Life Sci. 157:116-124. https://doi.org/10.1016/j.lfs.2016.06.009

Wang Q, Ren N, Cai Z, Lin Q, Wang Z, Zhang Q, Wu S, Li H. 2017. Paraquat and MPTP induce neurodegeneration and alteration in the expression profile of microRNAs: The role of transcription factor Nrf2. NPJ Parkinson's Dis. 3:31. https://doi.org/10.1038/s41531-017-0033-1

Wang R, Zhao X, Xu J, Wen Y, Li A, Lu M, Zhou J. 2018. Astrocytic JWA deletion exacerbates dopaminergic neurodegeneration by decreasing glutamate transporters in mice. Cell Death Dis. 9(3):352. https://doi.org/10.1038/s41419-018-0381-8

Wang XH, Souders CL, 2nd, Zhao YH, Martyniuk CJ. 2018. Paraquat affects mitochondrial bioenergetics, dopamine system expression, and locomotor activity in zebrafish (Danio rerio). Chemosphere. 191:106-117. https://doi.org/10.1016/j.chemosphere.2017.10.032

Watson MB, Nobuta H, Abad C, Lee SK, Bala N, Zhu C, Richter F, Chesselet MF, Waschek JA. 2013. PACAP deficiency sensitizes nigrostriatal dopaminergic neurons to paraquat-induced damage and modulates central and peripheral inflammatory activation in mice. Neuroscience. 240:277-286. https://doi.org/10.1016/j.neuroscience.2013.03.002

Widdowson PS, Farnworth MJ, Upton R, Simpson MG. 1996. No changes in behaviour, nigro-striatal system neurochemistry or neuronal cell death following toxic multiple oral paraquat administration to rats. Hum Exp Toxicol. 15(7):583-591. https://doi.org/10.1177/096032719601500706

Wills J, Credle J, Oaks AW, Duka V, Lee JH, Jones J, Sidhu A. 2012. Paraquat, but not maneb, induces synucleinopathy and tauopathy in striata of mice through inhibition of proteasomal and autophagic pathways. PLoS One. 7(1):e30745. https://doi.org/10.1371/journal.pone.0030745

Woolley DE, Gietzen DW, Gee SJ, Magdalou J, Hammock BD. 1989. Does paraquat (PQ) mimic MPP+ toxicity? Proc West Pharmacol Soc. 32:191-193.

Wu B, Song B, Yang H, Huang B, Chi B, Guo Y, Liu H. 2013. Central nervous system damage due to acute paraquat poisoning: An experimental study with rat model. Neurotoxicology. 35:62-70. https://doi.org/10.1016/j.neuro.2012.12.001

Yadav SK, Prakash J, Chouhan S, Singh SP. 2013. Mucuna pruriens seed extract reduces oxidative stress in nigrostriatal tissue and improves neurobehavioral activity in paraquat-induced Parkinsonian mouse model. Neurochem Int. 62(8):1039-1047. https://doi.org/10.1016/j.neuint.2013.03.015

Yadav SK, Rai SN, Singh SP. 2017. Mucuna pruriens reduces inducible nitric oxide synthase expression in Parkinsonian mice model. J Chem Neuroanat. 80:1-10. https://doi.org/10.1016/j.jchemneu.2016.11.009

Yang W, Chen L, Ding Y, Zhuang X, Kang UJ. 2007. Paraquat induces dopaminergic dysfunction and proteasome impairment in DJ-1-deficient mice. Hum Mol Genet. 16(23):2900-2910. https://doi.org/10.1093/hmg/ddm249

Yin L, Lu L, Prasad K, Richfield EK, Unger EL, Xu J, Jones BC. 2011. Genetic-based, differential susceptibility to paraquat neurotoxicity in mice. Neurotoxicol Teratol. 33(3):415-421. https://doi.org/10.1016/j.ntt.2011.02.012

Zega G, Candiani S, Groppelli S, De Bernardi F, Pennati R. 2010. Neurotoxic effect of the herbicide paraquat on ascidian larvae. Environ Toxicol Pharmacol. 29(1):24-31. https://doi.org/10.1016/j.etap.2009.09.001

Zeitoun-Ghandour S, Leszczyszyn OI, Blindauer CA, Geier FM, Bundy JG, Sturzenbaum SR. 2011. C. elegans metallothioneins: Response to and defence against ROS toxicity. Mol Biosyst. 7(8):2397-2406. https://doi.org/10.1039/c1mb05114h

Zhao F, Wang W, Wang C, Siedlak SL, Fujioka H, Tang B, Zhu X. 2017. Mfn2 protects dopaminergic neurons exposed to paraquat both in vitro and in vivo: Implications for idiopathic Parkinson's disease. Biochim Biophys Acta Mol Basis Dis. 1863(6):1359-1370. https://doi.org/10.1016/j.bbadis.2017.02.016

Zhou H, Huang C, Tong J, Xia XG. 2011. Early exposure to paraquat sensitizes dopaminergic neurons to subsequent silencing of PINK1 gene expression in mice. Int J Biol Sci. 7(8):1180-1187. https://doi.org/10.7150/ijbs.7.1180

E.5. In Vitro Studies

Certain studies in this list are also included in the Human Studies: Primary Endpoints list, the Animal Studies: Primary Endpoints list, and the Animal Studies: Secondary Endpoints list if they contained data relating to those endpoints in addition to in vitro endpoints.

Aiuchi T, Shirane Y, Kinemuchi H, Arai Y, Kim SK, Nakaya K, Nakamura Y. 1990. Effect of the tetraphenylboron ion on the inhibition of mitochondrial respiration in synaptosomes by the 1-methyl-4-phenylpyridinium ion (MPP(+)). Neurochem Int. 17(1):59-65.

Alural B, Ozerdem A, Allmer J, Genc K, Genc S. 2015. Lithium protects against paraquat neurotoxicity by NRF2 activation and miR-34a inhibition in SH-SY5Y cells. Front Cell Neurosci. 9:209. https://doi.org/10.3389/fncel.2015.00209

An JJ, Lee YP, Kim SY, Lee SH, Kim DW, Lee MJ, Jeong MS, Jang SH, Kang JH, Kwon HY et al. 2008. Transduction of familial amyotrophic lateral sclerosis-related mutant PEP-1-SOD proteins into neuronal cells. Mol Cells. 25(1):55-63.

Anandhan A, Lei S, Levytskyy R, Pappa A, Panayiotidis MI, Cerny RL, Khalimonchuk O, Powers R, Franco R. 2017. Glucose metabolism and AMPK signaling regulate dopaminergic cell death induced by gene (alpha-synuclein)-environment (paraquat) interactions. Mol Neurobiol. 54(5):3825-3842. https://doi.org/10.1007/s12035-016-9906-2

Bajo-Graneras R, Ganfornina MD, Martin-Tejedor E, Sanchez D. 2011. Apolipoprotein D mediates autocrine protection of astrocytes and controls their reactivity level, contributing to the functional maintenance of paraquat-challenged dopaminergic systems. Glia. 59(10):1551-1566. https://doi.org/10.1002/glia.21200

Barlow BK, Lee DW, Cory-Slechta DA, Opanashuk LA. 2005. Modulation of antioxidant defense systems by the environmental pesticide maneb in dopaminergic cells. Neurotoxicology. 26(1):63-75. https://doi.org/10.1016/j.neuro.2004.07.004

Barlow BK, Thiruchelvam MJ, Bennice L, Cory-Slechta DA, Ballatori N, Richfield EK. 2003. Increased synaptosomal dopamine content and brain concentration of paraquat produced by selective dithiocarbamates. J Neurochem. 85(4):1075-1086. https://doi.org/10.1046/j.1471-4159.2003.01773.x

Bonneh-Barkay D, Langston WJ, Di Monte DA. 2005. Toxicity of redox cycling pesticides in primary mesencephalic cultures. Antioxid Redox Signal. 7(5-6):649-653. https://doi.org/10.1089/ars.2005.7.649

Bonneh-Barkay D, Reaney SH, Langston WJ, Di Monte DA. 2005. Redox cycling of the herbicide paraquat in microglial cultures. Brain Res Mol Brain Res. 134(1):52-56. https://doi.org/10.1016/j.molbrainres.2004.11.005

Cantu D, Fulton RE, Drechsel DA, Patel M. 2011. Mitochondrial aconitase knockdown attenuates paraquat-induced dopaminergic cell death via decreased cellular metabolism and release of iron and H(2)O(2). J Neurochem. 118(1):79-92. https://doi.org/10.1111/j.1471-4159.2011.07290.x

Cantu D, Schaack J, Patel M. 2009. Oxidative inactivation of mitochondrial aconitase results in iron and H2O2-mediated neurotoxicity in rat primary mesencephalic cultures. PLoS One. 4(9):e7095. https://doi.org/10.1371/journal.pone.0007095

Caputi FF, Carretta D, Lattanzio F, Palmisano M, Candeletti S, Romualdi P. 2015. Proteasome subunit and opioid receptor gene expression down-regulation induced by paraquat and maneb in human neuroblastoma SH-SY5Y cells. Environ Toxicol Pharmacol. 40(3):895-900. https://doi.org/10.1016/j.etap.2015.09.019

Carroll CB, Zeissler ML, Chadborn N, Gibson K, Williams G, Zajicek JP, Morrison KE, Hanemann CO. 2011. Changes in iron-regulatory gene expression occur in human cell culture models of Parkinson's disease. Neurochem Int. 59(1):73-80. https://doi.org/10.1016/j.neuint.2011.05.006

Carroll CB, Zeissler ML, Hanemann CO, Zajicek JP. 2012. Delta(9)-tetrahydrocannabinol (Delta(9)-THC) exerts a direct neuroprotective effect in a human cell culture model of Parkinson's disease. Neuropathol Appl Neurobiol. 38(6):535-547. https://doi.org/10.1111/j.1365-2990.2011.01248.x

Case AJ, Agraz D, Ahmad IM, Zimmerman MC. 2016. Low-dose Aronia melanocarpa concentrate attenuates paraquat-induced neurotoxicity. Oxid Med Cell Longev. 2016:5296271. https://doi.org/10.1155/2016/5296271

Castello PR, Drechsel DA, Patel M. 2007. Mitochondria are a major source of paraquat-induced reactive oxygen species production in the brain. J Biol Chem. 282(19):14186-14193. https://doi.org/10.1074/jbc.M700827200

Chang X, Lu W, Dou T, Wang X, Lou D, Sun X, Zhou Z. 2013. Paraquat inhibits cell viability via enhanced oxidative stress and apoptosis in human neural progenitor cells. Chem Biol Interact. 206(2):248-255. https://doi.org/10.1016/j.cbi.2013.09.010

Chau KY, Cooper JM, Schapira AH. 2010. Rasagiline protects against alpha-synuclein induced sensitivity to oxidative stress in dopaminergic cells. Neurochem Int. 57(5):525-529. https://doi.org/10.1016/j.neuint.2010.06.017

Chau KY, Korlipara LV, Cooper JM, Schapira AH. 2009. Protection against paraquat and A53T alpha-synuclein toxicity by cabergoline is partially mediated by dopamine receptors. J Neurol Sci. 278(1-2):44-53. https://doi.org/10.1016/j.jns.2008.11.012

Chen AY, Tully T. 2018. A stress-enhanced model for discovery of disease-modifying gene: Ece1-suppresses the toxicity of alpha-synuclein A30P. Neurobiol Dis. 114:153-163. https://doi.org/10.1016/j.nbd.2018.03.003

Chen P, Li A, Zhang M, He M, Chen Z, Wu X, Zhao C, Wang S, Liang L. 2008. Protective effects of a new metalloporphyrin on paraquat-induced oxidative stress and apoptosis in N27 cells. Acta Biochim Biophys Sin (Shanghai). 40(2):125-132. https://doi.org/10.1111/j.1745-7270.2008.00386.x

Chen T, Tan J, Wan Z, Zou Y, Afewerky HK, Zhang Z, Zhang T. 2017. Effects of commonly used pesticides in China on the mitochondria and ubiquitin-proteasome system in Parkinson's disease. Int J Mol Sci. 18(12). https://doi.org/10.3390/ijms18122507

Chen TS, Koutsilieri E, Rausch WD. 1995. MPP+ selectively affects calcium homeostasis in mesencephalic cell cultures from embryonal C57/Bl6 mice. J Neural Transm Gen Sect. 100(2):153-163.

Chen ZH, Yoshida Y, Saito Y, Niki E. 2005. Adaptation to hydrogen peroxide enhances PC12 cell tolerance against oxidative damage. Neurosci Lett. 383(3):256-259. https://doi.org/10.1016/j.neulet.2005.04.022

Chinta SJ, Rane A, Poksay KS, Bredesen DE, Andersen JK, Rao RV. 2008. Coupling endoplasmic reticulum stress to the cell death program in dopaminergic cells: Effect of paraquat. Neuromolecular Med. 10(4):333-342. https://doi.org/10.1007/s12017-008-8047-9

Chinta SJ, Woods G, Demaria M, Rane A, Zou Y, McQuade A, Rajagopalan S, Limbad C, Madden DT, Campisi J et al. 2018. Cellular senescence is induced by the environmental neurotoxin paraquat and contributes to neuropathology linked to Parkinson's disease. Cell Rep. 22(4):930-940. https://doi.org/10.1016/j.celrep.2017.12.092

Choi HS, An JJ, Kim SY, Lee SH, Kim DW, Yoo KY, Won MH, Kang TC, Kwon HJ, Kang JH et al. 2006. PEP-1-SOD fusion protein efficiently protects against paraquat-induced dopaminergic neuron damage in a Parkinson disease mouse model. Free Radic Biol Med. 41(7):1058-1068. https://doi.org/10.1016/j.freeradbiomed.2006.06.006

Choi SH, Kim DW, Kim SY, An JJ, Lee SH, Choi HS, Sohn EJ, Hwang SI, Won MH, Kang TC et al. 2005. Transduced human copper chaperone for Cu,Zn-SOD (PEP-1-CCS) protects against neuronal cell death. Mol Cells. 20(3):401-408.

Choi WS, Abel G, Klintworth H, Flavell RA, Xia Z. 2010. JNK3 mediates paraquat- and rotenone-induced dopaminergic neuron death. J Neuropathol Exp Neurol. 69(5):511-520. https://doi.org/10.1097/NEN.0b013e3181db8100

Choi WS, Kruse SE, Palmiter RD, Xia Z. 2008. Mitochondrial complex I inhibition is not required for dopaminergic neuron death induced by rotenone, MPP+, or paraquat. Proc Natl Acad Sci U S A. 105(39):15136-15141. https://doi.org/10.1073/pnas.0807581105

Chorfa A, Betemps D, Morignat E, Lazizzera C, Hogeveen K, Andrieu T, Baron T. 2013. Specific pesticide-dependent increases in alpha-synuclein levels in human neuroblastoma (SH-SY5Y) and melanoma (SK-MEL-2) cell lines. Toxicol Sci. 133(2):289-297. https://doi.org/10.1093/toxsci/kft076

Chun HS, Gibson GE, DeGiorgio LA, Zhang H, Kidd VJ, Son JH. 2001. Dopaminergic cell death induced by MPP(+), oxidant and specific neurotoxicants shares the common molecular mechanism. J Neurochem. 76(4):1010-1021. https://doi.org/10.1046/j.1471-4159.2001.00096.x

Cicchetti F, Lapointe N, Roberge-Tremblay A, Saint-Pierre M, Jimenez L, Ficke BW, Gross RE. 2005. Systemic exposure to paraquat and maneb models early Parkinson's disease in young adult rats. Neurobiol Dis. 20(2):360-371. https://doi.org/10.1016/j.nbd.2005.03.018

Ciriolo MR, Aquilano K, De Martino A, Carri MT, Rotilio G. 2001. Differential role of superoxide and glutathione in S-nitrosoglutathione-mediated apoptosis: A rationale for mild forms of familial amyotrophic lateral sclerosis associated with less active Cu,Zn superoxide dismutase mutants. J Neurochem. 77(6):1433-1443. https://doi.org/10.1046/j.1471-4159.2001.00383.x

Cosenza M, Bidanset J, Johnson D. 1994. Effects of paraquat on the midbrain micromass cell culture system. In Vitro Toxicol.

Cristovao AC, Barata J, Je G, Kim YS. 2013. PKCdelta mediates paraquat-induced Nox1 expression in dopaminergic neurons. Biochem Biophys Res Commun. 437(3):380-385. https://doi.org/10.1016/j.bbrc.2013.06.085

Cristovao AC, Choi DH, Baltazar G, Beal MF, Kim YS. 2009. The role of NADPH oxidase 1-derived reactive oxygen species in paraquat-mediated dopaminergic cell death. Antioxid Redox Signal. 11(9):2105-2118. https://doi.org/10.1089/ars.2009.2459

Cristovao AC, Guhathakurta S, Bok E, Je G, Yoo SD, Choi DH, Kim YS. 2012. NADPH oxidase 1 mediates alpha-synucleinopathy in Parkinson's disease. J Neurosci. 32(42):14465-14477. https://doi.org/10.1523/jneurosci.2246-12.2012

Crum TS, Gleixner AM, Posimo JM, Mason DM, Broeren MT, Heinemann SD, Wipf P, Brodsky JL, Leak RK. 2015. Heat shock protein responses to aging and proteotoxicity in the olfactory bulb. J Neurochem. 133(6):780-794. https://doi.org/10.1111/jnc.13041

Day BJ, Patel M, Calavetta L, Chang LY, Stamler JS. 1999. A mechanism of paraquat toxicity involving nitric oxide synthase. Proc Natl Acad Sci U S A. 96(22):12760-12765. https://doi.org/10.1073/pnas.96.22.12760

de Oliveira MR, Andrade CMB, Furstenau CR. 2018. Naringenin exerts anti-inflammatory effects in paraquat-treated SH-SY5Y cells through a mechanism associated with the Nrf2/HO-1 axis. Neurochem Res. 43(4):894-903. https://doi.org/10.1007/s11064-018-2495-x de Oliveira MR, Ferreira GC, Schuck PF. 2016. Protective effect of carnosic acid against paraquat-induced redox impairment and mitochondrial dysfunction in SH-SY5Y cells: Role for PI3K/Akt/Nrf2 pathway. Toxicol In Vitro. 32:41-54. https://doi.org/10.1016/j.tiv.2015.12.005

de Oliveira MR, Peres A, Ferreira GC, Schuck PF, Gama CS, Bosco SMD. 2017. Carnosic acid protects mitochondria of human neuroblastoma SH-SY5Y cells exposed to paraquat through activation of the Nrf2/HO-1axis. Mol Neurobiol. 54(8):5961-5972. https://doi.org/10.1007/s12035-016-0100-3

de Oliveira MR, Peres A, Gama CS, Bosco SMD. 2017. Pinocembrin provides mitochondrial protection by the activation of the Erk1/2-Nrf2 signaling pathway in SH-SY5Y neuroblastoma cells exposed to paraquat. Mol Neurobiol. 54(8):6018-6031. https://doi.org/10.1007/s12035-016-0135-5

de Oliveira MR, Schuck PF, Bosco SMD. 2017. Tanshinone I induces mitochondrial protection through an Nrf2-dependent mechanism in paraquat-treated human neuroblastoma SH-SY5Y cells. Mol Neurobiol. 54(6):4597-4608. https://doi.org/10.1007/s12035-016-0009-x

de Rus Jacquet A, Tambe MA, Ma SY, McCabe GP, Vest JHC, Rochet JC. 2017. Pikuni-Blackfeet traditional medicine: Neuroprotective activities of medicinal plants used to treat Parkinson's disease-related symptoms. J Ethnopharmacol. 206:393-407. https://doi.org/10.1016/j.jep.2017.01.001

Del Pino J, Moyano P, Diaz GG, Anadon MJ, Diaz MJ, Garcia JM, Lobo M, Pelayo A, Sola E, Frejo MT. 2017. Primary hippocampal neuronal cell death induction after acute and repeated paraquat exposures mediated by AChE variants alteration and cholinergic and glutamatergic transmission disruption. Toxicology. 390:88-99. https://doi.org/10.1016/j.tox.2017.09.008

Delic V, Griffin JWD, Zivkovic S, Zhang Y, Phan TA, Gong H, Chaput D, Reynes C, Dinh VB, Cruz J et al. 2017. Individual amino acid supplementation can improve energy metabolism and decrease ROS production in neuronal cells overexpressing alpha-synuclein. Neuromolecular Med. 19(2-3):322-344. https://doi.org/10.1007/s12017-017-8448-8

Ding Q, Keller JN. 2001. Proteasome inhibition in oxidative stress neurotoxicity: Implications for heat shock proteins. J Neurochem. 77(4):1010-1017. https://doi.org/10.1046/j.1471-4159.2001.00302.x

Donaire V, Niso M, Moran JM, Garcia L, Gonzalez-Polo RA, Soler G, Fuentes JM. 2005. Heat shock proteins protect both MPP(+) and paraquat neurotoxicity. Brain Res Bull. 67(6):509-514. https://doi.org/10.1016/j.brainresbull.2005.08.002

Dou T, Yan M, Wang X, Lu W, Zhao L, Lou D, Wu C, Chang X, Zhou Z. 2016. Nrf2/ARE pathway involved in oxidative stress induced by paraquat in human neural progenitor cells. Oxid Med Cell Longev. 2016:8923860. https://doi.org/10.1155/2016/8923860

Dranka BP, Zielonka J, Kanthasamy AG, Kalyanaraman B. 2012. Alterations in bioenergetic function induced by Parkinson's disease mimetic compounds: Lack of correlation with superoxide generation. J Neurochem. 122(5):941-951. https://doi.org/10.1111/j.1471-4159.2012.07836.x

Drechsel DA, Patel M. 2009. Differential contribution of the mitochondrial respiratory chain complexes to reactive oxygen species production by redox cycling agents implicated in parkinsonism. Toxicol Sci. 112(2):427-434. https://doi.org/10.1093/toxsci/kfp223

Drechsel DA, Patel M. 2010. Respiration-dependent H2O2 removal in brain mitochondria via the thioredoxin/peroxiredoxin system. J Biol Chem. 285(36):27850-27858. https://doi.org/10.1074/jbc.M110.101196

Dupiereux I, Falisse-Poirrier N, Zorzi W, Watt NT, Thellin O, Zorzi D, Pierard O, Hooper NM, Heinen E, Elmoualij B. 2008. Protective effect of prion protein via the N-terminal region in mediating a protective effect on paraquat-induced oxidative injury in neuronal cells. J Neurosci Res. 86(3):653-659. https://doi.org/10.1002/jnr.21506

Eiamphungporn W, Yainoy S, Prachayasittikul V. 2015. Angiopep-2-mediated delivery of human manganese superoxide dismutase in brain endothelial cells and its protective effect against oxidative stress. Int J Pept Res Ther. 21(1):63-71. https://doi.org/10.1007/s10989-014-9433-9

Ernst A, Stolzing A, Sandig G, Grune T. 2004. Antioxidants effectively prevent oxidation-induced protein damage in OLN 93 cells. Arch Biochem Biophys. 421(1):54-60. https://doi.org/10.1016/j.abb.2003.10.008

Fei Q, Ethell DW. 2008. Maneb potentiates paraquat neurotoxicity by inducing key Bcl-2 family members. J Neurochem. 105(6):2091-2097. https://doi.org/10.1111/j.1471-4159.2008.05293.x

Fei Q, McCormack AL, Di Monte DA, Ethell DW. 2008. Paraquat neurotoxicity is mediated by a Bak-dependent mechanism. J Biol Chem. 283(6):3357-3364. https://doi.org/10.1074/jbc.M708451200

Feng LR, Maguire-Zeiss KA. 2011. Dopamine and paraquat enhance alpha-synuclein-induced alterations in membrane conductance. Neurotox Res. 20(4):387-401. https://doi.org/10.1007/s12640-011-9255-x

Filograna R, Godena VK, Sanchez-Martinez A, Ferrari E, Casella L, Beltramini M, Bubacco L, Whitworth AJ, Bisaglia M. 2016. Superoxide dismutase (SOD)-mimetic M40403 is protective in cell and fly models of paraquat toxicity: Implications for Parkinson disease. J Biol Chem. 291(17):9257-9267. https://doi.org/10.1074/jbc.M115.708057

Fischer LR, Glass JD. 2010. Oxidative stress induced by loss of Cu,Zn-superoxide dismutase (SOD1) or superoxide-generating herbicides causes axonal degeneration in mouse DRG cultures. Acta Neuropathol. 119(2):249-259. https://doi.org/10.1007/s00401-009-0631-z

Fordel E, Thijs L, Martinet W, Lenjou M, Laufs T, Van Bockstaele D, Moens L, Dewilde S. 2006. Neuroglobin and cytoglobin overexpression protects human SH-SY5Y neuroblastoma cells against oxidative stress-induced cell death. Neurosci Lett. 410(2):146-151. https://doi.org/10.1016/j.neulet.2006.09.027

Frederiksen CM, Clausen J. 1999. The effects of oxidative stress in in vitro cultured astroglial cells. Altern Lab Anim. 27(3):351-357. https://doi.org/10.1177/026119299902700307

Fujimori K, Fukuhara A, Inui T, Allhorn M. 2012. Prevention of paraquat-induced apoptosis in human neuronal SH-SY5Y cells by lipocalin-type prostaglandin D synthase. J Neurochem. 120(2):279-291. https://doi.org/10.1111/j.1471-4159.2011.07570.x

Gabbianelli R, Ferri A, Rotilio G, Carri MT. 1999. Aberrant copper chemistry as a major mediator of oxidative stress in a human cellular model of amyotrophic lateral sclerosis. J Neurochem. 73(3):1175-1180. https://doi.org/10.1046/j.1471-4159.1999.0731175.x

Garcia Garcia A, Anandhan A, Burns M, Chen H, Zhou Y, Franco R. 2013. Impairment of Atg5-dependent autophagic flux promotes paraquat- and MPP(+)-induced apoptosis but not rotenone or 6-hydroxydopamine toxicity. Toxicol Sci. 136(1):166-182. https://doi.org/10.1093/toxsci/kft188

Gegg ME, Cooper JM, Schapira AH, Taanman JW. 2009. Silencing of PINK1 expression affects mitochondrial DNA and oxidative phosphorylation in dopaminergic cells. PLoS One. 4(3):e4756. https://doi.org/10.1371/journal.pone.0004756

Gelinas S, Bureau G, Valastro B, Massicotte G, Cicchetti F, Chiasson K, Gagne B, Blanchet J, Martinoli MG. 2004. Alpha and beta estradiol protect neuronal but not native PC12 cells from paraquat-induced oxidative stress. Neurotox Res. 6(2):141-148.

Geter DR, Kan HL, Lowe ER, Rick DL, Charles GD, Gollapudi BB, Mattsson JL. 2008. Investigations of oxidative stress, antioxidant response, and protein binding in chlorpyrifos exposed rat neuronal PC12 cells. Toxicol Mech Methods. 18(1):17-23. https://doi.org/10.1080/15376510701389530

Ghersi-Egea JF, Livertoux MH, Minn A, Perrin R, Siest G. 1991. Enzyme mediated superoxide radical formation initiated by exogenous molecules in rat brain preparations. Toxicol Appl Pharmacol. 110(1):107-117.

Gomez-Sanchez R, Bravo-San Pedro JM, Niso-Santano M, Soler G, Fuentes JM, Gonzalez-Polo RA. 2010. The neuroprotective effect of talipexole from paraquat-induced cell death in dopaminergic neuronal cells. Neurotoxicology. 31(6):701-708. https://doi.org/10.1016/j.neuro.2010.07.005

Gonzalez-Polo R, Niso-Santano M, Moran JM, Ortiz-Ortiz MA, Bravo-San Pedro JM, Soler G, Fuentes JM. 2009. Silencing DJ-1 reveals its contribution in paraquat-induced autophagy. J Neurochem. 109(3):889-898. https://doi.org/10.1111/j.1471-4159.2009.06020.x

Gonzalez-Polo RA, Niso-Santano M, Ortiz-Ortiz MA, Gomez-Martin A, Moran JM, Garcia-Rubio L, Francisco-Morcillo J, Zaragoza C, Soler G, Fuentes JM. 2007. Inhibition of paraquat-induced autophagy accelerates the apoptotic cell death in neuroblastoma SH-SY5Y cells. Toxicol Sci. 97(2):448-458. https://doi.org/10.1093/toxsci/kfm040

Gonzalez-Polo RA, Rodriguez-Martin A, Moran JM, Niso M, Soler G, Fuentes JM. 2004. Paraquat-induced apoptotic cell death in cerebellar granule cells. Brain Res. 1011(2):170-176. https://doi.org/10.1016/j.brainres.2004.02.078

Gorina R, Sanfeliu C, Galito A, Messeguer A, Planas AM. 2007. Exposure of glia to pro-oxidant agents revealed selective Stat1 activation by H2O2 and Jak2-independent antioxidant features of the Jak2 inhibitor AG490. Glia. 55(13):1313-1324. https://doi.org/10.1002/glia.20542

Grunewald A, Gegg ME, Taanman JW, King RH, Kock N, Klein C, Schapira AH. 2009. Differential effects of PINK1 nonsense and missense mutations on mitochondrial function and morphology. Exp Neurol. 219(1):266-273. https://doi.org/10.1016/j.expneurol.2009.05.027

Grunewald A, Voges L, Rakovic A, Kasten M, Vandebona H, Hemmelmann C, Lohmann K, Orolicki S, Ramirez A, Schapira AH et al. 2010. Mutant Parkin impairs mitochondrial function and morphology in human fibroblasts. PLoS One. 5(9):e12962. https://doi.org/10.1371/journal.pone.0012962

Hara S, Endo T, Kuriiwa F, Kano S. 1991. Different effects of paraquat on microsomal lipid peroxidation in mouse brain, lung and liver. Pharmacol Toxicol. 68(4):260-265.

Hara S, Endo T, Kuriiwa F, Kano S. 1991. Effects of MPTP, MPP+, and paraquat on NADPH-dependent lipid peroxidation in mouse brain and lung microsomes. Biochem Med Metab Biol. 45(3):292-297.

Hara S, Endo T, Kuriiwa F, Kano S. 1991. Interaction between dual NADPH-dependent reactions of paraquat in mouse brain microsomes. Res Commun Chem Pathol Pharmacol. 73(1):119-122.

Hara S, Endo T, Kuriiwa F, Kano S. 1991. Mechanism of paraquat-stimulated lipid peroxidation in mouse brain and pulmonary microsomes. J Pharm Pharmacol. 43(10):731-733. https://doi.org/10.1111/j.2042-7158.1991.tb03468.x

Heinemann SD, Posimo JM, Mason DM, Hutchison DF, Leak RK. 2016. Synergistic stress exacerbation in hippocampal neurons: Evidence favoring the dual-hit hypothesis of neurodegeneration. Hippocampus. 26(8):980-994. https://doi.org/10.1002/hipo.22580

Hirata Y, Sugimura H, Takei H, Nagatsu T. 1986. The effects of pyridinium salts, structurally related compounds of 1-methyl-4-phenylpyridinium ion (MPP+), on tyrosine hydroxylation in rat striatal tissue slices. Brain Res. 397(2):341-344. https://doi.org/10.1016/0006-8993(86)90636-0

Hirayama N, Aki T, Funakoshi T, Noritake K, Unuma K, Uemura K. 2018. Necrosis in human neuronal cells exposed to paraquat. J Toxicol Sci. 43(3):193-202. https://doi.org/10.2131/jts.43.193

Hogberg HT, Kinsner-Ovaskainen A, Hartung T, Coecke S, Bal-Price AK. 2009. Gene expression as a sensitive endpoint to evaluate cell differentiation and maturation of the developing central nervous system in primary cultures of rat cerebellar granule cells (CGCs) exposed to pesticides. Toxicol Appl Pharmacol. 235(3):268-286. https://doi.org/10.1016/j.taap.2008.12.014

Hou RR, Chen JZ, Chen H, Kang XG, Li MG, Wang BR. 2008. Neuroprotective effects of (-)-epigallocatechin-3-gallate (EGCG) on paraquat-induced apoptosis in PC12 cells. Cell Biol Int. 32(1):22-30. https://doi.org/10.1016/j.cellbi.2007.08.007

Huang CL, Chao CC, Lee YC, Lu MK, Cheng JJ, Yang YC, Wang VC, Chang WC, Huang NK. 2016. Paraquat induces cell death through impairing mitochondrial membrane permeability. Mol Neurobiol. 53(4):2169-2188. https://doi.org/10.1007/s12035-015-9198-y

Huang CL, Lee YC, Yang YC, Kuo TY, Huang NK. 2012. Minocycline prevents paraquat-induced cell death through attenuating endoplasmic reticulum stress and mitochondrial dysfunction. Toxicol Lett. 209(3):203-210. https://doi.org/10.1016/j.toxlet.2011.12.021

Huang M, Lou D, Cai Q, Chang X, Wang X, Zhou Z. 2014. Characterization of paraquat-induced miRNA profiling response in hNPCs undergoing proliferation. Int J Mol Sci. 15(10):18422-18436. https://doi.org/10.3390/ijms151018422

Huang M, Lou D, Wang YP, Cai Q, Li HH. 2016. Paraquat inhibited differentiation in human neural progenitor cells (hNPCs) and down regulated miR-200a expression by targeting CTNNB1. Environ Toxicol Pharmacol. 42:205-211. https://doi.org/10.1016/j.etap.2016.01.018

Isaev NK, Stelmashook EV, Ruscher K, Andreeva NA, Zorov DB. 2004. Menadione reduces rotenone-induced cell death in cerebellar granule neurons. Neuroreport. 15(14):2227-2231.

Izumi Y, Ezumi M, Takada-Takatori Y, Akaike A, Kume T. 2014. Endogenous dopamine is involved in the herbicide paraquat-induced dopaminergic cell death. Toxicol Sci. 139(2):466-478. https://doi.org/10.1093/toxsci/kfu054

Izumi Y, Yamamoto N, Matsushima S, Yamamoto T, Takada-Takatori Y, Akaike A, Kume T. 2015. Compensatory role of the Nrf2-ARE pathway against paraquat toxicity: Relevance of 26S proteasome activity. J Pharmacol Sci. 129(3):150-159. https://doi.org/10.1016/j.jphs.2015.09.003

Janda E, Lascala A, Carresi C, Parafati M, Aprigliano S, Russo V, Savoia C, Ziviani E, Musolino V, Morani F et al. 2015. Parkinsonian toxin-induced oxidative stress inhibits basal autophagy in astrocytes via NQO2/quinone oxidoreductase 2: Implications for neuroprotection. Autophagy. 11(7):1063-1080. https://doi.org/10.1080/15548627.2015.1058683

Janda E, Parafati M, Aprigliano S, Carresi C, Visalli V, Sacco I, Ventrice D, Mega T, Vadala N, Rinaldi S et al. 2013. The antidote effect of quinone oxidoreductase 2 inhibitor against paraquat-induced toxicity in vitro and in vivo. Br J Pharmacol. 168(1):46-59. https://doi.org/10.1111/j.1476-5381.2012.01870.x

Jaroonwitchawan T, Chaicharoenaudomrung N, Namkaew J, Noisa P. 2017. Curcumin attenuates paraquat-induced cell death in human neuroblastoma cells through modulating oxidative stress and autophagy. Neurosci Lett. 636:40-47. https://doi.org/10.1016/j.neulet.2016.10.050

Kang D, Miyako K, Kuribayashi F, Hasegawa E, Mitsumoto A, Nagano T, Takeshige K. 1997. Changes of energy metabolism induced by 1-methyl-4-phenylpyridinium (MPP+)-related compounds in rat pheochromocytoma PC12 cells. Arch Biochem Biophys. 337(1):75-80. https://doi.org/10.1006/abbi.1996.9727

Kang X, Chen J, Xu Z, Li H, Wang B. 2007. Protective effects of Ginkgo biloba extract on paraquat-induced apoptosis of PC12 cells. Toxicol In Vitro. 21(6):1003-1009. https://doi.org/10.1016/j.tiv.2007.02.004

Kim DW, Eum WS, Jang SH, Kim SY, Choi HS, Choi SH, An JJ, Lee SH, Lee KS, Han K et al. 2005. Transduced Tat-SOD fusion protein protects against ischemic brain injury. Mol Cells. 19(1):88-96.

Kim S, Hwang J, Lee WH, Hwang DY, Suk K. 2008. Role of protein kinase Cdelta in paraquat-induced glial cell death. J Neurosci Res. 86(9):2062-2070. https://doi.org/10.1002/jnr.21643

Kim SJ, Kim JE, Moon IS. 2004. Paraquat induces apoptosis of cultured rat cortical cells. Mol Cells. 17(1):102-107.

Kim SU, Park YH, Min JS, Sun HN, Han YH, Hua JM, Lee TH, Lee SR, Chang KT, Kang SW et al. 2013. Peroxiredoxin I is a ROS/p38 MAPK-dependent inducible antioxidant that regulates NF-kappaB-mediated iNOS induction and microglial activation. J Neuroimmunol. 259(1-2):26-36. https://doi.org/10.1016/j.jneuroim.2013.03.006

Kind B, Koehler K, Krumbholz M, Landgraf D, Huebner A. 2010. Intracellular ROS level is increased in fibroblasts of triple A syndrome patients. J Mol Med (Berl). 88(12):1233-1242. https://doi.org/10.1007/s00109-010-0661-y

Klintworth H, Garden G, Xia Z. 2009. Rotenone and paraquat do not directly activate microglia or induce inflammatory cytokine release. Neurosci Lett. 462(1):1-5. https://doi.org/10.1016/j.neulet.2009.06.065

Klintworth H, Newhouse K, Li T, Choi WS, Faigle R, Xia Z. 2007. Activation of c-Jun N-terminal protein kinase is a common mechanism underlying paraquat- and rotenone-induced dopaminergic cell apoptosis. Toxicol Sci. 97(1):149-162. https://doi.org/10.1093/toxsci/kfm029

Kong M, Ba M, Liang H, Ma L, Yu Q, Yu T, Wang Y. 2012. 5'-Aza-dC sensitizes paraquat toxic effects on PC12 cell. Neurosci Lett. 524(1):35-39. https://doi.org/10.1016/j.neulet.2012.07.001

Kulkarni A, McNeill D, Gleichmann M, Mattson M, Wilson D, III. 2008. XRCC1 protects against the lethality of induced oxidative DNA damage in nondividing neural cells. Nucleic Acids Res. 36(15):5111-5121. https://doi.org/10.1093/nar/gkn480

Kwon HJ, Heo JY, Shim JH, Park JH, Seo KS, Ryu MJ, Han JS, Shong M, Son JH, Kweon GR. 2011. DJ-1 mediates paraquat-induced dopaminergic neuronal cell death. Toxicol Lett. 202(2):85-92. https://doi.org/10.1016/j.toxlet.2011.01.018

Lam PY, Ko KM. 2011. (-)Schisandrin B ameliorates paraquat-induced oxidative stress by suppressing glutathione depletion and enhancing glutathione recovery in differentiated PC12 cells. BioFactors. 37(1):51-57. https://doi.org/10.1002/biof.136

Lambert CE, Bondy SC. 1989. Effects of MPTP, MPP+ and paraquat on mitochondrial potential and oxidative stress. Life Sci. 44(18):1277-1284. https://doi.org/10.1016/0024-3205(89)90365-2

Lee CY, Lee CH, Shih CC, Liou HH. 2008. Paraquat inhibits postsynaptic AMPA receptors on dopaminergic neurons in the substantia nigra pars compacta. Biochem Pharmacol. 76(9):1155-1164. https://doi.org/10.1016/j.bcp.2008.08.006

Lee HJ, Han J, Jang Y, Kim SJ, Park JH, Seo KS, Jeong S, Shin S, Lim K, Heo JY et al. 2015. Docosahexaenoic acid prevents paraquat-induced reactive oxygen species production in dopaminergic neurons via enhancement of glutathione homeostasis. Biochem Biophys Res Commun. 457(1):95-100. https://doi.org/10.1016/j.bbrc.2014.12.085

Lee J, Kim S, Shin DH, Kim HJ, Lee K. 2011. Neuroprotective effect of Cu,Zn-superoxide dismutase fused to a TCTP-derived protein transduction domain. Eur J Pharmacol. 666(1-3):87-92. https://doi.org/10.1016/j.ejphar.2011.05.040

Lei S, Zavala-Flores L, Garcia Garcia A, Nandakumar R, Huang Y, Madayiputhiya N, Stanton RC, Dodds ED, Powers R, Franco R. 2014. Alterations in energy/redox metabolism induced by mitochondrial and environmental toxins: A specific role for glucose-6-phosphate-dehydrogenase and the pentose phosphate pathway in paraquat toxicity. ACS Chem Biol. 9(9):2032-2048. https://doi.org/10.1021/cb400894a

Lenzken SC, Romeo V, Zolezzi F, Cordero F, Lamorte G, Bonanno D, Biancolini D, Cozzolino M, Pesaresi MG, Maracchioni A et al. 2011. Mutant SOD1 and mitochondrial damage alter expression and splicing of genes controlling neuritogenesis in models of neurodegeneration. Hum Mutat. 32(2):168-182. https://doi.org/10.1002/humu.21394

Lertkaeo P, Limmongkon A, Srikummool M, Boonsong T, Supanpaiboon W, Surangkul D. 2017. Antioxidative and neuroprotective activities of peanut sprout extracts against oxidative stress in SK-N-SH cells. Asian Pac J Trop Biomed. 7(1):64-69.

Li F, Tian X, Zhou Y, Zhu L, Wang B, Ding M, Pang H. 2012. Dysregulated expression of secretogranin III is involved in neurotoxin-induced dopaminergic neuron apoptosis. J Neurosci Res. 90(12):2237-2246. https://doi.org/10.1002/jnr.23121

Li FR, Ge BA, Damirin A. 2017. Overexpression of p58ipk protects neuroblastoma against paraquat-induced toxicity. Int J Clin Exp Pathol. 10(8):8233-8242.

Li H, Wu S, Wang Z, Lin W, Zhang C, Huang B. 2012. Neuroprotective effects of tert-butylhydroquinone on paraquat-induced dopaminergic cell degeneration in C57BL/6 mice and in PC12 cells. Arch Toxicol. 86(11):1729-1740. https://doi.org/10.1007/s00204-012-0935-y

Li K, Cheng X, Jiang J, Wang J, Xie J, Hu X, Huang Y, Song L, Liu M, Cai L et al. 2017. The toxic influence of paraquat on hippocampal neurogenesis in adult mice. Food Chem Toxicol. 106(Pt A):356-366. https://doi.org/10.1016/j.fct.2017.05.067

Li QY, Pedersen C, Day BJ, Patel M. 2001. Dependence of excitotoxic neurodegeneration on mitochondrial aconitase inactivation. J Neurochem. 78(4):746-755. https://doi.org/10.1046/j.1471-4159.2001.00457.x

Li X, Sun AY. 1999. Paraquat induced activation of transcription factor AP-1 and apoptosis in PC12 cells. J Neural Transm (Vienna). 106(1):1-21. https://doi.org/10.1007/s007020050137

Li Z, Dong T, Proschel C, Noble M. 2007. Chemically diverse toxicants converge on Fyn and c-Cbl to disrupt precursor cell function. PLoS Biol. 5(2):e35. https://doi.org/10.1371/journal.pbio.0050035

Li Z, Zheng J, Zhang XF. 2018. Detrimental effects of paraquat on astrocytes-regulating synaptic functions. Dose Response. 16(2):1559325818761681. https://doi.org/10.1177/1559325818761681

Liddell JR, Obando D, Liu J, Ganio G, Volitakis I, Mok SS, Crouch PJ, White AR, Codd R. 2013. Lipophilic adamantyl- or deferasirox-based conjugates of desferrioxamine B have enhanced neuroprotective capacity: Implications for Parkinson disease. Free Radic Biol Med. 60:147-156. https://doi.org/10.1016/j.freeradbiomed.2013.01.027

Liu J, Narasimhan P, Song YS, Nishi T, Yu F, Lee YS, Chan PH. 2006. Epo protects SOD2-deficient mouse astrocytes from damage by oxidative stress. Glia. 53(4):360-365. https://doi.org/10.1002/glia.20289

Loo LS, McNamara JO. 2006. Impaired volume regulation is the mechanism of excitotoxic sensitization to complement. J Neurosci. 26(40):10177-10187. https://doi.org/10.1523/jneurosci.2628-06.2006

Lopert P, Day BJ, Patel M. 2012. Thioredoxin reductase deficiency potentiates oxidative stress, mitochondrial dysfunction and cell death in dopaminergic cells. PLoS One. 7(11):e50683. https://doi.org/10.1371/journal.pone.0050683

Lopert P, Patel M. 2014. Nicotinamide nucleotide transhydrogenase (Nnt) links the substrate requirement in brain mitochondria for hydrogen peroxide removal to the thioredoxin/peroxiredoxin (Trx/Prx) system. J Biol Chem. 289(22):15611-15620. https://doi.org/10.1074/jbc.M113.533653

Luo Y, Henricksen LA, Giuliano RE, Prifti L, Callahan LM, Federoff HJ. 2007. VIP is a transcriptional target of Nurr1 in dopaminergic cells. Exp Neurol. 203(1):221-232. https://doi.org/10.1016/j.expneurol.2006.08.005

Mailloux RJ, Yumvihoze E, Chan HM. 2015. Superoxide produced in the matrix of mitochondria enhances methylmercury toxicity in human neuroblastoma cells. Toxicol Appl Pharmacol. 289(3):371-380. https://doi.org/10.1016/j.taap.2015.11.001

Mak SK, Tewari D, Tetrud JW, Langston JW, Schule B. 2011. Mitochondrial dysfunction in skin fibroblasts from a Parkinson's disease patient with an alpha-synuclein triplication. J Parkinsons Dis. 1(2):175-183. https://doi.org/10.3233/jpd-2011-11025

Mangano EN, Peters S, Litteljohn D, So R, Bethune C, Bobyn J, Clarke M, Hayley S. 2011. Granulocyte macrophage-colony stimulating factor protects against substantia nigra dopaminergic cell loss in an environmental toxin model of Parkinson's disease. Neurobiol Dis. 43(1):99-112. https://doi.org/10.1016/j.nbd.2011.02.011

Manning-Bog AB, McCormack AL, Li J, Uversky VN, Fink AL, Di Monte DA. 2002. The herbicide paraquat causes up-regulation and aggregation of alpha-synuclein in mice: Paraquat and alpha-synuclein. J Biol Chem. 277(3):1641-1644. https://doi.org/10.1074/jbc.C100560200

Manthey D, Gamerdinger M, Behl C. 2010. The selective beta1-adrenoceptor antagonist nebivolol is a potential oestrogen receptor agonist with neuroprotective abilities. Br J Pharmacol. 159(6):1264-1273. https://doi.org/10.1111/j.1476-5381.2009.00610.x

Maracchioni A, Totaro A, Angelini DF, Di Penta A, Bernardi G, Carri MT, Achsel T. 2007. Mitochondrial damage modulates alternative splicing in neuronal cells: Implications for neurodegeneration. J Neurochem. 100(1):142-153. https://doi.org/10.1111/j.1471-4159.2006.04204.x

Margolis AS, Porasuphatana S, Rosen GM. 2000. Role of paraquat in the uncoupling of nitric oxide synthase. Biochim Biophys Acta. 1524(2-3):253-257. https://doi.org/10.1016/s0304-4165(00)00167-7

Martins JB, Bastos Mde L, Carvalho F, Capela JP. 2013. Differential effects of methyl-4-phenylpyridinium ion, rotenone, and paraquat on differentiated SH-SY5Y cells. J Toxicol. 2013:347312. https://doi.org/10.1155/2013/347312

McCarthy S, Somayajulu M, Sikorska M, Borowy-Borowski H, Pandey S. 2004. Paraquat induces oxidative stress and neuronal cell death; neuroprotection by water-soluble Coenzyme Q10. Toxicol Appl Pharmacol. 201(1):21-31. https://doi.org/10.1016/j.taap.2004.04.019

Meyerowitz J, Parker SJ, Vella LJ, Ng D, Price KA, Liddell JR, Caragounis A, Li QX, Masters CL, Nonaka T et al. 2011. C-Jun N-terminal kinase controls TDP-43 accumulation in stress granules induced by oxidative stress. Mol Neurodegener. 6:57. https://doi.org/10.1186/1750-1326-6-57

Miller RL, Sun GY, Sun AY. 2007. Cytotoxicity of paraquat in microglial cells: Involvement of PKCdelta- and ERK1/2-dependent NADPH oxidase. Brain Res. 1167:129-139. https://doi.org/10.1016/j.brainres.2007.06.046

Minelli A, Conte C, Grottelli S, Bellezza I, Cacciatore I, Bolanos JP. 2009. Cyclo(His-Pro) promotes cytoprotection by activating Nrf2-mediated up-regulation of antioxidant defence. J Cell Mol Med. 13(6):1149-1161. https://doi.org/10.1111/j.1582-4934.2008.00326.x

Minelli A, Conte C, Grottelli S, Bellezza I, Emiliani C, Bolanos JP. 2009. Cyclo(His-Pro) up-regulates heme oxygenase 1 via activation of Nrf2-ARE signalling. J Neurochem. 111(4):956-966. https://doi.org/10.1111/j.1471-4159.2009.06376.x

Mizuno K, Kume T, Muto C, Takada-Takatori Y, Izumi Y, Sugimoto H, Akaike A. 2011. Glutathione biosynthesis via activation of the nuclear factor E2-related factor 2 (Nrf2)--antioxidant-response element (ARE) pathway is essential for neuroprotective effects of sulforaphane and 6-(methylsulfinyl) hexyl isothiocyanate. J Pharmacol Sci. 115(3):320-328.

Moran JM, Gonzalez-Polo RA, Ortiz-Ortiz MA, Niso-Santano M, Soler G, Fuentes JM. 2008. Identification of genes associated with paraquat-induced toxicity in SH-SY5Y cells by PCR array focused on apoptotic pathways. J Toxicol Environ Health A. 71(22):1457-1467. https://doi.org/10.1080/15287390802329364

Moran JM, Ortiz-Ortiz MA, Ruiz-Mesa LM, Niso-Santano M, Bravosanpedro JM, Sanchez RG, Gonzalez-Polo RA, Fuentes JM. 2010. Effect of paraquat exposure on nitric oxide-responsive genes in rat mesencephalic cells. Nitric Oxide. 23(1):51-59. https://doi.org/10.1016/j.niox.2010.04.002

Morita K, Tokunaga I, Kubo S. 1999. Cytotoxic effect of paraquat on rat C6 glioma cells: Evidence for the possibility of non-oxidative damage to the cells. Jap J Pharmacol. 79(1):121-124.

Narasimhan M, Riar AK, Rathinam ML, Vedpathak D, Henderson G, Mahimainathan L. 2014. Hydrogen peroxide responsive miR153 targets Nrf2/ARE cytoprotection in paraquat induced dopaminergic neurotoxicity. Toxicol Lett. 228(3):179-191. https://doi.org/10.1016/j.toxlet.2014.05.020

Navarro-Yepes J, Anandhan A, Bradley E, Bohovych I, Yarabe B, de Jong A, Ovaa H, Zhou Y, Khalimonchuk O, Quintanilla-Vega B et al. 2016. Inhibition of protein ubiquitination by paraquat and 1-methyl-4-phenylpyridinium impairs ubiquitin-dependent protein degradation pathways. Mol Neurobiol. 53(8):5229-5251. https://doi.org/10.1007/s12035-015-9414-9

Nga AK-S, Tho L-Y, Lim C-H, Lim C-K, Say Y-H. 2016. Evaluation of neuroprotective properties of two synthetic prenylated xanthone analogues against paraquat and 6-hydroxydopamine toxicity in human neuroblastoma SHSY5Y cells. Trop J Pharm Res. 15(12):2611-2618.

Niso-Santano M, Bravo-San Pedro JM, Gomez-Sanchez R, Climent V, Soler G, Fuentes JM, Gonzalez-Polo RA. 2011. ASK1 overexpression accelerates paraquat-induced autophagy via endoplasmic reticulum stress. Toxicol Sci. 119(1):156-168. https://doi.org/10.1093/toxsci/kfq313

Niso-Santano M, Gonzalez-Polo RA, Bravo-San Pedro JM, Gomez-Sanchez R, Lastres-Becker I, Ortiz-Ortiz MA, Soler G, Moran JM, Cuadrado A, Fuentes JM. 2010. Activation of apoptosis signal-regulating kinase 1 is a key factor in paraquat-induced cell death: Modulation by the Nrf2/Trx axis. Free Radic Biol Med. 48(10):1370-1381. https://doi.org/10.1016/j.freeradbiomed.2010.02.024

Niso-Santano M, Moran JM, Garcia-Rubio L, Gomez-Martin A, Gonzalez-Polo RA, Soler G, Fuentes JM. 2006. Low concentrations of paraquat induces early activation of extracellular signal-regulated kinase 1/2, protein kinase B, and c-Jun N-terminal kinase 1/2 pathways: Role of c-Jun N-terminal kinase in paraquat-induced cell death. Toxicol Sci. 92(2):507-515. https://doi.org/10.1093/toxsci/kfl013

Noack H, Possel H, Rethfeldt C, Keilhoff G, Wolf G. 1999. Peroxynitrite mediated damage and lowered superoxide tolerance in primary cortical glial cultures after induction of the inducible isoform of NOS. Glia. 28(1):13-24.

Olesen BST, Zhang W, Clausen J, Vang O, Hansen PE. 2010. Effect of paraquat and amyloid-beta-peptide on the metabolism in primary astrocytes studied by 1H NMR. Open Mag Res J. 3:1-13.

Olesen BT, Clausen J, Vang O. 2008. Characterization of the transcriptional profile in primary astrocytes after oxidative stress induced by paraquat. Neurotoxicology. 29(1):13-21. https://doi.org/10.1016/j.neuro.2007.08.010

Ortiz-Ortiz MA, Moran JM, Bravosanpedro JM, Gonzalez-Polo RA, Niso-Santano M, Anantharam V, Kanthasamy AG, Soler G, Fuentes JM. 2009. Curcumin enhances paraquat-induced apoptosis of N27 mesencephalic cells via the generation of reactive oxygen species. Neurotoxicology. 30(6):1008-1018. https://doi.org/10.1016/j.neuro.2009.07.016

Ortiz-Ortiz MA, Moran JM, Gonzalez-Polo RA, Niso-Santano M, Soler G, Bravo-San Pedro JM, Fuentes JM. 2009. Nitric oxide-mediated toxicity in paraquat-exposed SH-SY5Y cells: A protective role of 7-nitroindazole. Neurotox Res. 16(2):160-173. https://doi.org/10.1007/s12640-009-9065-6

Ortiz-Ortiz MA, Moran JM, Ruiz-Mesa LM, Bonmatty RG, Fuentes JM. 2011. Protective effect of the glial cell line-derived neurotrophic factor (GDNF) on human mesencephalic neuron-derived cells against neurotoxicity induced by paraquat. Environ Toxicol Pharmacol. 31(1):129-136. https://doi.org/10.1016/j.etap.2010.09.013

Ortiz-Ortiz MA, Moran JM, Ruiz-Mesa LM, Bravo-San Pedro JM, Fuentes JM. 2010. Paraquat exposure induces nuclear translocation of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and the activation of the nitric oxide-GAPDH-Siah cell death cascade. Toxicol Sci. 116(2):614-622. https://doi.org/10.1093/toxsci/kfq146

Osakada F, Hashino A, Kume T, Katsuki H, Kaneko S, Akaike A. 2003. Neuroprotective effects of alpha-tocopherol on oxidative stress in rat striatal cultures. Eur J Pharmacol. 465(1-2):15-22. https://doi.org/10.1016/s0014-2999(03)01495-x

Osakada F, Hashino A, Kume T, Katsuki H, Kaneko S, Akaike A. 2004. Alpha-tocotrienol provides the most potent neuroprotection among vitamin E analogs on cultured striatal neurons. Neuropharmacology. 47(6):904-915. https://doi.org/10.1016/j.neuropharm.2004.06.029

Osakada F, Kawato Y, Kume T, Katsuki H, Sugimoto H, Akaike A. 2004. Serofendic acid, a sulfur-containing diterpenoid derived from fetal calf serum, attenuates reactive oxygen species-induced oxidative stress in cultured striatal neurons. J Pharmacol Exp Ther. 311(1):51-59. https://doi.org/10.1124/jpet.104.070334

Parker SJ, Meyerowitz J, James JL, Liddell JR, Crouch PJ, Kanninen KM, White AR. 2012. Endogenous TDP-43 localized to stress granules can subsequently form protein aggregates. Neurochem Int. 60(4):415-424. https://doi.org/10.1016/j.neuint.2012.01.019

Parker SJ, Meyerowitz J, James JL, Liddell JR, Nonaka T, Hasegawa M, Kanninen KM, Lim S, Paterson BM, Donnelly PS et al. 2012. Inhibition of TDP-43 accumulation by bis(thiosemicarbazonato)-copper complexes. PLoS One. 7(8):e42277. https://doi.org/10.1371/journal.pone.0042277

Peng J, Mao XO, Stevenson FF, Hsu M, Andersen JK. 2004. The herbicide paraquat induces dopaminergic nigral apoptosis through sustained activation of the JNK pathway. J Biol Chem. 279(31):32626-32632. https://doi.org/10.1074/jbc.M404596200

Peng J, Oo ML, Andersen JK. 2010. Synergistic effects of environmental risk factors and gene mutations in Parkinson's disease accelerate age-related neurodegeneration. J Neurochem. 115(6):1363-1373. https://doi.org/10.1111/j.1471-4159.2010.07036.x

Peng J, Peng L, Stevenson FF, Doctrow SR, Andersen JK. 2007. Iron and paraquat as synergistic environmental risk factors in sporadic Parkinson's disease accelerate age-related neurodegeneration. J Neurosci. 27(26):6914-6922. https://doi.org/10.1523/jneurosci.1569-07.2007

Peng J, Stevenson FF, Doctrow SR, Andersen JK. 2005. Superoxide dismutase/catalase mimetics are neuroprotective against selective paraquat-mediated dopaminergic neuron death in the substantial nigra: Implications for Parkinson disease. J Biol Chem. 280(32):29194-29198. https://doi.org/10.1074/jbc.M500984200

Peng J, Stevenson FF, Oo ML, Andersen JK. 2009. Iron-enhanced paraquat-mediated dopaminergic cell death due to increased oxidative stress as a consequence of microglial activation. Free Radic Biol Med. 46(2):312-320. https://doi.org/10.1016/j.freeradbiomed.2008.10.045

Ramachandiran S, Hansen JM, Jones DP, Richardson JR, Miller GW. 2007. Divergent mechanisms of paraquat, MPP+, and rotenone toxicity: Oxidation of thioredoxin and caspase-3 activation. Toxicol Sci. 95(1):163-171. https://doi.org/10.1093/toxsci/kfl125

Rathinam ML, Watts LT, Narasimhan M, Riar AK, Mahimainathan L, Henderson GI. 2012. Astrocyte mediated protection of fetal cerebral cortical neurons from rotenone and paraquat. Environ Toxicol Pharmacol. 33(2):353-360. https://doi.org/10.1016/j.etap.2011.12.027

Ravi SK, Narasingappa RB, Joshi CG, Girish TK, Vincent B. 2018. Neuroprotective effects of Cassia tora against paraquat-induced neurodegeneration: Relevance for Parkinson's disease. Nat Prod Res. 32(12):1476-1480. https://doi.org/10.1080/14786419.2017.1353504

Rhodes SL, Fitzmaurice AG, Cockburn M, Bronstein JM, Sinsheimer JS, Ritz B. 2013. Pesticides that inhibit the ubiquitin-proteasome system: Effect measure modification by genetic variation in SKP1 in Parkinson's disease. Environ Res. 126:1-8. https://doi.org/10.1016/j.envres.2013.08.001

Richardson JR, Quan Y, Sherer TB, Greenamyre JT, Miller GW. 2005. Paraquat neurotoxicity is distinct from that of MPTP and rotenone. Toxicol Sci. 88(1):193-201. https://doi.org/10.1093/toxsci/kfi304

Robb EL, Stuart JA. 2011. Resveratrol interacts with estrogen receptor-beta to inhibit cell replicative growth and enhance stress resistance by upregulating mitochondrial superoxide dismutase. Free Radic Biol Med. 50(7):821-831. https://doi.org/10.1016/j.freeradbiomed.2010.12.038

Rodriguez-Rocha H, Garcia Garcia A, Zavala-Flores L, Li S, Madayiputhiya N, Franco R. 2012. Glutaredoxin 1 protects dopaminergic cells by increased protein glutathionylation in experimental Parkinson's disease. Antioxid Redox Signal. 17(12):1676-1693. https://doi.org/10.1089/ars.2011.4474

Rodriguez-Rocha H, Garcia Garcia A, Pickett C, Li S, Jones J, Chen H, Webb B, Choi J, Zhou Y, Zimmerman MC et al. 2013. Compartmentalized oxidative stress in dopaminergic cell death induced by pesticides and complex I inhibitors: Distinct roles of superoxide anion and superoxide dismutases. Free Radic Biol Med. 61:370-383. https://doi.org/10.1016/j.freeradbiomed.2013.04.021

Roedding AS, Tong SY, Au-Yeung W, Li PP, Warsh JJ. 2013. Chronic oxidative stress modulates TRPC3 and TRPM2 channel expression and function in rat primary cortical neurons: Relevance to the pathophysiology of bipolar disorder. Brain Res. 1517:16-27. https://doi.org/10.1016/j.brainres.2013.04.025

Roede JR, Hansen JM, Go YM, Jones DP. 2011. Maneb and paraquat-mediated neurotoxicity: Involvement of peroxiredoxin/thioredoxin system. Toxicol Sci. 121(2):368-375. https://doi.org/10.1093/toxsci/kfr058

Roede JR, Uppal K, Park Y, Tran V, Jones DP. 2014. Transcriptome–metabolome wide association study (TMWAS) of maneb and paraquat neurotoxicity reveals network level interactions in toxicologic mechanism. Toxicol Rep. 1:435-444.

Rohrdanz E, Schmuck G, Ohler S, Kahl R. 2001. The influence of oxidative stress on catalase and MnSOD gene transcription in astrocytes. Brain Res. 900(1):128-136. https://doi.org/10.1016/s0006-8993(01)02277-6

Rossi L, Marchese E, Lombardo MF, Rotilio G, Ciriolo MR. 2001. Increased susceptibility of copper-deficient neuroblastoma cells to oxidative stress-mediated apoptosis. Free Radic Biol Med. 30(10):1177-1187.

Ruggeri P, Farina AR, Di Ianni N, Cappabianca L, Ragone M, Ianni G, Gulino A, Mackay AR. 2014. The TrkAIII oncoprotein inhibits mitochondrial free radical ROS-induced death of SH-SY5Y neuroblastoma cells by augmenting SOD2 expression and activity at the mitochondria, within the context of a tumour stem cell-like phenotype. PLoS One. 9(4):e94568. https://doi.org/10.1371/journal.pone.0094568

Said SI, Pakbaz H, Berisha HI, Raza S. 2000. NMDA receptor activation: Critical role in oxidant tissue injury. Free Radic Biol Med. 28(8):1300-1302.

Sanders LH, Paul KC, Howlett EH, Lawal H, Boppana S, Bronstein JM, Ritz B, Greenamyre JT. 2017. Editor's highlight: Base excision repair variants and pesticide exposure increase Parkinson's disease risk. Toxicol Sci. 158(1):188-198. https://doi.org/10.1093/toxsci/kfx086

Sandstrom J, Broyer A, Zoia D, Schilt C, Greggio C, Fournier M, Do KQ, Monnet-Tschudi F. 2017. Potential mechanisms of development-dependent adverse effects of the herbicide paraquat in 3D rat brain cell cultures. Neurotoxicology. 60:116-124. https://doi.org/10.1016/j.neuro.2017.04.010

Sandstrom von Tobel J, Zoia D, Althaus J, Antinori P, Mermoud J, Pak HS, Scherl A, Monnet-Tschudi F. 2014. Immediate and delayed effects of subchronic paraquat exposure during an early differentiation stage in 3D-rat brain cell cultures. Toxicol Lett. 230(2):188-197. https://doi.org/10.1016/j.toxlet.2014.02.001

Sapolsky RM, Packan DR, Vale WW. 1988. Glucocorticoid toxicity in the hippocampus: In vitro demonstration. Brain Res. 453(1-2):367-371. https://doi.org/10.1016/0006-8993(88)90180-1

Sasaki N, Baba N, Matsuo M. 2001. Cytotoxicity of reactive oxygen species and related agents toward undifferentiated and differentiated rat phenochromocytoma PC12 cells. Biol Pharm Bull. 24(5):515-519.

Sashourpour M, Zahri S, Radjabian T, Ruf V, Pan-Montojo F, Morshedi D. 2017. A study on the modulation of alpha-synuclein fibrillation by Scutellaria pinnatifida extracts and its neuroprotective properties. PLoS One. 12(9):e0184483. https://doi.org/10.1371/journal.pone.0184483

Schmuck G, Ahr HJ, Schluter G. 2000. Rat cortical neuron cultures: An in vitro model for differentiating mechanisms of chemically induced neurotoxicity. In Vitro Mol Toxicol. 13(1):37-50.

Schmuck G, Rohrdanz E, Tran-Thi QH, Kahl R, Schluter G. 2002. Oxidative stress in rat cortical neurons and astrocytes induced by paraquat in vitro. Neurotox Res. 4(1):1-13. https://doi.org/10.1080/10298420290007574

Schmuck G, Schluter G. 1996. An in vitro model for toxicological investigations of environmental neurotoxins in primary neuronal cell cultures. Toxicol Ind Health. 12(5):683-696. https://doi.org/10.1177/074823379601200507

Shen W, Wang L, Pi R, Li Z, Rikang W. 2015. L-F001, a multifunctional ROCK inhibitor prevents paraquat-induced cell death through attenuating ER stress and mitochondrial dysfunction in PC12 cells. Biochem Biophys Res Commun. 464(3):794-799. https://doi.org/10.1016/j.bbrc.2015.07.035

Shimizu K, Matsubara K, Ohtaki K, Shiono H. 2003. Paraquat leads to dopaminergic neural vulnerability in organotypic midbrain culture. Neurosci Res. 46(4):523-532.

Singh M, Murthy V, Ramassamy C. 2012. Standardized extracts of Bacopa monniera protect against MPP+- and paraquat-induced toxicity by modulating mitochondrial activities, proteasomal functions, and redox pathways. Toxicol Sci. 125(1):219-232. https://doi.org/10.1093/toxsci/kfr255

Singh SP, Chhunchha B, Fatma N, Kubo E, Singh SP, Singh DP. 2016. Delivery of a protein transduction domain-mediated Prdx6 protein ameliorates oxidative stress-induced injury in human and mouse neuronal cells. Am J Physiol Cell Physiol. 310(1):C1-16. https://doi.org/10.1152/ajpcell.00229.2015

Snider BJ, Moss JL, Revilla FJ, Lee CS, Wheeler VC, Macdonald ME, Choi DW. 2003. Neocortical neurons cultured from mice with expanded CAG repeats in the huntingtin gene: Unaltered vulnerability to excitotoxins and other insults. Neuroscience. 120(3):617-625. https://doi.org/10.1016/s0306-4522(03)00382-8

Song C, Kanthasamy A, Jin H, Anantharam V, Kanthasamy AG. 2011. Paraquat induces epigenetic changes by promoting histone acetylation in cell culture models of dopaminergic degeneration. Neurotoxicology. 32(5):586-595. https://doi.org/10.1016/j.neuro.2011.05.018

Stelmashook EV, Genrikhs EE, Aleksandrova OP, Amelkina GA, Zelenova EA, Isaev NK. 2016. NMDA-receptors are involved in Cu2+/paraquat-induced death of cultured cerebellar granule neurons. Biochemistry (Mosc). 81(8):899-905. https://doi.org/10.1134/s0006297916080113

Stelmashook EV, Isaev NK, Zorov DB. 2007. Paraquat potentiates glutamate toxicity in immature cultures of cerebellar granule neurons. Toxicol Lett. 174(1-3):82-88. https://doi.org/10.1016/j.toxlet.2007.08.012

Sun AY, Li X. 2000. Paraquat is a model environmental neurotoxin for studying Parkinson's disease. In: Neurotoxic Factors in Parkinson's Disease and Related Disorders. Springer. p. 247-257.

Sun HN, Kim SU, Huang SM, Kim JM, Park YH, Kim SH, Yang HY, Chung KJ, Lee TH, Choi HS et al. 2010. Microglial peroxiredoxin V acts as an inducible anti-inflammatory antioxidant through cooperation with redox signaling cascades. J Neurochem. 114(1):39-50. https://doi.org/10.1111/j.1471-4159.2010.06691.x

Sun Y, Zheng J, Xu Y, Zhang X. 2018. Paraquat-induced inflammatory response of microglia through HSP60/TLR4 signaling. Hum Exp Toxicol. 37(11):1161-1168. https://doi.org/10.1177/0960327118758152

Tauskela JS, Aylsworth A, Hewitt M, Brunette E, Mealing GA. 2012. Preconditioning induces tolerance by suppressing glutamate release in neuron culture ischemia models. J Neurochem. 122(2):470-481. https://doi.org/10.1111/j.1471-4159.2012.07791.x

Thakar JH, Hassan MN. 1988. Effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), cyperquat (MPP+) and paraquat on isolated mitochondria from rat striatum, cortex and liver. Life Sci. 43(2):143-149. https://doi.org/10.1016/0024-3205(88)90291-3

Toyoda Y, Erkut C, Pan-Montojo F, Boland S, Stewart MP, Müller DJ, Wurst W, Hyman AA, Kurzchalia TV. 2014. Products of the Parkinson's disease-related glyoxalase DJ-1, D-lactate and glycolate, support mitochondrial membrane potential and neuronal survival. Biol Open. 3(8):777-784. https://doi.org/10.1242/bio.20149399

Unnithan AS, Jiang Y, Rumble JL, Pulugulla SH, Posimo JM, Gleixner AM, Leak RK. 2014. N-acetyl cysteine prevents synergistic, severe toxicity from two hits of oxidative stress. Neurosci Lett. 560:71-76. https://doi.org/10.1016/j.neulet.2013.12.023

Uversky VN, Li J, Bower K, Fink AL. 2002. Synergistic effects of pesticides and metals on the fibrillation of α-synuclein: Implications for Parkinson's disease. Neurotoxicology. 23(4-5):527-536.

Uversky VN, Li J, Fink AL. 2001. Pesticides directly accelerate the rate of alpha-synuclein fibril formation: A possible factor in Parkinson's disease. FEBS Lett. 500(3):105-108. https://doi.org/10.1016/s0014-5793(01)02597-2

Vaccari A, Saba P. 1995. The tyramine-labelled vesicular transporter for dopamine: A putative target of pesticides and neurotoxins. Eur J Pharmacol. 292(3-4):309-314.

van der Merwe C, van Dyk HC, Engelbrecht L, van der Westhuizen FH, Kinnear C, Loos B, Bardien S. 2017. Curcumin rescues a PINK1 knock down SH-SY5Y cellular model of Parkinson's disease from mitochondrial dysfunction and cell death. Mol Neurobiol. 54(4):2752-2762. https://doi.org/10.1007/s12035-016-9843-0

Velez-Pardo C, Jimenez-Del-Rio M, Lores-Arnaiz S, Bustamante J. 2010. Protective effects of the synthetic cannabinoids CP55,940 and JWH-015 on rat brain mitochondria upon paraquat exposure. Neurochem Res. 35(9):1323-1332. https://doi.org/10.1007/s11064-010-0188-1

Vilas-Boas V, Silva R, Guedes-de-Pinho P, Carvalho F, Bastos ML, Remiao F. 2014. RBE4 cells are highly resistant to paraquat-induced cytotoxicity: Studies on uptake and efflux mechanisms. J Appl Toxicol. 34(9):1023-1030. https://doi.org/10.1002/jat.2926

Vivarelli S, Lenzken SC, Ruepp MD, Ranzini F, Maffioletti A, Alvarez R, Muhlemann O, Barabino SM. 2013. Paraquat modulates alternative pre-mRNA splicing by modifying the intracellular distribution of SRPK2. PLoS One. 8(4):e61980. https://doi.org/10.1371/journal.pone.0061980

Vogt M, Bauer MK, Ferrari D, Schulze-Osthoff K. 1998. Oxidative stress and hypoxia/reoxygenation trigger CD95 (APO-1/Fas) ligand expression in microglial cells. FEBS Lett. 429(1):67-72. https://doi.org/10.1016/s0014-5793(98)00562-6

Vornov JJ, Park J, Thomas AG. 1998. Regional vulnerability to endogenous and exogenous oxidative stress in organotypic hippocampal culture. Exp Neurol. 149(1):109-122. https://doi.org/10.1006/exnr.1997.6673

Wang C, Ko HS, Thomas B, Tsang F, Chew KC, Tay SP, Ho MW, Lim TM, Soong TW, Pletnikova O et al. 2005. Stress-induced alterations in parkin solubility promote parkin aggregation and compromise parkin's protective function. Hum Mol Genet. 14(24):3885-3897. https://doi.org/10.1093/hmg/ddi413

Wang F, Franco R, Skotak M, Hu G, Chandra N. 2014. Mechanical stretch exacerbates the cell death in SH-SY5Y cells exposed to paraquat: Mitochondrial dysfunction and oxidative stress. Neurotoxicology. 41:54-63. https://doi.org/10.1016/j.neuro.2014.01.002

Wang Q, Zhan Y, Ren N, Wang Z, Zhang Q, Wu S, Li H. 2018. Paraquat and MPTP alter microRNA expression profiles, and downregulated expression of miR-17-5p contributes to PQ-induced dopaminergic neurodegeneration. J Appl Toxicol. 38(5):665-677. https://doi.org/10.1002/jat.3571

Wang QL, Guo C, Qi J, Ma JH, Liu FY, Lin SQ, Zhang CY, Xie WD, Zhuang JJ, Li X. 2019. Protective effects of 3beta-angeloyloxy-8beta, 10beta-dihydroxyeremophila-7(11)-en-12, 8alpha-lactone on paraquat-induced oxidative injury in SH-SY5Y cells. J Asian Nat Prod Res. 21(4):364-376. https://doi.org/10.1080/10286020.2017.1423057

Wang X, Zaidi A, Pal R, Garrett AS, Braceras R, Chen XW, Michaelis ML, Michaelis EK. 2009. Genomic and biochemical approaches in the discovery of mechanisms for selective neuronal vulnerability to oxidative stress. BMC Neurosci. 10:12. https://doi.org/10.1186/1471-2202-10-12

Wang XF, Li S, Chou AP, Bronstein JM. 2006. Inhibitory effects of pesticides on proteasome activity: Implication in Parkinson's disease. Neurobiol Dis. 23(1):198-205. https://doi.org/10.1016/j.nbd.2006.02.012

Wu XF, Block ML, Zhang W, Qin L, Wilson B, Zhang WQ, Veronesi B, Hong JS. 2005. The role of microglia in paraquat-induced dopaminergic neurotoxicity. Antioxid Redox Signal. 7(5-6):654-661. https://doi.org/10.1089/ars.2005.7.654

Yan M, Dou T, Lv W, Wang X, Zhao L, Chang X, Zhou Z. 2017. Integrated analysis of paraquat-induced microRNAs-mRNAs changes in human neural progenitor cells. Toxicol In Vitro. 44:196-205. https://doi.org/10.1016/j.tiv.2017.06.010

Yang W, Sun AY. 1998. Paraquat-induced free radical reaction in mouse brain microsomes. Neurochem Res. 23(1):47-53.

Yang W, Tiffany-Castiglioni E. 2005. The bipyridyl herbicide paraquat produces oxidative stress-mediated toxicity in human neuroblastoma SH-SY5Y cells: Relevance to the dopaminergic pathogenesis. J Toxicol Environ Health A. 68(22):1939-1961. https://doi.org/10.1080/15287390500226987

Yang W, Tiffany-Castiglioni E. 2007. The bipyridyl herbicide paraquat induces proteasome dysfunction in human neuroblastoma SH-SY5Y cells. J Toxicol Environ Health A. 70(21):1849-1857. https://doi.org/10.1080/15287390701459262

Yang W, Tiffany-Castiglioni E. 2008. Paraquat-induced apoptosis in human neuroblastoma SH-SY5Y cells: Involvement of p53 and mitochondria. J Toxicol Environ Health A. 71(4):289-299. https://doi.org/10.1080/15287390701738467

Yang W, Tiffany-Castiglioni E, Koh HC, Son IH. 2009. Paraquat activates the IRE1/ASK1/JNK cascade associated with apoptosis in human neuroblastoma SH-SY5Y cells. Toxicol Lett. 191(2-3):203-210. https://doi.org/10.1016/j.toxlet.2009.08.024

Yang W, Tiffany-Castiglioni E, Lee MY, Son IH. 2010. Paraquat induces cyclooxygenase-2 (COX-2) implicated toxicity in human neuroblastoma SH-SY5Y cells. Toxicol Lett. 199(3):239-246. https://doi.org/10.1016/j.toxlet.2010.09.005

Yang WL, Sun AY. 1998. Paraquat-induced cell death in PC12 cells. Neurochem Res. 23(11):1387-1394.

Yoshimura Y, Watanabe Y, Shibuya T. 1993. Inhibitory effects of calcium channel antagonists on motor dysfunction induced by intracerebroventricular administration of paraquat. Pharmacol Toxicol. 72(4-5):229-235.

Zaidi A, Fernandes D, Bean JL, Michaelis ML. 2009. Effects of paraquat-induced oxidative stress on the neuronal plasma membrane Ca(2+)-ATPase. Free Radic Biol Med. 47(10):1507-1514. https://doi.org/10.1016/j.freeradbiomed.2009.08.018

Zhan X, Li F, Chu Q, Pang H. 2018. Effects of PQ's cytotoxicity on secretory vesicles in astroglia: Expression alternation of secretogranin II and its potential interaction with intracellular factors. Biochem Biophys Res Commun. 497(2):675-682. https://doi.org/10.1016/j.bbrc.2018.02.130

Zhang ZX, Song XF, Du XY, Cui Y, Dai JS. 2012. Protective effect of tyrosol on apoptosis in PC12 cell induced by paraquat. Afr J Pharm Pharmacol. 6(29):2224-2228. https://doi.org/10.5897/ajpp12.396

Zhao F, Wang W, Wang C, Siedlak SL, Fujioka H, Tang B, Zhu X. 2017. Mfn2 protects dopaminergic neurons exposed to paraquat both in vitro and in vivo: Implications for idiopathic Parkinson's disease. Biochim Biophys Acta Mol Basis Dis. 1863(6):1359-1370. https://doi.org/10.1016/j.bbadis.2017.02.016

Zhao X, Wang R, Xiong J, Yan D, Li A, Wang S, Xu J, Zhou J. 2017. JWA antagonizes paraquat-induced neurotoxicity via activation of Nrf2. Toxicol Lett. 277:32-40. https://doi.org/10.1016/j.toxlet.2017.04.011

Zhong C, Liu XH, Hao XD, Chang J, Sun X. 2013. Synthesis and biological evaluation of novel neuroprotective agents for paraquat-induced apoptosis in human neuronal SH-SY5Y cells. Eur J Med Chem. 62:187-198. https://doi.org/10.1016/j.ejmech.2012.12.037

Zhou Q, Zhang H, Wu Q, Shi J, Zhou S. 2017. Pharmacological manipulations of autophagy modulate paraquat-induced cytotoxicity in PC12 cells. Int J Biochem Mol Biol. 8(2):13-22.

Zhou Y, Jiang H, Gu J, Tang Y, Shen N, Jin Y. 2013. MicroRNA-195 targets ADP-ribosylation factor-like protein 2 to induce apoptosis in human embryonic stem cell-derived neural progenitor cells. Cell Death Dis. 4:e695. https://doi.org/10.1038/cddis.2013.195

Zhou Y, Li F, Tian X, Wang B, Ding M, Pang H. 2014. Changes in phosphatidylinositol 3-kinase 55 kDa gamma expression and subcellular localization may be caspase 6 dependent in paraquat-induced SH-SY5Y apoptosis. Hum Exp Toxicol. 33(7):761-771. https://doi.org/10.1177/0960327113499044

Appendix F. Supplemental Figures

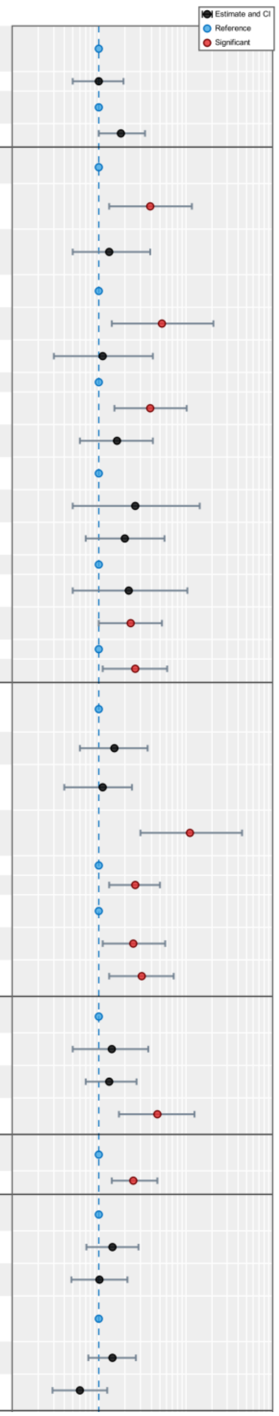
Figures

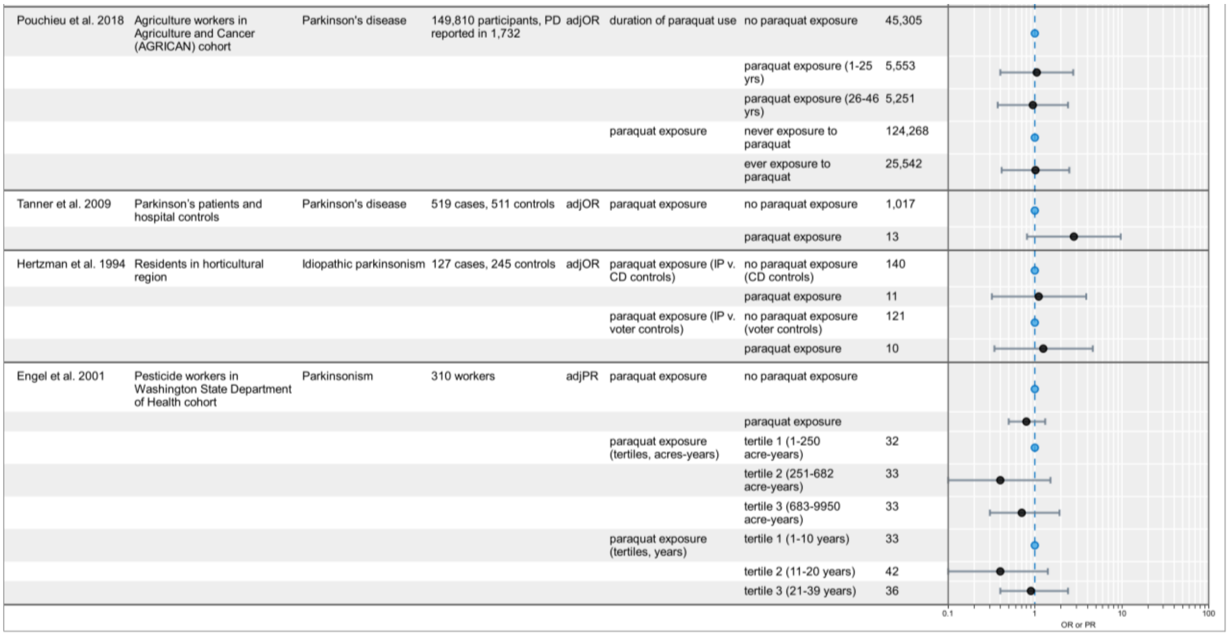
			Study Design					
Country	**State/Region**	**Study Population**	**Case-control**	**Cohort (Prospective)**	**Cohort (Retrospective)**	**Cross-sectional**	**Ecological**	**Grand Total**
United States	8 movement disorder research centers**	Parkinson's patients and hospital controls	1					1
	California	Central Valley, CA residents	2					2
		Parkinson's Environment and Genes Study (PEG) participants	4					4
	Iowa and North Carolina	Farming and Movement Evaluation (FAME) participants*	4					4
		Pesticide workers and spouses in Agricultural Health Study (AHS) coho..		1		1		1
	Nebraska	Residents of rural Nebraska					1	1
	Texas	Parkinson's patients and controls from East Texas neurology practice	1					1
	Washington	Group Health Cooperative (GHC) of Washington State	2					2
		Pesticide workers in Washington State Department of Health cohort				1		1
Canada	British Columbia	Parkinson's patients and controls from a mountainous rural area	1					1
	Okanagan Valley, British Columbia	Residents in horticultural region	1					1
France	11 regions	Agriculture workers in Agriculture and Cancer (AGRICAN) cohort				1		1
Netherlands	4 regions	Parkinson's patients and controls from five hospitals	2					2
United Kingdom	Widnes	Paraquat production workers			1			1
Taiwan, Province Of China	Taipei	Parkinson's patients and hospital controls	1					1
Grand Total			19	1	1	3	1	24

Figure F-1. Number of Epidemiological Studies of Parkinson's Disease-related Outcomes Following Paraquat Exposure

Some studies might have characterized multiple populations or used multiple study designs and therefore could be listed multiple times. Row and column totals and grand total shown in the figure represent counts of distinct references.
Interactive figure and additional study details in Tableau (NTP, 2019b).
Created using Tableau.

Study	Population Name	Parkinsonism Outcome	Population Description	Metric	Comparison Set	Exposure Group	Group N
Kamel et al. 2007	Pesticide workers and spouses in Agricultural Health Study (AHS) cohort	Parkinson's disease (incidence)	78 reported PD, 55,931 did not report PD	adjOR	ever/never use paraquat	never use paraquat	48,616
						ever use paraquat	7,393
		Parkinson's disease (prevalence)	83 reported PD, 79,557 did not report PD	adjOR	ever/never use paraquat	never use paraquat	68,360
						ever use paraquat	11,280
Furlong et al. 2015	Farming and Movement Evaluation (FAME) participants	Parkinson's disease	69 cases, 237 controls	adjOR	paraquat (glove controlling hygiene)	no paraquat exposure	
						paraquat (glove use <=50%, controlling hygiene)	
						paraquat (glove use >50%, controlling hygiene)	
					paraquat (glove use after 1994)	no paraquat exposure	
						paraquat (glove use after 1994 <=50%)	
						paraquat (glove use after 1994 >50%)	
					paraquat (glove use)	no paraquat exposure	
						paraquat (glove use <=50%)	
						paraquat (glove use >50%)	
					paraquat (hygiene use after 1994)	no paraquat exposure	
						paraquat (<2 hygiene practices after 1994)	
						paraquat (2-3 hygiene practices after 1994)	
					paraquat (hygiene use)	no paraquat exposure	
						paraquat (<2 hygiene practices)	
						paraquat (2-3 hygiene practices)	
					paraquat use	never use paraquat	222
						ever use paraquat	70
Goldman et al. 2012	Farming and Movement Evaluation (FAME) participants	Parkinson's disease	87 cases, 343 controls	adjOR	paraquat exposure (homozygous deletion genotype for GSTT1)	no paraquat exposure (no deletion of GSTT1)	192
						paraquat exposure (no deletion of GSTT1)	58
						no paraquat exposure (homozygous deletion of GSTT1)	59
						paraquat exposure (homozygous deletion of GSTT1)	15
					paraquat use (Y,N)	never use paraquat	
						ever use paraquat	
					paraquat use (years lifetime)	never use paraquat	
						ever use paraquat (<=4 yrs)	
						ever use paraquat (>4 yrs)	
Kamel et al. 2014	Farming and Movement Evaluation (FAME) participants	Parkinson's disease	89 cases, 336 controls (males only)	adjOR	paraquat exposure (dietary fat intake)	no paraquat exposure (high fat diet)	115
						paraquat exposure (high fat diet)	38
						no paraquat exposure (low fat diet)	121
						paraquat exposure (low fat diet)	26
Tanner et al. 2011	Farming and Movement Evaluation (FAME) participants	Parkinson's disease	110 cases, 358 controls	adjOR	paraquat use	no paraquat exposure	396
						ever use paraquat	72
van der Mark M et al. 2014	Parkinson's patients and controls from five hospitals	Parkinson's disease	444 cases, 876 controls	adjOR	paraquat exposure	never use paraquat	1,229
						paraquat exposure (>0-3.80)	47
						paraquat exposure (>3.80)	44
					paraquat exposure (non-self-report corrected)	never use paraquat	1,211
						paraquat exposure (>0-4.38)	60
						paraquat exposure (>4.38)	49





Pouchieu et al. 2018	Agriculture workers in Agriculture and Cancer (AGRICAN) cohort	Parkinson's disease	149,810 participants, PD reported in 1,732	adjOR	duration of paraquat use	no paraquat exposure	45,305
						paraquat exposure (1-25 yrs)	5,553
						paraquat exposure (26-46 yrs)	5,251
					paraquat exposure	never exposure to paraquat	124,268
						ever exposure to paraquat	25,542
Tanner et al. 2009	Parkinson's patients and hospital controls	Parkinson's disease	519 cases, 511 controls	adjOR	paraquat exposure	no paraquat exposure	1,017
						paraquat exposure	13
Hertzman et al. 1994	Residents in horticultural region	Idiopathic parkinsonism	127 cases, 245 controls	adjOR	paraquat exposure (IP v. CD controls)	no paraquat exposure (CD controls)	140
						paraquat exposure	11
					paraquat exposure (IP v. voter controls)	no paraquat exposure (voter controls)	121
						paraquat exposure	10
Engel et al. 2001	Pesticide workers in Washington State Department of Health cohort	Parkinsonism	310 workers	adjPR	paraquat exposure	no paraquat exposure	
						paraquat exposure	
					paraquat exposure (tertiles, acres-years)	tertile 1 (1-250 acre-years)	32
						tertile 2 (251-682 acre-years)	33
						tertile 3 (683-9950 acre-years)	33
					paraquat exposure (tertiles, years)	tertile 1 (1-10 years)	33
						tertile 2 (11-20 years)	42
						tertile 3 (21-39 years)	36

Figure F-2. Occupational Paraquat Exposure and Parkinsonism Outcomes

Interactive figure and additional study details in HAWC (NTP, 2019a).
Created using HAWC.
Tomenson and Campbell (2011) is not included in this visualization because study results are provided as standardized mortality ratios and not odds ratios.
Kamel et al. (2007) is classified here as a prospective cohort study but includes a prospective analysis (incidence) and cross-sectional analysis (prevalence).
Pouchieu et al. (2018) is classified here as a cross-sectional analysis. The study evaluates the AGRICAN cohort, but results were from the baseline questionnaire only.

Study	Population Name	Parkinsonism Outcome	Population Description	Metric	Comparison Set	Exposure Group	Group N
Costello et al. 2009	Central Valley, CA residents	Parkinson's disease	368 cases, 341 controls	adjOR	exposure status (1974-1999)	no paraquat exposure	241
						paraquat only exposure	301
Wang et al. 2011	Central Valley, CA residents	Parkinson's disease	362 cases, 341 controls	adjOR	residential exposure status	no paraquat exposure	258
						paraquat exposure	234
					workplace exposure status	no paraquat exposure	355
						paraquat exposure	159
Gatto et al. 2009	Parkinson's Environment and Genes Study (PEG) participants	Parkinson's disease	368 cases, 341 controls	adjOR	low/high paraquat exposure vs. no exposure	no paraquat exposure	570
						low paraquat exposure	62
						high paraquat exposure	77
					paraquat exposure by route vs. no exposure	no paraquat exposure	271
						ambient paraquat only	299
						ambient and well water paraquat	139
					paraquat exposure vs. no exposure	no paraquat exposure	570
						any paraquat exposure	139
Gatto et al. 2010	Parkinson's Environment and Genes Study (PEG) participants	Parkinson's disease	333 cases, 336 controls	adjOR	paraquat exposure (alpha-synuclein REP1 genotype)	reference	
						low/no exposure (homozygous or heterozygous for 259 genotype)	
						high exposure (homozygous or heterozygous for 259 genotype)	
						low/no exposure (homozygous or heterozygous for 263 genotype)	
						high exposure (homozygous or heterozygous for 263 genotype)	
		Parkinson's disease (onset <=68 years)		adjOR	paraquat exposure (alpha-synuclein REP1 genotype)	reference	
						low/no exposure (homozygous or heterozygous for 259 genotype)	
						high exposure (homozygous or heterozygous for 259 genotype)	
						low/no exposure (homozygous or heterozygous for 263 genotype)	
						high exposure (homozygous or heterozygous for 263 genotype)	
		Parkinson's disease (onset >68 years)		adjOR	paraquat exposure (alpha-synuclein REP1 genotype)	reference	
						low/no exposure (homozygous or heterozygous for 259 genotype)	
						high exposure (homozygous or heterozygous for 259 genotype)	
						low/no exposure (homozygous or heterozygous for 263 genotype)	
						high exposure (homozygous or heterozygous for 263 genotype)	
Lee et al. 2012	Parkinson's Environment and Genes Study (PEG) participants	Idiopathic Parkinson's disease	357 cases, 754 controls	adjOR	paraquat exposure	no paraquat exposure	651
						paraquat exposure	460
Sanders et al. 2017	Parkinson's Environment and Genes Study (PEG) participants	Parkinson's disease	619 cases, 854 controls	adjOR	paraquat exposure	no paraquat exposure	
						ambient paraquat exposure	
					paraquat exposure by genotype	none/low exposure (w 0-1 risk genotypes)	
						high exposure (w 0-1 risk genotypes)	
						none/low exposure (w 2 risk genotypes)	
						high exposure (w 2 risk genotypes)	

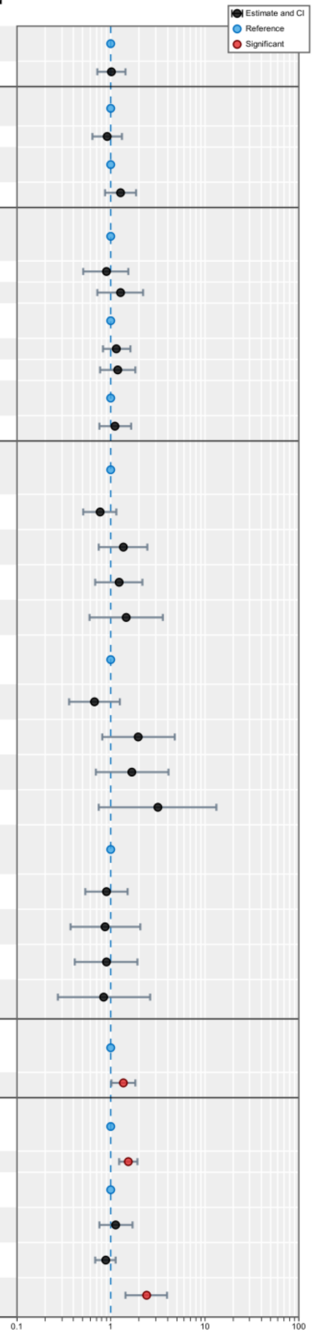


Figure F-3. Environmental Paraquat Exposure and Parkinsonism Outcomes

Interactive figure and additional study details in HAWC (NTP, 2019a).
Created using HAWC.
For Lee et al. (2012), the result is significant, but authors did not provide a p value.

Study	Population Name	Parkinsonism Outcome	Population Description	Metric	Comparison Set	Exposure Group	Group N
Firestone et al. 2005	Group Health Cooperative (GHC) of Washington State	Parkinson's disease	250 cases, 388 controls	adjOR	paraquat exposure vs. no exposure	no paraquat exposure	393
						any paraquat exposure	4
Firestone et al. 2010	Group Health Cooperative (GHC) of Washington State	Parkinson's disease	404 cases, 526 controls	adjOR	paraquat exposure vs. no exposure	no paraquat exposure	573
						any paraquat exposure	5
Brouwer et al. 2017	Parkinson's patients and controls from five hospitals	Parkinson's disease	352 cases, 607 controls	adjOR	residential exposure to paraquat, distance 0-50 m	no paraquat exposure (0-50 m)	
						ever exposure to paraquat (0-50 m)	
						tertile 1 (cumulative, 0-50 m)	
						tertile 2 (cumulative, 0-50 m)	
						tertile 3 (cumulative, 0-50 m)	
					residential exposure to paraquat, distance >50-100 m	no paraquat exposure (>50-100 m)	
						ever exposure to paraquat (>50-100 m)	
						tertile 1 (cumulative, >50-100 m)	
						tertile 2 (cumulative, >50-100 m)	
						tertile 3 (cumulative, >50-100 m)	
					residential exposure to paraquat, distance 0-100 m	no paraquat exposure (0-100 m)	
						ever exposure to paraquat (0-100 m)	
						tertile 1 (cumulative, 0-100 m)	
						tertile 2 (cumulative, 0-100 m)	
						tertile 3 (cumulative, 0-100 m)	
Liou et al. 1997	Parkinson's patients and hospital controls	Parkinson's disease	120 cases, 240 controls	adjOR	duration of paraquat use	0 years	307
						1-19 years	20
						>20 years	33
				OR	paraquat use	no paraquat use	
						paraquat use	
Dhillon et al. 2008	Parkinson's patients and controls from East Texas neurology practice	Parkinson's disease	100 cases, 84 controls	OR	paraquat exposure	never personally used/mixed or applied	179
						ever personally used/mixed or applied	5

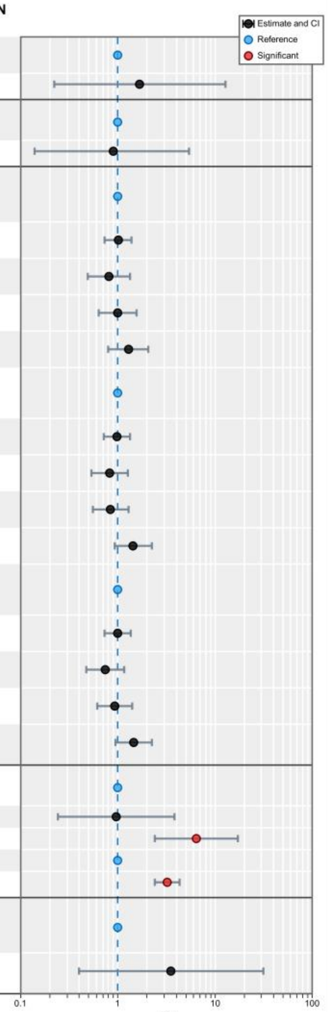


Figure F-4. General Population Paraquat Exposure and Parkinsonism Outcomes

Interactive figure and additional study details in HAWC (NTP, 2019a).
Created using HAWC.
Hertzman et al. (1990) is not included in this visualization. Hertzman et al. reported that odds ratios could not be calculated because four Parkinson's disease patients and no controls reported paraquat contact.
Wan and Lin (2016) is also not included in this visualization because it is an ecological spatial analysis with results not comparable with results from other studies.

Effect	Species: Drosophila	Frog	Nematode	Zebrafish	Grand Total
Dopamine (DA and metabolite levels, DAT and receptor expression, TH immunoreactivity)	9	1	1	5	16
Alpha synuclein, tau phosphorylation, tubulin	1		2		3
Other neurotransmitters (levels, receptors)	5			1	6
General mRNA, protein, or gene expression	10		1	2	13
Mitochondrial effects	3	1	2	3	9
Other (apoptosis, etc.)	2	1	3	1	7
Oxidative stress	12		3	5	20
Survival (whole animal)	22		4	1	27
Grand Total	28	2	8	6	44

Figure F-5. Number of Studies that Evaluated Secondary Animal Effects Following Paraquat Exposures in Nonmammalian Models

Some studies might have characterized multiple health effects or species and therefore could be listed multiple times. Row and column totals and grand total shown in the figure represent counts of distinct references.
Interactive figure and additional study details in Tableau (NTP, 2019b).
Created using Tableau.

Appendix G. Supplemental Files

The following supplemental files are available at https://doi.org/10.22427/NTP-DATA-RR-16.

G.1. Protocol Information

Protocol
parkinsons_protocol_508.pdf

G.2. Tableau Dataset

Excel Data File
ohat_parkinsondataset.xlsx

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