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WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

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1 INTRODUCTION

Paraquat dichloride, commonly referred to as "Paraquat," is one of the most widely used herbicides registered in the United States. Paraquat is used to control weeds in agricultural and non-agricultural use sites and is also used as a defoliant on crops prior to harvest. Paraquat is subject to the registration review process is mandated under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), which requires EPA reevaluate pesticides on a 15-year cycle to determine if they continue to meet the FIFRA standard for registration. As part of registration review, OPP is responsible for assessing if there is new data or information that warrants a new human health risk assessment by OPP. To support this effort, OPP performed a systematic literature review of peer reviewed epidemiology studies that examined the association between paraquat exposure and adverse health effects. The specific aims of the review were to:

1. Conduct a literature search and assemble a database of epidemiological studies examining the human health effects associated with paraquat exposure.
2. Review, summarize, and assess the quality of the assembled literature.

This report describes the systematic review approach and summarizes results of OPP's evaluation of study findings. This evaluation focused on characterizing results and identifying strengths and limitations with respect to health outcomes evaluated in the literature. **Section 2** provides a description of literature search methodology and evaluation approach. **Section 3** then provides a synthesis of findings by health outcome groupings and is followed by a summary of conclusions in **Section 4**. The evaluation and conclusions of this report are also integrated into the Hazard Characterization component of OPP's Draft Human Health Risk Assessment regarding adverse health outcomes and paraquat exposure.[1]

2 SYSTEMATIC LITERATURE METHODS AND ASSESSMENT APPROACH

2.1 Review Framework

The National Academy of Sciences National Research Council (NRC) and the National Academy of Medicine (formerly the Institute of Medicine) define systematic review as "a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies." NRC in a 2014 report identified systematic literature review strategies as "appropriate for EPA" and "specifically applicable to epidemiology and toxicity evaluations."[2]

EPA's Office of Pesticide Programs (OPP) published a framework for incorporating epidemiological data in risk assessments for pesticides which described a systematic review process relying on standard methods for collecting, evaluating, and integrating the scientific data supporting OPP decisions (US EPA, 2016). The epidemiology framework characterized "fit for purpose" systematic reviews for incorporating human epidemiology data in OPP risk assessments for pesticides, meaning that the complexity and scope

[1] W. Britton (2019). Paraquat Dichloride: Draft Human Health Risk Assessment in Support of Registration Review. D430827. U.S. June 2019.
[2] NRC (2014). Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: National Academies Press.

of each systematic review is tailored to a specific analysis and follows the key characteristics outlined in the Cochrane Handbook:[3]

- a clearly stated set of objectives with pre-defined eligibility criteria for studies;
- an explicit, reproducible methodology;
- a systematic search to identify all relevant studies;
- an assessment of the validity of the findings from the identified studies; and
- a systematic presentation and synthesis of the characteristics and findings of the included studies.

Following the procedures described in the OPP epidemiology framework, OPP conducted a formalized literature review to collect, evaluate, and integrate evidence from relevant epidemiological literature on the association between paraquat exposure and human health outcomes to evaluate whether exposure to these chemicals is associated with an increased (or decreased) risk of adverse health outcomes.

2.2 Literature Search Methodology

2.2.1 Systematic Literature Search

The literature search methodology followed the guidance provided in the National Toxicology Program/Office of Health Assessment and Translation (NTP/OHAT*) Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration,* January 9, 2015. For the search, the following population, exposure, comparator, and outcome of interest (PECO) criteria below guided the inclusion/exclusion criteria and selection of terms.

- **Population of interest:** Population studied must be humans with no restrictions, including no restrictions on age, life stage, sex, country of residence/origin, race/ethnicity, lifestyle, or occupation
- **Exposure:** Exposure studied must be to paraquat in any application via any route of exposure.
- **Comparator:** Exposed or case populations must be compared to a population with low/no exposure or to non-cases to arrive at a risk/effect size estimate of a health outcome associated with paraquat exposure.
- **Outcome:** All reported human health effects, with no restrictions on human system affected (effects could be based on survey or other self-report, medical records, biomarkers, publicly available health data, or measurements from human sample populations).

Based on these PECO criteria, inclusion/exclusion terms were identified and a literature search was conducted in PubMed, PubMed Central, Science Direct, Toxline, SCIELO (Scientific Electronic Library Online), and SciSearch. The initial search included all published articles through July-2017 and updated search was conducted in July-2018 to identify articles that were published after the initial search. Results were limited to those with human subjects and an English language abstract. The terms used in the searches where chosen from those in **Table 1**. Terms within each column were combined with OR, and terms between columns were combined with AND, except for the Excluded Terms which were combined with either NOT or AND NOT.

[3] Higgins, J. P., & Green, S. (Eds.). (2011). Cochrane handbook for systematic reviews of interventions (Vol. 4). John Wiley & Sons.

Table 1: Paraquat Literature Search Terms

Paraquat Terms	Health Effects/Disease Terms	Exposure Terms	Methods Terms	Excluded Terms
Paraquat	Health effect*	Expose*	Epidemiolog*	Drosophila
Paraquat[mh]	Health impact*	Environmental exposure[mh]	Epidemiologic methods[mh]	Rat/rats
Methyl viologen	Adverse effects [subheading]	Occupational exposure[mh]	Epidemiologic studies[mh]	Mouse/mice
Gramoxone	Illness*	Prenatal exposure, delayed effects[mh]	Epidemiology [subheading]	Rodent*
	Environmental illness[mh]	Poison*	Case control	Monkey*
	Occupational illness[mh]	Poisoning[subheading]	Retrospective	Zebrafish
	Disease*	Toxic*	Prospective	Trout
	Agricultural workers' diseases[mh]	Intoxication*	Cohort	Fish
	Medical	Toxicity[subheading]	Longitudinal	Foxhound*
	Hospital*	Accident*	Cross-sectional	Bird*
	Mortality	Accidents, occupational[mh]	Incidence[mh]	Sheep
	Death	Inhalation/inhale*	Occupational stud*	Suicid*
	Pregnancy outcome*	Absorb*	Community stud*	Treatment*
	Pregnancy outcome[mh]	Skin absorption[mh]	Environment* stud*	Therap*
	Birth defect*	Contaminat*	Health survey*	Prognostic
	Birth weight	Food contamination[mh]		Prognosis
	Birth weight[mh]	Ingest*		Case report*
	Parkinson/Parkinson's	Consum*/consumption		
	Paralysis agitans	Drink*		
	Parkinson disease[mh]	Water		
	Amyotrophic lateral sclerosis	Herbicides[mh]		
	Neurologi*/neurotoxi*/neurodegenerat*/neuromuscular*	Pesticides[mh]		
	Neurodegenerative disease[mh]			
	Kidney/renal			
	Arthritis			
	Respirat*			
	Pulmonary/lung			
	Thyroid			
	Cardiac /myocardial			
	Cancer*			
	Carcinogen*			
	Neoplasms[mh]			
	Leukemia/myeloma/lymphoma/			
	Hodgkin's/sarcoma			
	Cancer sites: prostate/breast/ovar*/			
	colon/colorectal/liver/pancrea*/			
	bladder			

[mh] indicates a Medical Subject Heading (MeSH) in PubMed
[subheading] indicates a qualifier used to describe a specific aspect of a MeSH heading
* indicates truncation (*i.e.,* that alternate endings were searched)

Based on the PECO criteria and search terms described above, the literature search aimed to identify original, peer-reviewed articles on epidemiologic studies. Exclusion criteria were also identified prior to collecting potentially relevant publications. Articles were excluded for the following reasons: not full text (*e.g.,* abstracts); not peer-reviewed; not in English; non-human study subjects; in-vitro studies; fate and transport studies; outcome other than human health effects (*e.g.,* environmental measures); experimental model system studies; no paraquat-specific investigation (*e.g.,* general herbicide); no risk/effect estimate reported (*e.g.,* case studies/series); no original data (*e.g.,* review publications).[4] In addition, the review focused on epidemiology studies and excluded articles on acute poisonings and overexposure.

A key element of the inclusion/exclusion criteria hinged on the definition of "human health effect" outcomes. For the purposes of the epidemiology literature review, OPP considered human health effects via the toxicological paradigm presented by the NRC as pathologies or health impairments subsequent to altered structure/function.[5] Thus, studies with outcomes of altered structure (*e.g.,* DNA alteration, sister chromatid exchange, cell proliferation) or biomarker or other exposure outcomes (*e.g.,* in breast milk, urine, cord blood, or plasma) that did not also include an associated health pathology (*e.g.,* cancer, asthma, birthweight) failed to meet the inclusion criteria for "human health effects" for the purposes of this epidemiology literature review.

2.2.2 Supplemental Literature Search

To supplement the open literature search described above, OPP reviewed publications resulting from the Agricultural Health Study (AHS) for articles that satisfied the inclusion/exclusion criteria. The AHS is a federally funded study that evaluates associations between pesticide exposures and cancer and other health outcomes and represents a collaborative effort between the US National Cancer Institute (NCI), National Institute of Environmental Health Sciences (NIEHS), CDC's National Institute of Occupational Safety and Health (NIOSH), and the US EPA.

The AHS maintains on its website an electronic list of publications resulting from AHS studies using the AHS cohort.[6] These articles were imported into Endnote, and Endnote was used to run a full text search ("Any Field + PDF with Notes") for "Paraquat", to ensure all AHS publications relevant to the epidemiology literature review were identified. AHS articles that satisfied the inclusion/exclusion criteria as described above were selected for inclusion in the epidemiology literature review.

The final phase of data collection was a reference review of articles captured in the open literature search, the AHS publication search, and previously published OPP documents. References were examined to identify relevant publications that were not captured in either the open literature search or the AHS publication search. Resulting articles from this reference review that satisfied inclusion/exclusion criteria were selected for inclusion in the epidemiology literature review.

2.2.3 Literature Search Results

587 unique articles were identified across the search engines and assembled in an EndNote Library. The title and abstract of each article were screened for potential relevance using the PECO criteria and exclusion criteria described in **Section 2.2**. EPA identified 55 articles based on this approach and 3 additional articles that were cited by the articles screened. Of these 58 articles, one was unable to be

[4] While the search focused on original peer-reviewed articles, the OPP does seek out and consider other sources of information that are not peer-reviewed (e.g. letters to the editor, corrections, commentary) on a case-by-case basis when this information provides clarification or other material findings or information of relevance to our evaluation of the literature.
[5] Henderson, R., Hobbie, J., Landrigan, P., Mattisoti, D., Perera, F., Pfttaer, E., ... & Wogan, G. (1987). Biological markers in environmental health research. Environmental Health Perspectives, 7, 3-9.
[6] Agricultural Health Study: Publications https://aghealth.nih.gov/news/publications.html

obtained (Kelley et al, 1994), one (Hirose et al, 1986) was not available in English, and three articles (Gorell et al, 1998; Rajput et al, 1987; and Rugberg et al, 2011) were reviewed, but did not include paraquat-specific analysis. This yielded a total of 53 articles.

The supplement search of the AHS electronic list identified an additional 56 articles that included the term "paraquat" in their text or tables. Review of these articles yielded an additional 21 articles that reported effect estimates for paraquat exposure in the AHS study population. In most cases, the paraquat effect estimates were included in a summary result table in the article, but not described in the article's abstract, title, keywords, or discussion/conclusion.

A summary of the literature search and supplemental AHS search is provided in **Figure 1** below.

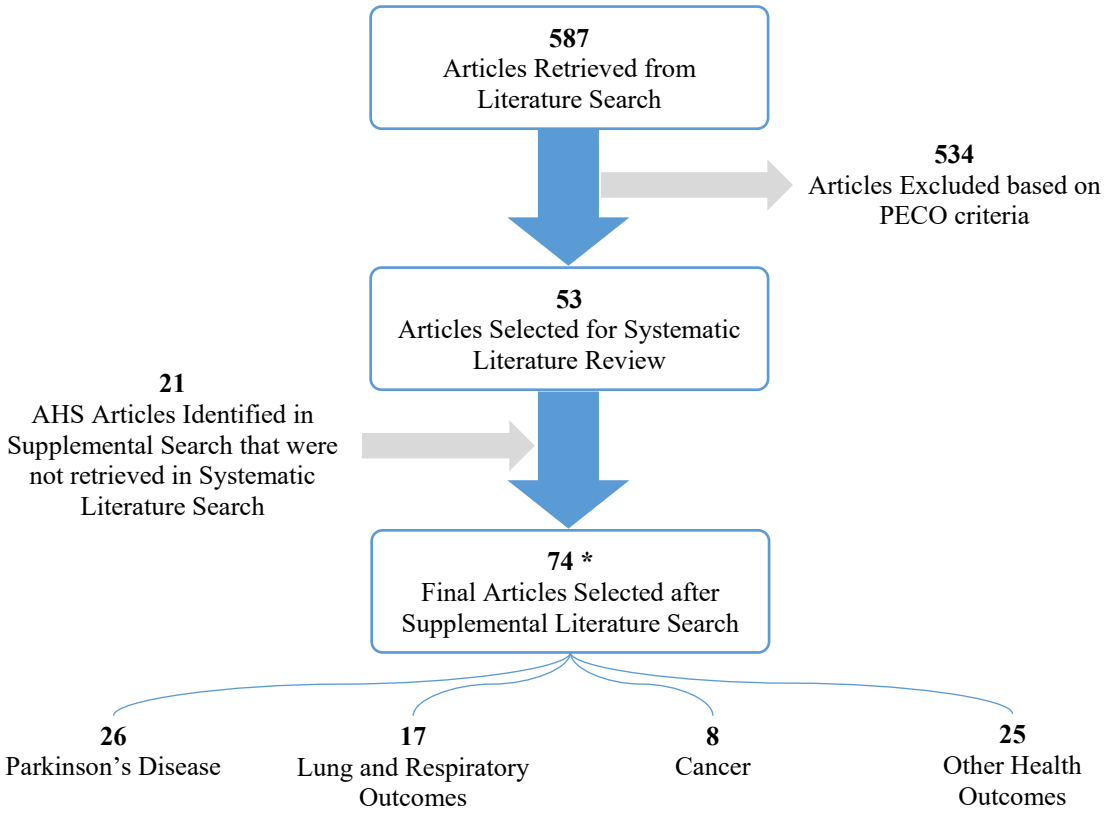


Figure 1: Summary of Literature Search Results.

** Number of articles on health outcomes do not sum because some articles reported on multiple outcomes in a single article.*

2.3 Literature Review and Evaluation Approach

2.3.1 Study Review and Quality Assessment

A total of 74 peer-reviewed epidemiologic articles were identified for OPP's literature review and evaluation. Each article was reviewed and relevant information was summarized on study design, results, conclusions, the strengths and weaknesses of each study per the epidemiology framework (US EPA, 2016), and recount details including the exposure measurement, outcome ascertainment, number of participants (n), number exposed/number of cases, number in reference (un-exposed/control) group, effect

measure (*e.g.,* odds ratio (OR), relative risk (RR), hazard ratio (HR)) and associated estimates of uncertainty and/or statistical significance (*e.g.,* confidence interval (CI), p-value), confounders considered, and methods of analysis. OPP considered these elements in assessing the quality of each publication and its applicability to an overall assessment of the health effects associated with paraquat exposure.

The assessment of study quality followed the OPP Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides (herein called the OPP framework) (US EPA, 2016). As shown in **Table 2** below, the study quality assessment considered aspects such as design, conduct, analysis, and interpretation of study results, including whether study publications incorporated a clearly articulated hypothesis; adequate assessment of exposure; critical health windows; valid and reliable outcome ascertainment; a sample representative of the target population; analysis of potential confounders; characterization of potential systematic biases; evaluation and reporting of statistical power; and use of appropriate statistical modeling techniques.

Table 2: Epidemiology Study Quality Considerations. Adapted from Table 2 in US EPA (2016).

Parameter	High	Moderate	Low
Exposure assessment	Exposure assessment includes information on paraquat or metabolite in the body, quantitative air sample data, or high-quality questionnaire on chemical-specific exposure assessment during relevant exposure window	Questionnaire based individual level information on paraquat	Low quality questionnaire-based exposure assessment, or ecologic exposure assessment, with or without validation
Outcome Assessment	Standardized tool, validated in study population; or, medical record review with trained staff	Standardized tool, not validated in population, or screening tool; or, medical record review, methods unstated	Subject report, without additional validation
Confounder control	Good control for important confounders relevant to paraquat study question, and standard confounders	Moderately good control of confounders, standard variables, not all variables for paraquat study question	Multi-variable analysis not performed, no adjustments
Statistical Analysis	Appropriate to study question and design, supported by adequate sample size, maximizing use of data, reported well (not selective)	Acceptable methods, questionable study power (esp. sub-analyses), analytic choices that lose information, not reported clearly	Minimal attention to statistical analyses, comparisons not performed or described clearly
Risk of (other) bias (selection, differential misclassification, other)	Major sources of other potential biases not likely present, present but analyzed, unlikely to influence magnitude and direction of the risk estimate	Other sources of bias present, acknowledged but not addressed in study, may influence magnitude but not direction of estimate	Major study biases present, unacknowledged or unaddressed in study, cannot exclude other explanations for study finding

Note: Overall study quality ranking based on comprehensive assessment across the parameters.

Study design influenced the assessment of study quality. Cohort studies, which enable researchers to assess the temporality of exposure in relation to health outcome and to consider multiple health outcomes, were generally considered higher quality than other study designs. Case-control studies, which are susceptible to recall bias, were generally considered lower quality than nested case-control studies, which

may be less susceptible to selection and recall bias. Cross sectional studies cannot distinguish temporality for exposure in relation to health outcomes; therefore, cross-sectional studies were generally considered lower quality than cohort or case-control studies, and were regarded as hypothesis-generating in the absence of additional studies supporting an observed association. The lowest quality study design considered was ecologic studies, due to an inability to extrapolate observed associations from the group level to the individual level (ecological fallacy) inherent in the ecologic study design. Ecologic studies were generally regarded as hypothesis-generating studies (US EPA, 2016).

Studies that characterized the exposure-response relationship (*e.g.,* with a dose-response curve or trend statistic) were, in general, considered higher quality than studies that did not characterize exposure-response. Studies that specified temporality (*i.e.,* those that determined exposure preceded a health outcome) and studies that specified uncertainties in the analysis were, in general, considered higher quality than studies that failed to specify temporality and studies that lacked an examination of uncertainty. Consistent results between study groups (*e.g.,* a significant and positive association seen for both farmers and commercial applicator study groups within a single study) bolstered the assessment of study quality.

Risk estimates (estimates of effect) reported in epidemiological studies were generally considered as follows:

- no evidence of a positive association between exposure and outcome (*e.g.,* OR $\leq$ 1.00);
- no evidence of a significant positive association (*e.g.,* OR > 1.00 but not significant);
- evidence of a slight positive association (*e.g.,* 1.00 < OR < 1.30 and significant);
- evidence of a positive association (*e.g.,* 1.30 $\leq$ OR < 2.0 and significant);
- evidence of a moderately strong (*e.g.,* 2.0 $\leq$ OR < 3.0 and significant) or strong (*e.g.,* OR $\geq$ 3.0 and significant) positive association[7].

However, we recognize that results that fail to attain statistical significance may still indicate clinical, biological, and/or public health importance and may warrant further exploration (US EPA, 2016). We particularly noted large observed associations (*e.g.,* OR $\geq$ ~2.5) even in the absence of significance, perhaps indicating a smaller than optimal sample size. Conversely, we also recognized that statistical significance does not necessarily imply clinical or biological importance, particularly with larger than necessary sample sizes and other study elements that influence the reliability of estimated effects.

2.3.2 Categories of Evidence

The categories of evidence described in **Table 3** are guided by several documents that have been developed by EPA and others. These include as a main reference a document developed by the Institute of Medicine (now the Academy of Medicine)[8] which detailed various "Categories of Association" which

[7] For articles that reported ORs, RRs, and HRs, the confidence interval (CI) acted as a proxy for significance testing, with CIs that do not contain the null value (OR / RR / HR = 1.00) considered significant. P-value significance considered a critical value of $\alpha = 0.05$ unless otherwise specified by the authors and noted in the summaries here.

[8] IOM (1998). Veterans and Agent Orange Update 1998. National Academy Press. Washington, DC. https://www.nap.edu/read/6415/chapter/1. Some of this material is derived from and/or consistent with U.S. Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004 and its Chapter 1 "Introduction and Approach to Causal Inference", available at: https://www.ncbi.nlm.nih.gov/books/NBK44695/. Much of this material is also presented in a more recent National Academies publication from 2018: National Academies of Sciences, Engineering, and Medicine 2018. *Gulf War and Health: Volume 11: Generational Health Effects of Serving in the Gulf War*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25162.

describes guidance for drawing conclusions regarding the overall strength of the evidence that exists regarding any putative linkage between an exposure and a health effect (IOM, 1998). Also considered in developing OPP's categories of evidence were the National Toxicology Program's OHAT document on systematic review and evidence integration (Woodruff and Sutton, 2014), OPP's epidemiologic framework document (US EPA, 2016), and EPA's Preamble to the Integrated Science Assessments which serve as a scientific foundation for the review of EPA's National Ambient Air Quality Standards (US EPA, 2016).

In this memorandum, each category is assigned based on a case-by-case approach that considers the weight of the epidemiological evidence and expert judgement and not a binding or inflexible formulaic approach in deciding the number and/or quality of studies that would be necessary to assign a specific evidence category. When assigning a level of evidence category to an exposure and the body of evidence pertaining to that health effect, the level of quality of the studies available in the peer-reviewed literature for that health effect, the strength of the associations (effect sizes) and consistency of the association in magnitude and direction across available studies was considered, as described in OPP's epidemiologic framework document.

Table 3*:* Categories of Evidence.

Evidence Category	Description
Sufficient Epidemiological Evidence of a Clear Associative or Causal Relationship	*Sufficient epidemiological evidence to suggest a clear associative or causal relationship between the exposure and the outcome.* There is high confidence in the available evidence to suggest that a clear associative or causal relationship exists between the exposure and the health outcome of interest. Studies are minimally influenced by chance, bias, and confounding. Further, additional epidemiological data, evidence, or investigations are unlikely to substantively affect the overall magnitude or direction of the observed association or result in a meaningful change with respect to any conclusions regarding this association. This level of evidence might be met, for example, if several high- or moderate- quality studies on different study populations, by different authors, in different settings, and/or using different epidemiological study designs that are likely to be minimally influenced by bias and confounding show a clear associative or causal relationship that is consistent among studies with respect to magnitude and direction of effect sizes. Such evidence is strengthened when one or more high- or moderate-quality studies also demonstrate dose-response trends with the range of these doses (exposures) considered sufficient to cover the range of expected human exposure levels (including the high end) and the evidence base consists of a least one high-quality prospective cohort study.

Evidence Category	Description
Limited but Insufficient Epidemiological Evidence of an Association	*Limited but insufficient epidemiological evidence to conclude that there is a clear associative or causal relationship between the exposure and the outcome.* There is some confidence that the available evidence accurately reflects a clear association between the exposure and the outcome, but the evidence is limited because the studies are of insufficient quantity, quality, (internal) validity, or consistency of the study results or because chance, bias, and confounding could not be ruled out with confidence. While the present body of evidence suggests that a relationship between exposure and disease outcome may possibly exist, additional high- or moderate-quality epidemiological data, evidence, or investigations could affect the overall magnitude or direction of the observed associations and might result in a meaningful change to this level of evidence category. This level of evidence category might be met, for example, if the body of evidence is: (1) based at least on one high-quality study suggesting a statistically significant relationship and the results of other high or moderate quality studies are mixed, contradictory, imprecise, ambiguous, or inconsistent; (2) based on several moderate-quality studies which show a relationship between exposure and outcome that is less pronounced than in (1); or (3) based on many studies (both moderate and possibly low-quality studies) showing a generally consistent direction and for which additional and more thorough analysis would be needed to make the determination of a relationship.
Insufficient Epidemiological Evidence of an Association	*Insufficient epidemiological evidence to conclude that there is a clear associative or causal relationship between the exposure and the outcome*. There is minimal confidence in the available evidence that the findings accurately reflect an association between the exposure and the outcome because the studies are of insufficient quantity, quality, (internal) validity, consistency, or statistical power to permit a conclusion to be reached, and/or chance, bias, or confounding may play an important role and cannot be ruled out. Further, additional high- or moderate-quality epidemiological data, evidence, or investigations could substantively affect the overall magnitude or direction of any observed associations. This level of evidence category might be met, for example, if the body of evidence is: (1) too small to permit conclusions, such as when there are no available studies to validate or corroborate the findings of a single moderate- or low-quality study; (2) based entirely on one or more studies judged to be of low-quality; or (3) based on multiple moderate- or low-quality studies, but the heterogeneity of exposures, outcomes, and methods leads to mixed, conflicting, imprecise, ambiguous, or contradictory conclusions.
No Epidemiological Evidence of an Association	*No epidemiological evidence to conclude that there is a clear associative or causal relationship between the exposure and the outcome.* There is no epidemiological evidence to suggest the presence of an association between an exposure and outcome. This level of evidence category might be met, for example, if the body of evidence consists of high- or moderate-quality studies that show no evidence of a statistically significant association and generally appear to have small effect sizes, and/or for which chance bias, or confounding may play an important role.

Evidence Category	Description
Sufficient Evidence of No Causal Relationship	*Sufficient epidemiological evidence to suggest there is no causal relationship between the exposure and the outcome.* There is high confidence in the available evidence to suggest there is no causal relationship between the exposure and the outcome. The studies are minimally influenced by chance, bias, and confounding, and it is unlikely that additional epidemiological data, evidence, or investigations would meaningfully affect the current overall magnitude, direction, or conclusions about the association. This level of evidence category might be met, for example, if at least one high-quality study with adequate power (*e.g.,* ≥80%) to detect a meaningful effect size determined to be of substantive importance fails to show an effect and no other high or moderate quality studies provide affirmative evidence against this null result. In addition, data would also exist that suggests no significant dose-response trends are present with the range of these doses (exposures) considered sufficient to cover the range of expected human exposure levels (including the high end) and the evidence base consists of a least one high-quality prospective cohort study.

2.3.3 Background and Quality Considerations for the Agricultural Health Study

Many studies reviewed in this memorandum are part of the Agricultural Health Study (AHS). AHS is a federally funded effort begun in the early 1990s that evaluates associations between pesticide exposures and cancer and other health outcomes. The participant cohort includes more than 50,000 licensed private (farmer) and commercial pesticide applicators from Iowa and North Carolina in addition to their spouses (for a total of more than 90,000 participants). The AHS is a prospective cohort design in which enrollment occurred from 1993 – 1997; data collection is ongoing from both applicator and spousal participants. Because the AHS is a prospective cohort design, this means that much of the exposure information is collected *prior to* the diagnosis (or detection) of the disease, and this can potentially limit to a substantial degree issues potentially related to (case) recall bias which can be a serious methodological weakness of many case-control studies. Such recall biases can be common among case-control designs where individuals that are either diseased (cases) or not (controls) are asked about their exposure histories. To the extent that cases and controls can differentially recall such exposures, such case-control designs can be subject to considerable biases. For the nested case- control studies within the AHS, this can potentially lead to recall biases depending on the degree to which either the study collects information from farmers (or next of kin) after the disease diagnosis and whether cases and controls are asked to provide supplemental information or more detailed questionnaires regarding exposure history or other practices. Cancer determination in the AHS is through cancer registries in the states of IA and NC and are considered reliable.

While the AHS generally provides high quality information with reliable data regarding pesticide usage and lifestyle factors and information on specific pesticides rather than simply pesticide classes or groups, collecting such exposure information can be complex and it can be difficult to judge its validity or reliability. The AHS has been reviewed in this regard, and has been found to be generally reliable: the study design/questionnaire is particularly advantageous because it collects information on individual pesticides -- and not just groups or classes of pesticides as is characteristic of a number of other epidemiology studies. But individuals -- particularly over a number of years or decades – are exposed to a number and variety of pesticides which can complicate epidemiological analyses by introducing confounders or sometimes “collinearity” whereby it can be difficult to isolate causal or suggestive factors contributing to disease. In addition, field studies have shown wide variation in work and hygienic practices among farmers (and farm workers) and exposures – and especially exposures over long time

periods time - can thus be difficult to accurately assess. The AHS does have in place an algorithm that attempts to account for certain work or hygienic practices by adjusting estimated exposures to account for use by farmers of personal protective equipment and practices; this algorithm considered such work and hygienic practices, including the mix of activities performed (*e.g.,* mixing/loading vs. application) and provides exposure estimates on both a cumulated (lifetime day)- and intensity-weighted cumulated (intensity-weighted lifetime day)- basis. Nevertheless, the AHS algorithms assume that total (cumulated) lifetime exposure depends on the multiplicative product of annual frequency of applications by a farmer and the associated number of years of application and this may not be strictly true and could systematically overestimate or underestimate exposures. Too, use practices such as application equipment and methods for a given pesticide can change over time, in addition to formulations (and farming practices in general) which can add additional uncertainties with respect to any assessment of cumulated exposure.

3 LITERATURE REVIEW AND EVALUATION

This section presents a review and evaluation of the epidemiologic literature on the potential association between paraquat exposure and adverse health outcomes. The review and evaluation is organized by health outcome, including *Parkinson's Disease* (**Section 3.1**), *Lung Function and Respiratory Effects* (**Section 3.2**), *Cancer* (**Section 3.3**), and *Other Health Outcomes* (**Section 3.4**). For each of the health outcome sections, individual study articles are summarized and then an overall evaluation of findings is characterized. **Appendix A** provides additional tabular summary of all studies, organized by health outcome, with respect to their design, methods, results, and study quality.

3.1 Parkinson's Disease (26 Articles)

The relationship between paraquat exposure and Parkinson's disease (PD) was evaluated in 13 study populations comprised of three agricultural cohorts, nine hospital-based study populations, and one PD registry in Nebraska (a total of 26 articles).[9] For several study populations, results on the relationship between paraquat and PD are described in multiple articles, typically a primary article that specifically examined the association between paraquat and other pesticides with PD and (potentially multiple) secondary articles that subsequently explored potential effect modification by environmental, dietary, and behavioral factors. The study participants (*e.g.,* cases and controls) included in these secondary articles overlap with the participants in the primary articles; therefore, these secondary articles help further characterize and extend the findings of primary articles but do not provide additional, independent information on any putative association between paraquat and PD.

The literature review in **Section 3.1.1** below – organized by agricultural study populations, hospital-based study populations, and a single registry-based study – describes both primary results on the association between paraquat and PD and secondary results on effect modifiers. This is followed by an overall evaluation of the available evidence on occupational and non-occupational paraquat exposure in **Section 3.1.2**.

3.1.1 Literature Review

Agricultural Study Populations

Agricultural Health Study (AHS) and Farming and Agricultural Movement Evaluation (FAME) Study (High Quality: FAME Study [Goldman et al., 2012; Furlong et al., 2015; Tanner et al., 2011; Kamel et al., 2014]; Moderate Quality: Kamel et al., 2007; Shrestha et al., 2018)

As described in **Section 2.3.3**, AHS is a large cohort study that began enrollment in 1993. Potential AHS participants were identified from among individuals applying for certification to use restricted-use pesticides in Iowa and North Carolina. AHS originally enrolled 52,393 private applicators, 32,345 spouses, and 4,916 commercial applicators. Follow-up of the AHS cohort included collecting information using Phase 2, Phase 3, and Phase 4 interviews in 1999-2003, 2005-2010, and 2013-2015, respectively, to evaluate cancer and non-cancer endpoints, including Parkinson's disease. Commercial applicators participated in Phase 2 follow-up, but did not participate in subsequent phases of follow-up in AHS.[10]

[9] An additional article, Tomenson and Campbell (2011), examined mortality risk from PD and other major causes among workers manufacturing paraquat between 1961 and 1995. This study only identified one case of Parkinson's disease-specific mortality and is further described in *Mortality* under **Section 3.4** on *page 56*.

[10] AHS Website. About the Study: Available online at: https://aghealth.nih.gov/about/. [Accessed May 22, 2019]

Numerous add-on studies of specific health outcomes have leveraged the AHS study cohort to evaluate specific health outcomes in more detail. FAME is an AHS add-on study that used a case-control design nested within the AHS cohort to evaluate potential risk factors for PD. Using the AHS cohort, subjects suspected to have PD based on diagnoses from self-reports or state mortality files were screened cases. Screened controls were selected by stratified random sampling of all AHS participants. Controls were frequency-matched to cases by age (< 40, 40–49, 50–59, 60–64, 65–69, ≥ 70 years), sex, and state (Iowa or North Carolina) at a ratio of approximately 3 controls per case. The FAME study screened 170 cases and 644 controls. After screening cases and controls, the FAME study enrolled 115 cases and 383 controls after accounting for ineligible subjects, refusals, etc.

Five articles examined the relationship between paraquat exposure and PD within the AHS cohort, including one study of the entire AHS cohort (Kamel et al., 2007) and four FAME studies that relied on many of the same PD cases and used a case-control design to assess relationship between paraquat and PD (Tanner et al., 2011) and effect modifiers; these effect modifiers investigated included gene-by-environment interaction (Goldman et al., 2012), dietary fat intake (Kamel et al., 2014), and behavioral factors related to reducing occupational pesticide exposure (Furlong et al., 2015). In addition to these five articles, a more recent AHS publication reported on the association between paraquat use, as well as use of other pesticides, and the prodromal PD symptom dream enacting behavior (Shrestha et al., 2018).

The results of the five PD studies and one study on dream enacting behavior are summarized below:

Examination of Self-Reported PD in AHS Cohort

- Kamel et al. (2007) investigated the relationship between self-reported pesticide exposure in the AHS cohort and prevalent PD cases identified at enrollment (1993-1997) and incident PD cases identified during Phase 2 follow-up (1999-2003). At enrollment, study subjects, including pesticide applicators and their spouses, provided detailed information on lifetime pesticide use. Enrollment and follow-up questionnaires were also used to determine whether subjects reported a physician-diagnosed PD. There were 83 study subjects reporting PD diagnosis at enrollment (prevalent cases) and 78 study subjects reporting PD diagnosis after AHS (incident cases). Logistic regression was used to evaluate the relationship of either prevalent PD or incident PD to general pesticide use and specific pesticides, including paraquat, adjusting for age, state, and type of participant (applicator or spouse), race, education, and smoking. Based on this approach, the investigators reported no evidence of a significant positive association with prevalent PD (OR = 1.8; 95% CI, 1.0-3.4, n = 14 paraquat exposed cases) and no evidence of an association with incident PD (OR = 1.0; 95% CI, 0.5-1.9, n = 11 paraquat exposed cases).[11]

Examination of Clinically Confirmed PD in FAME Nested Case-Control Study of AHS Cohort

- Tanner et al. (2011) investigated the relationship between pesticides, including paraquat, in the FAME nested case-control study. The FAME study included 115 cases and 383 frequency-matched controls, of which 110 cases and 358 controls provided complete information available on pesticide use and application practices. Computer-assisted telephone interviews were used to obtain detailed information on pesticide use for 31 selected pesticides. For every subject, each pesticide was categorized by ever/never use and lifetime days of use. Of the 31 pesticides selected, 18 pesticides were reported to be used by at least 10 subjects and individually analyzed

[11] Epidemiologists distinguish between incident and prevalent case of disease when quantifying the disease rate in a population. *Incident Cases* are new cases of disease in a population of interest and *Prevalent Cases* are existing cases of disease in a population of interest (Rothman and Greenland, 1998). In the context of AHS, incident PD cases reported diagnosis of PD after enrollment in AHS, whereas prevalent PD cases reported PD diagnosis during enrollment.

using logistic regression. Based on this approach, the investigators reported evidence of a moderately strong positive association for ever use of paraquat (OR = 2.5, 95% CI, 1.4-4.7, n = 23 exposed cases). The investigators further examined the cumulative lifetimes days of paraquat exposure and reported that the effect estimate increased from an OR of 2.4 (95% CI: 1.0-5.5, n = 10 exposed cases) in individuals reporting ≤ median paraquat use of 8 lifetime days to an OR of 3.6 (95% CI: 1.6-8.1, n = 13 exposed cases) in individuals reporting > median paraquat use of 8 lifetime days.

- In additional analysis of the FAME case-control study, Goldman et al. (2012) investigated whether the risk of Parkinson's disease associated with paraquat exposure is modified by polymorphisms in the genes encoding for glutathione S-transferase M1 (GSTM1) and glutathione S-transferase T1 (GSTT1). The investigators genotyped 87 cases of Parkinson's disease and 343 controls matched on age, gender, and state of residence. Exposure to paraquat was either self-reported or reported by a proxy respondent and, for the interaction analysis, characterized as either "ever" versus "never" exposed. Years of lifetime paraquat use was also assessed and stratified into 3 categories: (i) never used; (ii) used less than the median of 4 years; or (iii) used more than the median. Unconditional logistic regression was used to estimate unadjusted and covariate-adjusted (age, gender, state, and cigarette smoking) odds ratios for self-reported paraquat exposure and Parkinson's disease and for the evaluation of multiplicative paraquat exposure effect modification by polymorphisms in the genes encoding GSTM1 and T1 GSTT1. As previously reported by Tanner et al. (2011), the investigators reported evidence of moderately strong positive association between paraquat use and PD (OR = 2.6, 95% CI: 1.3-5.0, n = 21 exposed cases). With regard to interaction between GSTT1 and paraquat use, there was no evidence of a significant positive association among paraquat users with functional GSTT1 (OR = 1.5, 95% CI: 0.6-3.6, n = 12 exposed cases with functional GSTT1) relative to non-exposed male participants with functional GSTT1. However, paraquat users with the homozygous deletion of GSTT1 had an 11-fold increased odd of Parkinson's disease, relative to non-exposed male participants with homozygous deletion of GSTT1 (OR = 11.1; 95% CI: 3.0-44.6, n = 9 exposed cases). A similar interaction between paraquat exposure and GSTM1 genotype was not observed (data not reported in manuscript). Based on this analysis of interaction between GSTT1 and paraquat use, the investigators reported evidence that the GSTT1 genotype was a statistically significant modifier of the relative odds of Parkinson's disease comparing paraquat-exposed and non-exposed study participants (p-interaction = 0.027).
- In additional analysis of the FAME case-control study, Kamel et al. (2014) investigated if the potential association of PD with paraquat or rotenone is modified by dietary fat intake. Food intake was assessed using a self-administered food frequency questionnaire. Total energy and dietary fats were estimated using Diet*Calc software version 1.4.3. Daily intakes of total fat, saturated fat, monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs), and individual PUFAs were expressed as a percentage of total energy (nutrient density), and then categorized in tertiles based on distributions in the control group; the lowest tertile was used as the reference group. Multivariable logistic regression models were used to perform the analyses, adjusting for age, sex, state, smoking, and total energy. The analyses for paraquat included 61 cases (18 exposed to paraquat) and 239 frequency-matched male controls (46 exposed to paraquat). With regard to paraquat and potential effect modification with dietary fat, the OR for paraquat was 4.2 (95% CI: 1.5-11.6, n = 11 paraquat exposed cases) in individuals with low PUFA intake but 1.2 (95% CI: 0.4-3.4, n = 7 exposed to paraquat) in those with high PUFA intake (p-interaction = 0.10). The OR for paraquat was 4.0 (95% CI: 1.5-10.9, n = 11 paraquat exposed cases) in individuals with low N-6 (omega 6) PUFA intake but 1.2 (95% CI: 0.4-3.3, n = 7 exposed to paraquat) in those with high N-6 (omega 6) PUFA intake (p-interaction = 0.08). The

OR for paraquat was 3.8 (95% CI: 1.4-10.3, n = 11 paraquat exposed cases) in individuals with low linoleic acid intake but 1.2 (95% CI: 0.4-3.3, n = 7 paraquat exposed cases) in those with high linoleic acid intake (p-interaction = 0.09).

- In additional analysis of the FAME case-control study, Furlong et al. (2015) investigated whether use of gloves and workplace hygiene modified the association between pesticide exposure and PD. The investigators collected questionnaire data on the use of protective gloves, other personal protective equipment (PPE), and hygiene practices from 69 cases and 237 controls (22 cases reported using paraquat). Unconditional logistic regression was then used to evaluate the associations between PD and pesticides, PPE, and hygiene practices and obtain stratum-specific estimates from interaction models. Based on this approach, the investigators reported no evidence of significant positive association between paraquat exposure and PD among protective glove users (OR = 1.6, 95% CI: 0.6-4.2, n = 8 paraquat exposed cases reporting use of protective gloves) and evidence of a strong positive association among non-glove users, defined as report of using gloves less than 50% of the time (OR = 3.9, 95% CI: 1.3-11.7, n = 14 paraquat exposed cases reporting no use of protective gloves).

Examination of Self-Reported Dream Enacting Behavior in AHS Cohort

- Shrestha et al. (2018) conducted a prospective study of the AHS cohort to examine the association between pesticide exposure, including paraquat, and dream enacting behavior. 51,350 male farmers were enrolled in the AHS between 1993-1997 and administered follow-up questionnaires in 4 phases to obtain follow-up information on pesticide use, potential confounders, and medical information. The most recent follow-up questionnaire was administered in 2013-2015 and included screening questions on prodromal PD symptoms including dream enacting behavior, olfactory impairment, constipation, daytime sleepiness, depression, anxiety, and several motor symptoms such as tremor and, small handwriting. 23,478 of the 51,350 (46%) male farmers originally enrolled in AHS completed this questionnaire and were included in the statistical analysis of the association between pesticide use and dream enacting behavior. AHS participants provided self-reported information on dream enacting behavior and were asked, "Have you ever been told, or suspected yourself, that you seem to 'act out dreams' while sleeping?" If they answered yes, they were prompted to answer additional questions on the frequency of symptoms. Pesticide use was assessed using the AHS enrollment questionnaire and focused on ever use of 49 specific pesticides, including paraquat. Enrollment data was also used on demographic and lifestyle risk factors and information on head injury was obtain from a subsequent take home questionnaire and the phase 2 follow-up questionnaire in 1999-2003. After collecting data on the outcome of interest and pesticide use, multivariable logistic regression was used to assess the relationship between pesticide exposure and dream enacting behavior, adjusting for age, smoking, alcohol consumption, marital status, education, state, and head injury. Based on this approach, the investigators reported no evidence of an association between ever-never use of paraquat and dream enacting behavior (OR = 1.1, 95% CI: 0.9-1.3, n = 339 exposed cases).

In summary, six articles examined the relationship between paraquat exposure and PD in the AHS study population. This included three primary articles that first examined the association between paraquat and either PD (Kamel et al., 2007; Tanner et al., 2011) or dream enacting behavior; Shrestha et al., 2018) and three secondary articles that were conducted as part of FAME and explored potential effect modification by dietary, behavioral factors, and genetic factors (Goldman et al., 2012; Kamel et al., 2014; Furlong et al., 2015). There was also overlap in the study population examined in each individual article regardless of whether they were identified as primary or secondary. Therefore, the results of AHS studies should not be evaluated independently. Further characterization of areas of overlap with respect to study population, follow-up, and exposure assessment methods are summarized in **Table 4** below. As summarized, Kamel

et al. (2007) and the FAME nested case-control studies are based on the same study period that covered AHS enrollment during 1993-1997 through phase 2 follow-up in 1999-2003. The FAME studies clinically confirmed PD diagnosis, but the total number of paraquat exposed cases was essentially the same - 25 total exposed cases in Kamel et al. (2007) and 23 in the FAME studies - suggesting there was considerable overlap in the subjects used in this group of studies. Shrestha et al. (2018) was the only fully prospective study and included more extensive follow-up of the AHS cohort though phase 5 follow-up in 2013-2015.

Table 4: Summary of Design Elements of AHS and FAME Studies on PD and the PD Prodromal Symptom Dream Enacting Behavior.

Study	Design (# Exposed Cases)	Study Period	Exposure	Outcome
Examination of Self-Reported PD in AHS Cohort				
Kamel et al. (2007)	Cohort Cross-Sectional n = 11 incident, 14 prevalent)	1993-1997 (Enrollment) to 1999-2003 (Phase 2 Follow-up)	Ever/Never Paraquat Use	AHS Survey Instrument – ‘‘Has a doctor ever told you that you had been diagnosed with Parkinson’s disease?’
Examination of Clinically Confirmed PD in FAME Nested Case-Control Study of AHS Cohort				
Tanner et al. (2011)	Nested Case-Control n = 23 incident/prevalent	1993-1997 (Enrollment) to 1999-2003 (Phase 2 Follow-up)	Ever/Never Paraquat Use and Cumulative Lifetime Use	Agreement of 2 neurologists on PD diagnosis
Goldman et al. (2012)	‘’	‘’	+ Genetic Factors	‘’
Kamel et al. (2014)	‘’	‘’	+ Dietary Fat Intake	‘’
Furlong et al. (2015)	‘’	‘’	+ Use of PPE	‘’
Examination of Self-Reported Dream Enacting Behavior in AHS Cohort				
Shrestha et al. (2018)	Prospective Cohort (n = 339)	1993-1997 (Enrollment) to 2013-2015 (Phase 5 Follow-up)	Ever/Never Paraquat Use	AHS Survey Instrument – “Have you ever been told, or suspected yourself, that you seem to ‘act out dreams’ while sleeping?”

With regard to study quality, Kamel et al. (2007) was of moderate quality based on the study quality criteria outlined in the OPP framework. The primary strength of the study was that it leveraged the AHS study cohort, which provides relevant information on U.S. agricultural populations and reliable information on pesticide usage on specific pesticides rather than simply pesticide classes. The study has several limitations, however, including the lack of clinical confirmation of self-reported PD cases and a relatively small number of cases reporting use of paraquat (14 prevalent cases and 10 incident cases). The study may also be subject to recall bias if prevalent cases recall previous exposure differently than study subject without PD. This potential for bias is particularly important because Kamel et al. (2007) reported – separately – on both prevalent and incident cases, with prevalent cases reporting an OR of 1.8 (95% CI, 1.0-3.4, n = 14 paraquat exposed cases) and incident cases (for which no recall bias would be expected) reporting an OR of 1.0 (95% CI, 0.5-1.9, n = 11 paraquat exposed cases).

The FAME studies used a nested case-control design that enabled the investigators to clinically confirm PD diagnosis and obtain more detailed information on potential genetic, dietary, and occupational hygiene risk factors. For this reason, the FAME studies were determined to be of high quality based on the OPP study quality criteria. While the FAME studies improved upon Kamel et al. (2007), particularly

by confirming PD diagnosis by two neurologists, the studies appear to examine many of the same PD cases as Kamel et al. and share similar limitations, including the relatively small number of paraquat exposed PD cases (23 exposed cases) and potential for recall bias. Furthermore, the study's statistical analysis curiously combined incident and prevalent PD cases (prevalent cases would be potentially subject to recall bias and incident cases would not). This consideration is of importance because Kamel et al. (2007) previously stratified their analysis by incident and prevalent cases and reported results that suggested that recall bias (from prevalent cases) could be substantial. As such, the FAME studies do not provide additional information to help clarify this issue.

Finally, Shrestha et al. (2018) was of moderate quality and had several strengths, including its prospective design and the reliability of the AHS questionnaire to ascertain pesticide exposure for paraquat and other specific pesticides. While the study had several strengths, it was determined to be of moderate quality because of limitations in the ascertainment of the outcome dream enacting behavior and the potential risk of bias due to loss to follow-up. Ascertainment of the outcome dream enacting behavior relied on self-report by survey participants and may have introduced misclassification if participants cannot reliably report that their symptoms are consistent typical prodromal PD symptoms. Given that the study was prospective, this source of outcome misclassification is likely to be non-differential because study subjects provided information on pesticide use before reporting dream enacting behavior during Phase 5 follow-up in 2013-2015. Loss to follow-up is another important limitation because only 46% of the study subjects originally enrolled completed the Phase 4 survey in 2013-2015. This may introduce selection bias if study subject participation in the follow-up phases is related to their disease status for PD and other health outcomes.

French Agriculture and Cancer (AGRICAN) PD Study (<u>Low Quality</u>: Pouchieu et al. 2018)

Pouchieu et al. (2018) conducted a cross-sectional study within the French AGRICAN cohort, a large prospective cohort of adults involved with agriculture in France. The primary aim of AGRICAN is to assess the relationship between agricultural exposures and cancer, but the study has secondary aims that focus on other health outcomes, including respiratory and neurologic conditions. The AGRICAN study population included all adults aged 18 years and older, both active and retired, who were farm owners, farmworkers, and individuals working for companies or organizations related to agriculture (*e.g.,* private insurance companies, banks, extension agents, foresters and gardeners, affiliated with a French Health insurance system for agricultural professionals). Individuals also had to have paid at least 12 quarterly contributions to the French health insurance for agricultural professionals and be living in 2011 in 1 of 11 French regions with certified cancer registries.

A total of 181,842 individuals were enrolled in AGRICAN and completed a self-administered questionnaire between 2005 and 2007. The enrollment questionnaire was used to collected data on demographics, existing health conditions, lifestyle risk factors, and occupational history. For occupational history, study subjects provided job history information on farm activities related to the care of 5 animal types and 13 crop types. The self-reported crop history information was used to assess exposure to specific pesticide by developing a crop-exposure matrix based on French pesticide use information, including pesticide registration, sales, and recommended use practices. Self-reported PD was also ascertained in the enrollment questionnaire.

A total of 1,732 study subjects self-reported being diagnosed with PD by a physician (244 exposed to paraquat), representing 1.2% of the enrolled study population. Multivariable logistic regression was used to assess the association between prevalent PD and (i) self-report of working on 18 crop/livestock categories and (ii) 14 specific pesticides, including paraquat, based on the investigators crop-exposure matrix. Based on this approach, ever/never use of paraquat was positively associated with PD in a

regression model that did not adjust for potential pesticide exposure to other pesticides (OR = 1.43, 95% CI: 1.17-1.75). After adjusting for co-exposure to other pesticides; however, the investigators reported no evidence of a positive association (OR = 1.01, 95% CI: 0.41-2.49). Additional analysis was performed to assess cumulative exposure using unexposed individuals as a reference group. Based on this analysis, the investigators similarly reported no evidence of an association (*1-25 years paraquat exposure* – OR = 1.05, 95% CI: 0.40-2.76; *26-46 years paraquat exposure* – OR = 0.94, 95% CI: 0.37-2.41).

Overall, Pouchieu et al. (2018) was of low quality based on the study quality criteria outlined in the OPP framework. While the study leveraged an existing prospective study of French agricultural workers, the study used a cross-sectional design that relied on the AGRICAN enrollment questionnaire to assess exposure and identify prevalent PD cases. As such, the study was unable to assess the temporal association between paraquat exposure and PD. The study's exposure assessment relied on the AGRICAN the study enrollment questionnaire and only asked general questions on livestock and crop categories. Pesticide exposure was then assigned using a livestock/crop-exposure matrix that relied on expert judgement. This approach was not validated and the investigators reported a high degree of correlation between pesticides (50% of correlation coefficients > 0.80), suggesting that the investigators had limited ability to evaluate paraquat and other specific pesticides in isolation. Furthermore, the study reported positive associations between each of the 18 livestock/crop categories and PD that served the basis of the pesticide exposure assessment. As such, it appears unlikely that the investigators' approach can evaluate pesticide-specific exposure to paraquat.

Washington State Department of Public Health PD Study (Low Quality: Engel et al. 2001)

The Washington State Department of Health conducted a cohort study in 1972-1976 that examined the effects of pesticide exposure on lifespan of select subpopulations within Washington State, including orchardists, pesticide applicators, pesticide formation plant workers, and other farm/agricultural workers. The "Polks Wenatchee City Directory" was used to identify unexposed subjects who were frequency matched to exposed cases by age, race, and degree of occupational physical activity. Based on this study population, Engel et al. 2001 conducted a follow-up cross-sectional study to investigate the relationship between parkinsonism and lifetime occupational pesticide exposure. Of the 1,300 original study participants, 323 were enrolled (25%), while 977 could not be enrolled because there were deceased (n = 439), could not be contacted (n = 245), resided outside the study area (n = 12), lost to follow-up (n = 122), or refused to participate (n = 159). This included 238 exposed individuals and 72 unexposed individuals (exposure could not be determined for 13).

Each study subject received a physical examination to confirm the presence of clinical symptoms of PD. Subjects also completed a self-administered questionnaire to ascertain information on farming and pesticide use, including years of farming, crops grown, acres for each crop, pesticide use practices, application methods, and use of personal protective equipment. Generalized linear regression with a binomial distribution and log link function was then used to estimate prevalence ratios adjusting for age and smoking. Based on this approach, the investigators examined the relationship between well water use, general use of pesticides, general use of 5 pesticide classes, and use of 13 specific pesticides, including paraquat. With respect to paraquat, no evidence of an association was reported for ever/never use (Prevalence Ratio = 0.8, 95% CI: 0.5 – 1.3, n = 20 exposed cases) or tertiles of years exposure (*Tertile 2 vs Tertile 1* – Prevalence Ratio = 0.4, 95% CI: 0.1- 1.4; *Tertile 3 vs Tertile 1* – Prevalence Ratio = 0.9, 95% CI: 0.4- 2.4). Similar results were also reported for tertiles of acre-years of exposure.

Overall, Engel et al. (2001) was of low quality based on the study quality criteria outlined in the OPP framework. While the study was based on a previous cohort of agricultural workers conducted in the

1970s and included physical examination to confirm the presence of clinical symptoms of PD, the participation rate was only 25% due to loss to follow-up, which may have introduced selection bias. The study also used a cross-sectional design and was unable to assess the temporal relationship between paraquat exposure and onset of PD. Finally, the study relied on a questionnaire to ascertain paraquat exposure and did not provide any information to demonstrate that it has been validated to assess cumulative exposure to paraquat or other specific pesticides.

Hospital-Based Study Populations

Central Valley, CA/Parkinson's Environment and Genes (PEG) Study (Moderate Quality: Costello et al., 2008; Gatto et al., 2009; Ritz et al., 2009; Gatto et al., 2010; Wang et al., 2011; Lee et al., 2012; Sanders et al., 2017; Paul et al., 2018)

The PEG Study used a case-control design to assess rural PD patients diagnosed in a community clinical community setting and investigate the interaction between genetics and environmental susceptibility. Study participants resided in predominantly rural communities in central California, including Fresno, Tulare, and Kern Counties and were recruited during an initial recruitment period in 2001-2007 and more recent second round of recruitment in 2010-2015.

During the initial 2001-2007 study recruitment period, cases were recruited from clinics in the three counties of interest and qualified for inclusion if they were diagnosed with PD between 1998 and 2007 and lived in California for at least 5 years prior to diagnosis. Of the 563 initially eligible PD cases, 473 (84%) were examination by a movement specialist confirmed to have 'probable' or 'possible' PD, yielding 377 PD cases. Complete demographics were not obtained for 9 cases, resulting in enrollment of 368 PD cases into the study. During the second 2010-2015 round of recruitment, the state-mandated pilot California PD registry was used to identify 4,672 PD patients living in the Fresno, Tulare, and Kern Counties. The investigators could contact 2,363 of these individuals and identified 581 potential cases that were eligible for the study. Of these eligible cases, 376 were enrolled in the study after examination by a movement specialist to confirm their PD diagnosis.

Control subjects were enrolled in the PEG study from 2001-2011 using 2 sampling strategies. The first sampling strategy was to mail letters of invitation to a selection of randomly selected residential units in each of the 3 counties. A sample of 1,212 potential controls were screened for eligibility. Eligibility criteria for controls were not having PD, being at least 35 years of age, currently residing primarily in 1 of the 3 designated counties, and living in California for at least 5 years prior to the screening. Only 1 control per household was allowed to enroll. Of the 755 eligible controls, 346 (46%) enrolled. Complete demographics were not obtained for 5 controls, resulting in enrollment of 341 controls into the study. The second sampling strategy used clustered random selection of 5 households that were visited in person. Based on this second approach, an additional 1,241 eligible controls were identified. Of the eligible controls, 634 declined participation and 607 controls were enrolled in the study (only 183 completed an abbreviated interview and 77 were not genotyped).

Pesticide exposure was assigned using residential history information from cases and control, combined with California pesticide use reporting data. Specifically, lifetime residential addresses were geocoded and pesticide application rates from agricultural uses (in pounds per acre per year) within 500 m of each subject's home were estimated by using a GIS-based approach that combined California pesticide use reporting data and land-use maps.

There was a total of eight articles with results on the association between paraquat exposure and PD in the PEG Study. These case-control studies are summarized below:

- Costello et al. (2009) investigated whether exposure to paraquat or maneb, alone or in combination, increases the risk of PD in a study of 368 confirmed PD cases and 341 controls aged 65 years or older. Using residential history, pesticide use reporting data, land-use maps, and GIS, as described above, residential maneb and paraquat pesticide exposures were estimated for each study participant. The assessment derived estimates of time specific (1974-1989, 1990-1999, and 1974-1999) total exposure of for maneb and paraquat. For analysis purposes maneb and paraquat exposure was categorized as no exposure, paraquat only exposure, maneb only exposure, and both paraquat and maneb exposure, for each of the time windows 1974-1999, 1974-1989, and 1990-1999. Unconditional logistic regression models were used to evaluate the association of PD with maneb and paraquat, alone or in combination. Based on this approach, the investigators reported no evidence of a positive association for paraquat only exposure (OR = 1.01, 95% CI: 0.71-1.43, n = 149 exposed cases) or maneb only exposure (OR = 3.04, 95% CI: 0.30 – 30.86, n = 3 exposed cases), but reported evidence of a positive association for both paraquat and maneb exposure combined (OR = 1.75, 95% CI: 1.13- 2.73, n = 88 exposed cases).
- Gatto et al. (2009) investigated whether exposure to paraquat from private well-water consumption in areas with historical agricultural pesticide use was associated with an increased risk of PD. Assessment of potential well-water exposure was also based on CA Pesticide Use Report data, based on the same 500-m spatial buffer, and combined with self-reports of private wells as drinking water sources at a residential address. Based on this approach, the investigators used multivariable unconditional logistic regression models to analyze the data and reported no evidence of a significant positive association between paraquat exposure from well water (OR = 1.10, 95% CI: 0.75-1.63, n = 79 exposed cases). This observation did not meaningfully change when exposure was stratified by low and high exposure, and after adjustment for ambient exposure (*i.e.,* residential proximity to pesticide applications).
- Ritz et al. (2009) genotyped 324 cases of Parkinson's disease and 334 controls subjects to investigate gene-pesticide exposure interaction. The investigators determined polymorphisms in genes encoding the dopamine transporter (DAT) protein. The study examined paraquat/maneb combined exposure and did not specifically report results on paraquat exposure alone. [12]
- Gatto et al. (2010) investigated the interaction of alpha-synuclein gene (SNCA) variations with smoking and paraquat exposure. As described by the authors, several single nucleotide polymorphisms (SNPs) and haplotypes in the SNCA promoter have been observed to be associated with familial PD, so the investigators were interested in examining if there may be a gene-environment interaction that makes some individuals more susceptible to pesticide exposure. The study used the PEG case-control design and GIS approach to estimate exposure, but only reported on paraquat even though other studies examined other pesticides. Blood and buccal samples were obtained from study subjects to determine genomic information on SNCA variants. Multivariable unconditional logistic regression was then used to calculate OR for

[12] No substantial elevations in Parkinson's disease risk were observed among study participants with "zero/low" residential maneb and paraquat exposure, regardless of the total number of susceptibility alleles present. However, among subjects with "high" estimated residential exposure to maneb and paraquat together, estimated odds of Parkinson's disease increased with increasing number of susceptibility alleles present, relative to a reference group with no susceptibility alleles and "none/low" maneb and paraquat pesticide exposure. Odds of Parkinson's disease was not elevated among subjects with zero susceptibility alleles and "High" maneb and paraquat exposure (OR = 0.88; 95% CI: 0.22-3.48), but Parkinson's disease odds were elevated among subjects with one susceptibility allele and "high" pesticide exposure (OR = 2.99; 95% CI: 0.88-10.21), and particularly elevated among those with 2 or more susceptibility alleles and above-the-median maneb and paraquat exposure (OR = 4.53; 95% CI: 1.70-12.09), with the latter being statistically significant.

genetic subtypes and effect modification between these subtypes. The investigators then stratified this genotype analysis by paraquat exposure using median exposure value in the control group to identify their high exposure group. Based on this approach, the investigators reported no evidence of a significant positive association between high exposure and PD, stratified by the presence of specific SNCA genotype variants (SNCA 259 Allele – OR = 1.45, 95% CI: 0.59-3.59; SNCA 263 Allele – OR = 1.35, 95% CI: 0.74-2.46, n = 31 exposed cases). The investigators also reported evidence of effect modification between the presence of the SNCA 259 allele. The investigators further explored this interaction by stratifying the analysis by age of onset (≤68 years vs > 68 years) and reported no evidence of a significant positive association in subjects with PD onset ≤68 years (OR = 3.15, 95% CI: 0.74-13.37, n = 13 exposed cases), although the OR was greater than 3.0, and no evidence of an association in subjects with PD onset > 68 years (OR = 0.84, 95% CI: 0.27-2.62, n = 18 exposed cases).

- Wang et al. (2011) investigated the association between PD and pesticide exposure by examining workplace address as part of the general PEG GIS-based approach that used California pesticide use reporting data. Data analyses were performed using unconditional logistic regression models, adjusted for age, sex, ethnicity, education, having a 1st degree family member with PD, and smoking. As compared to those not exposed to paraquat, maneb or ziram, the investigators reported no evidence of a significant association between paraquat only and either workplace address (OR = 1.26, 95% CI: 0.86-1.86, n = 81 exposed cases) or residential address (OR = 0.91, 95% CI: 0.63-1.31, n = 109 exposed cases) and PD. In a combined analysis of workplace/residential address, that did not exclude exposure to maneb and ziram, the investigators reported evidence of a positive association between paraquat exposure and PD (OR = 1.50, 95% CI: 1.03-2.18, n = 162 exposed cases).

- Lee et al. (2012) investigated the interaction between self-reported traumatic brain injury (TBI) and paraquat exposure in the PEG study. The paraquat exposure assessment methodology was similar to that employed by Costello et al. (2009), but also incorporated workplace address in the assessment. The data analysis included 357 cases and 754 controls and used unconditional logistic regression, adjusting for age, gender, smoking, race, county, and education, to investigate the main effects and the interaction between self-reported TBI and paraquat exposure. Based on this approach, the investigators reported evidence of a positive association between PD and paraquat exposure (OR = 1.36, 95% CI: 1.02-1.81, n = 169 exposure-cases). With respect to effect modification, the investigators reported no evidence of a significant positive interaction between paraquat exposure and TBI. Specifically, the association between TBI and PD was 1.70 (95% CI: 0.95-3.04) for never exposed to paraquat subjects and was 3.01 (95% CI: 1.51-6.01) for ever exposed to paraquat subjects. However, this elevation in the association between TBI vs. PD due to the paraquat exposure was not statistically significant (OR for interaction = 1.29, 95% CI: 0.52-3.19).

- Sanders et al. (2017) investigated the potential effect modification between paraquat exposure and single nucleotide polymorphisms (SNPs) in base excision repair (BER) genes. BER is a major pathway for repairing oxidative DNA damage in cells and may play a role in the susceptibility. This study was based on the original PEG case-control study, but continued enrollment through 2013 and included 619 PD cases recruited from clinics and 854 controls recruited using Medicare enrollee lists and residential tax-collector records. The study also used the same GIS-based exposure assessment approach and considered both residential and occupation address with respect to CA pesticide use land-use data. While previous PEG studies focused on other pesticides, Sanders et al.'s exposure assessment considered pesticides considered mitochondrial complex 1 inhibitors and and/or oxidative stressors as reported in Tanner at al., (2011). In order to obtain genetic information, all study subjects provided blood and

saliva samples that were analyzed for SNP selection and genotype. After performing logistic regression, the investigators reported evidence of a positive association between paraquat residential/workplace exposure and PD (OR = 1.54, 95% CI: 1.23-1.93, n = 245 exposed cases). In their examination of interaction between paraquat exposure and genetic susceptibility, the investigators reported no evidence of a significant positive association between paraquat exposure in subjects with no more than 1 risk alleles (OR = 1.13, 95% CI: 0.75-1.70, n = 48 exposed cases) compared to those with 1 or fewer risk alleles and a strong positive association in subjects with 2 or more risk alleles (OR = 2.38, 95% CI: 1.44-3.95, n = 22 exposed cases). Similar associations were reported for other pesticides examined by the investigators, both in their analysis of pesticides and PD and their examination of interaction between exposure and genetic susceptibility.

- Paul et al. (2018) investigated the association between PD and symptom progression and genes that encode for Nuclear factor-erythroid 2 related factor 2 (NFE2L2 SNPs) and peroxisome proliferator activator receptor γ coactivator 1α (PPARGC1α). The study also examined paraquat/maneb combined exposure but did not specifically report results on paraquat exposure alone.

Overall, the eight PEG studies were of moderate quality based on the study quality criteria outlined in the OPP framework. All studies relied on the same general case-control design and included similar cases and controls, although the investigators continued to enroll study subjects in subsequent studies. The primary strengths of PEG were the recruitment of cases with clinically confirmed PD diagnosis. Additionally, the GIS-based approach used in the PEG studies was not subject to recall bias present in other case-control studies that relied on questionnaires to ascertain past exposure to paraquat. While PEG's recruitment of cases was a strength, controls were recruited separately using a population-based approach that relied on Medicare enrollee lists and residential tax-collector records. This approach may have introduced selection bias if cases and controls represent populations with different demographics, lifestyle factors, potential for exposure, and willingness to participate in the study. Similarly, while the GIS-based exposure approach was not subject to recall bias, reported results suggest that the approach had limited ability to investigate exposure to paraquat specifically, rather than general residential/workplace proximity to agricultural land in the three counties of interest. In addition, there is also no published information on the measurement of paraquat residue levels in residential/workplace environments or ground water. Given that this approach has not been validated, it is unclear if being present at addresses within 500 m of agricultural land can provide a reliable estimate of true exposure. The investigators also published limited information on the correlation between different pesticides and control for co-exposure inconsistently when reporting results. The issue of correlation between pesticides is acknowledged by the investigators, but not fully examined in the analyses reported in their eight published articles. In Gatto et al. (2009), for example, the investigators indicate that of the subjects assigned chlorpyrifos exposure based on their residential address, 91% were also exposed to paraquat. Similarly, of the paraquat exposed individuals, 73% were exposed to diazinon, 82% to methomyl, and 80% to propargite. If this degree of correlation is present in PEG, then the study may have limited ability to examine paraquat specific effects with regard to PD.

North American Multicenter PD Study (Moderate Quality: Tanner et al., 2009)

Tanner et al. (2009) conducted a case-control study to investigate the association between occupational and toxicant exposures and parkinsonism in 8 North American movement disorder centers. Cases were recruited from the 8 movement disorder centers between July 1, 2004 and May 31, 2007 and clinically evaluated using the following inclusion criteria: (1) parkinsonism of no known cause, defined as 2 or more signs (resting tremor, bradykinesia, rigidity, and postural reflex impairment), 1 of which must be resting tremor or bradykinesia; (2) diagnosis within 8 years to minimize the risk of survival bias; and (3) absence of dementia. Controls were frequency-matched (age, sex, location) and were either nonblood

relatives or acquaintances of cases (excluding spouses) or nonblood relatives or acquaintances of other patients of the 8 movement clinics. Additional controls were also recruited using a commercial list of telephone numbers.

Study subjects were informed that the aim of the study was to investigate environmental risk factors for parkinsonism. They were then interviewed using a standardized computer-assisted phone interview to collect information on potential risk factors, including questions on the use tobacco, caffeine, and alcohol, head injury, and occupational history. To determine toxicant exposure, the investigators identified specific occupations and exposures a priori and included more detailed follow-up questions in their standardized questionnaire. This included pesticide use in general and 8 specific pesticides: 2,4-D, paraquat, permethrin, dieldrin, mancozeb, rotenone, maneb, and diquat. After obtaining questionnaire data on risk factors, job history, and toxicant exposures, the authors evaluated the association with occupations, job tasks, and exposures using the Wilcoxon rank sum test for continuous variables and the Fisher exact test for categorical variables. Logistic regression was also used to calculate ORs and adjust for age, sex, race/ethnicity, smoking, caffeine, alcohol, head injury, and duration of task.

A total of 519 cases and 511 controls completed the questionnaire (91% of enrollees). Based on these cases and controls, ORs are reported for 33 standard occupational categories and job tasks, including pesticide use. For pesticide use in general, the investigators reported evidence of a positive association with parkinsonism (OR = 1.90, 95% CI: 1.12-3.21, based on 44 cases). For the 44 cases reporting pesticide use, the investigators examined the association for the 8 specific *a priori* pesticides and reported no evidence of a significant positive association between paraquat and parkinsonism (OR = 2.80, 95% CI: 0.81-9.72, based on 9 exposed cases). While not statistically significant, the OR estimate was moderately strong (*i.e.,* OR > 2.0).

Overall, Tanner et al. (2009) was of moderate quality based on the study quality criteria outlined in the OPP framework. The investigators clinically confirmed PD cases, but used a more limited exposure assessment approach that relied on a questionnaire that was not validated and only enabled analysis of ever/never use of paraquat. The study may also be subject to recall bias because cases and controls may recall previous use of paraquat and other pesticides differently. Lastly, the study included only 9 PD cases that reported paraquat use, so it may not provide a reliable effect estimate due to the small number of exposure cases.

Netherlands PD Study (Moderate Quality: Van der Mark et al., 2014; Brouwer et al., 2017)

A hospital-based case-control study was conducted in the Netherlands to investigate risk factors associated with PD. The study initially examined possible risk reductions associated with intake of coffee, alcohol, and cigarettes, but also investigated the relationship between pesticides and PD. Cases and controls were recruited from 5 hospitals in 4 regions of the Netherlands between 2010-2012. Cases were Parkinson's disease patients identified by doctors practicing in the neurology department in each of 5 hospitals. For each case, 2 matched controls were recruited from a patient population of adults with non-neurodegenerative symptoms (median nerve neuropathy, ulnar nerve neuropathy, thoracic and lumbar disc disease, sciatica) seen at the same neurology department as each case. The investigators enrolled 444 cases and 876 controls in the study, representing 45% of eligible cases and 35% of eligible controls, respectively. Among those that provided a reason for their non-participation (50% of non-participants), a health-related excuse and non-interest were frequently cited. Cases and controls were matched on gender, age, and time-of-diagnosis, and logistic regression was used to estimate ORs and adjust for confounding.

The study was used to examine the occupational pesticide exposure (Van der Mark et al., 2014) and residential pesticide exposure (Brouwer et al., 2017). In both subsequent investigations, study authors

considered pesticide use in general and specific pesticides, including paraquat. These studies are described below:

- Van der Mark et al. (2014) evaluated the association between years of occupational paraquat exposure and PD using a conditional logistic regression model that adjusted for cigarette smoking, coffee consumption, occupational skill and status, and endotoxin exposure. Exposure to paraquat was estimated by first linking participants' self-reported crops grown at their farm to a crop-exposure matrix. In this matrix, per-decade estimations are given for the percentage of farms that applied paraquat on a type of crop and the yearly frequency of application. Expert judgment regarding the probabilities and frequencies of paraquat application were provided by 2 former farm workers who estimated probability and frequency of use of paraquat allowed for use on potatoes, cereals, beets, maize, tulip bulbs and fruit, back to the year 1960. Estimates for other field crops, vegetables, and flowers in green houses were derived from data from Statistics Netherlands that gathered statistics on use of specific active ingredients after 1995. For periods prior to 1995, probability and frequency of application for the crops not covered by the experts were extrapolated from trends for crops for which expert estimations were available, though details were not provided. For analysis, estimated paraquat exposures were categorized into 3 levels: no exposure (411 cases and 818 controls), exposure between 0 and 3.8 years (18 cases and 29 controls), and exposure greater than 3.8 years (15 cases and 29 controls). Based on this approach, the investigators reported no evidence of a significant positive association. The adjusted odds ratios for association between PD and paraquat exposure were as follows, with "no exposure" being the reference group: > 0-3.8 years (OR = 1.42, 95% CI: 0.71-2.85); > 3.8 years (OR = 1.01, 95% CI: 0.48-2.12).
- Brouwer et al. (2017) investigated the association of environmental exposure to pesticides and PD. Pesticide exposure was assessed using a GIS-based approach that relied on residential address information and land-use data on crops in the Netherlands. Land-use datasets from each year since 1961 defined areas likely treated with specific pesticides, based on expert judgement, within circular rings around the residential addresses, and served as a proxy for environmental pesticide exposure. For each residential address (corresponding to a subject in the study) and each pesticide, the estimated crop area present within 0-100 m (also within 0-50 m and within > 50-100 m) was multiplied by the estimated probability and frequency of pesticide use to estimate the total surface area in hectares (ha) treated with the pesticide during the specific year. These estimates were summed across years (up to the year preceding case-diagnosis) to obtain an estimate of the subject's cumulative environmental exposures (ha-years). For control subjects, cumulative environmental exposures were calculated through the year preceding the diagnosis year of the matched case. Conditional logistic regression was used to determine adjusted ORs. Based on this approach, paraquat environmental exposure within 0-100 m of residence, there was no evidence of an association when comparing subjects ever exposed and not exposed (OR = 1.00, 95% CI: 0.73 - 1.36). In further analysis based on tertiles, there was no evidence of a significant positive association among subjects in the highest exposure tertile and those not exposed (OR = 1.46, 95% CI: 0.95 – 2.23) and no association in the middle exposure tertile (OR = 0.93, 95% CI: 0.61 – 1.40) or low exposure tertile (OR = 0.74, 95% CI: 0.47 – 1.16). A test of trend among the tertiles was not statistically significant (p = 0.19).

Van der Mark et al. (2014) and Brouwer et al. (2017) assessed occupational and non-occupational paraquat exposure, respectively, and were of moderate quality based on the study quality criteria outlined in the OPP framework. Both studies utilized the same underlying dataset from a hospital-based case-control study that recruited cases and controls from the same hospital neurology departments. While this recruitment approach was a strength of the studies, participation was relatively low, with 45% of eligible

cases and 35% of eligible controls participating. In addition, Van der Mark et al. (2014) assessed potential occupational paraquat exposure using a crop-exposure matrix and Brouwer et al. (2017) assessed potential environmental paraquat exposure by linking residential address to land-use data. Both these approaches relied on expert judgement to assign paraquat usage to specific crop types and may be subject to misclassification. Additionally, the GIS-based exposure approach used in Brouwer et al. (2017) lacked land-use data on pesticide application and instead estimated exposure more generically using spatial crop information and expert judgement on the frequency/probability of specific pesticide use these crops. As with the PEG studies, this approach may be limited in assessing exposure to paraquat specifically if there is a strong degree of correlation across pesticides. The investigators did not adjust for pesticide co-exposure in their statistical analysis, but reported a median Spearman correlation coefficient of 0.63 (range 0.36-1.00) for the 21 pesticides that were examined in their primary analysis. For paraquat specifically, the median Spearman correlation coefficient was 0.43 (range 0.36-0.99), based on values reported in Figure A1 of Appendix to Brouwer et al. (2017), suggesting correlation across pesticides was present in their study.

Taiwan PD Study (Moderate Quality: Liou et al., 1997)

Liou et al. (1997) conducted a hospital-based case-control study and evaluated duration of paraquat exposure among other environmental risk factors for Parkinson's disease in Taiwan. Parkinson's disease cases (n = 120) and controls (n = 240) were selected from patients at the National Taiwan University Hospital in Taipei between July 1993 and June 1995. Controls were matched to cases on age and sex. Assessment of duration of past paraquat exposures (among other pesticide exposures) was based on self-report using a survey administered during a structured interview. After obtaining data, conditional logistic regression was used to estimate ORs for paraquat and other risk factors of interest. Based on this approach, the investigators reported no evidence of an association in the 1-19 years of paraquat use category (OR = 0.96, 95% CI: 0.24-3.83, n = 7 exposed cases) but evidence of a strong positive association for the ≥20 years paraquat use category (OR = 6.44, 95% CI: 2.41-17.2, n = 24 exposed cases). The investigators more generally examined duration of herbicides/pesticides and reported no evidence of a significant positive association in the 1-19 years of use category (OR = 1.41, 95% CI: 0.52-3.85, n = 14 exposed cases) and evidence of a strong positive association for the ≥20 years use category (OR = 6.72, 95% CI: 2.62-17.21, n = 32 exposed cases). The investigators further examined the association within subjects reporting use of herbicides/pesticides and reported that participants reporting use of paraquat and other herbicides/pesticides had twice the odds of PD, compared with those who had been exposed to herbicides/ pesticides other than paraquat (OR 2.0, p-value < 0.01)

Overall, Liou et al. (1997) was of moderate quality based on the study quality criteria outlined in the OPP framework. The primary strength of the study was that it used a hospital-based case-control design to enroll PD patients as patients and match them to controls that were recruited from the same hospital. The exposure assessment, however, relied on a general questionnaire on pesticide use and may have introduced recall bias if cases and controls recall their past pesticide use differently.

Western Washington State Study (Low Quality: Firestone et al., 2005 and 2010)

This population-based case-control study in Western Washington State enrolled 404 incident PD cases and 526 age- and sex-matched control participants from the Group Health Cooperative (GHC) and the University of Washington. Paraquat exposure was ascertained from self-reported work histories (including job titles and industrial toxicant exposures). A panel of neurologists confirmed case status. Exposure to pesticides, including paraquat, was self-reported along with exposure to other workplace toxicants. Unconditional logistic regression models were used for both data analysis, adjusting for age, smoking status, sex (only included in the 2005 data analysis; the 2010 data analysis only included males), and ethnicity (only included in the 2010 data analysis). Firestone et al. (2005) reported no evidence of a

significant positive association (OR = 1.67, 95% CI: 0.22-12.76) and Firestone et al. (2010) reported no evidence of an association (OR = 0.9, 95% CI: 0.14-5.43); however, few subjects reported paraquat use (2 cases in the 2005 study and 2 cases in the 2010 study).

Given the small number of exposed cases (n = 2 exposed cases per study), Firestone et al. (2005 and 2010) were of low quality because they provide insufficient information on the association between paraquat exposure and PD and contributed limited weight in OPP's evaluation of findings.

East Texas Case-Control Study (Low Quality: Dhillon et al., 2008)

Dhillon et al. (2008) conducted a case-control study set in an East Texas population to evaluate associations between Parkinson's disease and self-reported exposure to paraquat among other pesticide products, organic pesticides, and other occupational and environmental exposures. The study base for this case-control study consisted of residents of counties located in the East Texas region. Cases (n = 100) were recruited from a cohort of 800 Parkinson's disease patients followed within a neurology practice at a local medical center neurological institute located in East Texas. Inclusion criteria included the following: age 50+ years, living in the East Texas region, and completing the interview survey. Control participants (n = 84) were selected from the same neurology practice as the cases, met the same inclusion and exclusion criteria, and had no history of Parkinson's disease. Participants self-reported "Ever Personally Used/Mixed or Applied" paraquat on a standardized questionnaire. The Chi-square test was used to evaluate the association between exposure and disease. The obtained odds ratio and its 95% confidence interval were not adjusted for potential confounders. Dhillon et al. (2008) reported no evidence of a significant positive association between ever having personally used, mixed, or applied paraquat and odds of Parkinson's disease (OR = 3.5, 95% CI: 0.4, 31.6). However, only 5 study participants reported paraquat exposure (4 cases and 1 control) and the statistical power to evaluate the association was correspondingly limited.

Given the small number of exposed cases (n = 4 exposed cases) and the weakness of statistical method used for data analysis, Dhillon et al. (2008) was of low quality and provides inadequate information on the association between paraquat exposure and PD and contributed limited weight in OPP's evaluation of findings.

British Columbia Case-Control Studies (Low Quality: Hertzman et al., 1990, 1994)

- Hertzman et al. (1990) conducted a case-control study in the rural Kootenay region of British Colombia to investigate the associations between PD and self-reported exposure to occupational and environmental exposures including paraquat. At the time of the study, Kootenay had a population of around 80,000 and forestry, agriculture, and smelting were industries in the region. The investigators identified potential cases by contacting physicians practicing in the region, and requesting that they identify their Parkinson's disease patients. These patients were then contacted and invited to participate in the study. Potential controls participants were randomly selected from electoral rolls (92% of all adult residents of the area are reportedly on the regional rolls). Potential controls were then contacted by mail and asked to complete and return the questionnaire if they were over 50 years of age. Seventy-eight percent of the potential controls (n = 129) returned a completed questionnaire, and thus constitute the control group. The analysis was, however, restricted to cases and controls between age 50 and 79 years of age (57 cases and 122 controls). Hertzman et al. (1990) only had 4 exposed cases and no exposed controls so the study population, so the study could not calculate an effect estimate or adjust for confounding.

Given the small number of exposed cases (n = 4), Hertzman et al. (1990) was low quality and provides insufficient information on the association between paraquat exposure and PD and contributed limited weight in OPP's evaluation of findings.

- Hertzman et al. (1994) conducted a second case-control study of PD in the Okanagan Valley of British Columbia, which is a horticultural region with a population of approximately 200,000 people at the time of the study. The study aimed to build on the previous work reported in Hertzman et al. (1990) by focusing on a region where they expected there be a high prevalence of pesticide use in orchards. The study population consisted of PD cases who were identified by contacting physicians in the region, including 160 general practitioners, 3 neurologists, and 25 internal medicine specialists (6 doctors refused to participate). Based on this recruitment approach, 159 potential cases were identified and 142 cases were enrolled in the study after medical examination to confirm their PD diagnosis. Two control groups were included in the study. The first consisted of individuals aged 45-80 years were randomly selected from electoral rolls which were estimated to cover 92% of the regional population and be representative of the Okanagan general population. The second control group consisted of individuals with chronic cardiac disease, who were also recruited through regional physicians. Participation rates in the voter control group (n = 124 study subjects) and chronic cardiac disease patients (n = 121 study subjects) were 61% and 79%, respectively. All cases and controls were interviewed to obtain information on personal, occupational, and chemical exposure. This included 79 different pesticides that were used in the orchard industry in the region. Statistical analysis was then performed to calculate ORs of exposure to occupational exposure to different chemicals, including paraquat. The specific statistical approach was not provided, but the investigators do report that they computed Fisher exact test statistics and used a hierarchical analysis to model exposure by individual chemical, chemicals used together, and chemical classes. Based on this approach, the investigators reported no evidence of a significant positive between paraquat exposure and PD, based on either control group (PD Cases vs. Voter Control Group – OR = 1.25, 95% CI: 0.34-4.63; PD Cases vs Chronic Cardiac Disease Controls – OR = OR = 1.11, 95% CI: 0.32-3.87, n = 6 exposed cases. However, there were only 6 exposed cases, so paraquat exposure appears to be very limited in the investigator's study population.

  Given the small number of exposed cases (n = 6), Hertzman et al. (1994) was of low quality and provides insufficient information on the association between paraquat exposure and PD and contributed limited weight in OPP's evaluation of findings.

PD Registry-Based Studies

Nebraska PD Registry Study (Low Quality: Wan and Lin, 2016)

Wan and Lin (2016) conducted an ecologic study that investigated the association between county-level incidence of PD in Nebraska and country-level pesticide exposure, including paraquat, based on GIS land-use and pesticide usage data. The study utilized the Nebraska PD registry to identify PD cases and characterize their spatial distribution and county-level incidence. Nebraska established a PD registry as a result of 1996 state legislation that requires reporting of new Parkinson's cases diagnosed since January 1, 1997, although the registry also includes prevalence data on persons with PD diagnosis before 1997. The Nebraska Department of Health and Human Services maintains the PD registry and uses various sources to identify, including physician-required reports on patients who are newly diagnosed with PD within 60 days of diagnosis and semiannual reporting from pharmacies on patients who received 1 or more anti-PD medications. Based on this approach, 6,557 PD incidence cases were identified from 1997 through 2008. County-level exposure was estimated by the investigators using a GIS-based approach that combined

2005 land-use data on 19 major crop categories in Nebraska with county-level pesticide use information on 20 pesticides, including paraquat. Nebraska, however, does not maintain data on pesticide use information, so usage was derived using annual estimates from USGS. After estimating county-level PD incidence and pesticide usage, the investigators performed OLS linear regression at both the county-level and by further grouping counties based on a spatial analysis used to identify hot spots/cold spots. Based on this approach, the investigators reported no association between country-level PD incidence and any of the pesticides investigated (quantitative results not reported). The second analysis introduced a dummy variable into their regression model that adjusted for a reported hotspot of 4 counties where the incidence of PD was observed to be higher. This second analysis was conducted separately for each of 20 pesticides and stratified by quartile of exposure. Rate ratios were not calculated, but the investigators report their regression coefficients relative to quartile 1 for each pesticide. The investigators report statistically significant coefficient for Quartile 3 and 4 of paraquat exposure, but not Quartile 2 (Q2 vs Q1: 0.343, $p > 0.05$); Q3 vs Q1: 0.255, $p < 0.05$; Q4 vs Q1: 0.231, $p < 0.05$). The investigators, however, only highlighted findings that exhibited an increase an PD incidence as quartile of exposure increased, which did not include paraquat.

Overall, Wan and Lin (2016) was of low quality based on the study quality criteria outlined in the OPP framework. The primary reason for this determination is that the study used an ecologic design that does not provide individual-level information on paraquat exposure and PD. In addition to the general limitation of the study's ecologic design, the exposure assessment approach was limited with respect to evaluating paraquat exposure because it relies on generic information on land-use data and pesticide use data. In addition, the study used OLS linear regression to evaluate the association between PD incident rate and various pesticides and other factors. It is generally more appropriate to use Poisson regression to analyze count and rate data, so there appear to be issues with the investigators' statistical approach.

3.1.2 Evaluation of Findings

The association between paraquat exposure and PD was investigated in 13 study populations that may have been exposed to paraquat as a result of their occupation or living in rural communities that are in close proximity to agricultural land where paraquat may have been applied. A summary of the key effect estimates from these studies is provided in **Figure 2** at the end of this section.

OPP's evaluation of findings and overall conclusions on the association between paraquat exposure and PD are summarized in the sections below for occupational and non-occupational study populations. Occupational and non-occupational study populations are discussed separately because these populations are likely to be exposed through different exposure pathways that vary in terms of magnitude, frequency, and duration. Occupational study populations, in particular, are more likely to experience exposure as a result of direct use of paraquat in agriculture, whereas non-occupational study populations may be exposed to lower-level environmental concentrations.

Occupational Paraquat Exposure

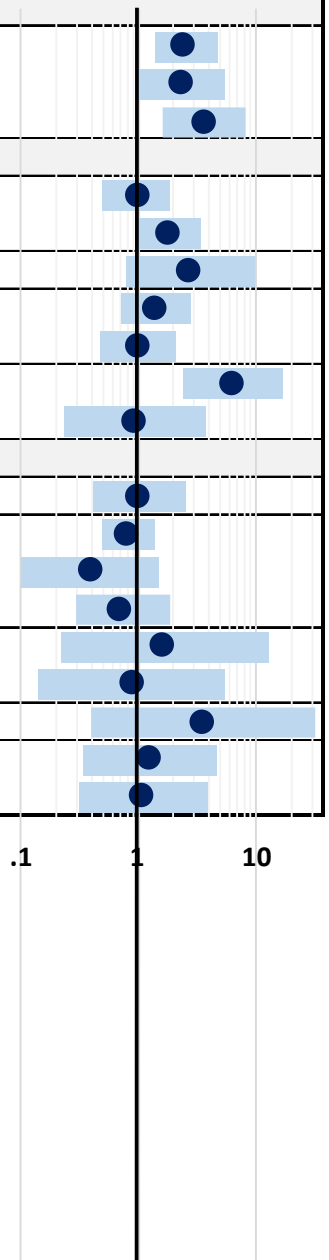
The relationship between occupational paraquat exposure and PD was investigated in 11 study populations, including AHS/FAME, the French AGRICAN, a follow-up study of the cohort by the Washington State Department of Public Health, and eight hospital-based studies. A summary of the

primary findings on these study populations, including design, results, and assessment of quality, is provided in the **Table 5** below.[13]

[13] Secondary articles further explore potential effect modification by environmental, dietary, and behavioral factors, but do not provide additional, independent information on the association between paraquat and PD. Secondary articles further expand upon, characterize, and extend the findings of primary articles and are summarized in *Summary of Reported PD Findings* **Figure 2** and **Appendix A, Table A-1**.

Table 5: Summary of the Primary PD Findings from Occupational Study Populations, including Design Elements, Results, and Assessment of Quality, Grouped by Quality Rating.

Study Population	Primary Article	Design	Exposure	Outcome	Comparison	# Exposed Cases	Effect Estimate (OR, 95% CI)
High Quality							
AHS/FAME [1]	Tanner, et al., 2011	Nested Case-Control	Questionnaire	Clinical Exam	Ever/Never (Incident + Prevalent Cases)	23	
					≤ Median (8 Lifetime Days)	10	
					> Median (8 Lifetime Days)	13	
Moderate Quality							
AHS	Kamel, et al., 2007	Cohort/Cross-Sectional	Questionnaire	Questionnaire	Ever/Never (Incident Cases)	11	
					Ever/Never (Prevalent Cases)	14	
NA Multicenter	Tanner et al., 2009	Case-Control	Questionnaire	Clinical Exam	Ever/Never	9	
Netherlands	van der Mark, et al., 2014	Case-Control	Questionnaire	Clinical Exam	>0-3.8 years	18	
					>3.8 years	15	
Taiwan	Liou, et al., 1997	Case-Control	Questionnaire	Clinical Exam	≥20 years using paraquat/Never	24	
					1-19 years using paraquat/Never	7	
Low Quality							
French AGRICAN	Pouchieu et al. 2018	Cross-Sectional	Questionnaire	Questionnaire	Ever/Never (Adjusted)	244	
WA Dept Public Health	Engel et al. 2001	Case-Control	Questionnaire		Ever/Never	20	
					Second Tertile (vs Tertile 1)		
					Third Tertile (vs Tertile 1)		
Western WA State	Firestone, et al. (2005)	Case-Control	Questionnaire	Clinical Exam	Ever/Never	2	
	Firestone, et al. (2010)	Case-Control	Questionnaire	Clinical Exam	Ever/Never	2	
East Texas	Dhillon, et al., 2008	Case-Control	Questionnaire	Clinical Exam	Ever/Never	4	
British Columbia	Hertzman et al., 1994	Case-Control	Questionnaire	Clinical Exam	Ever/Never (Voter Controls)	6	
					Ever/Never (Disease Controls)	6	



[1] Secondary articles included: Goldman et al., 2012; Furlong et al., 2015; Kamel et al., 2014.

The AHS (Kamel et al, 2007) and FAME (Tanner et al, 2011) studies provide the most relevant evidence on the association between paraquat and U.S. exposure and were designated to be of moderate and high quality, respectively. Both of these studies were based on the AHS study cohort and had overlap in the PD cases that were included in their analysis. Their primary strengths included AHS's focus on agricultural exposure in the U.S. and ability to recruit exposed and unexposed individuals from well-characterized agricultural populations in Iowa and North Carolina. The AHS studies also obtained information on demographic and lifestyle factors that could act as confounders and further explored potential effect modification of genetic factors and occupational hygiene practices. The results of AHS and FAME provide some evidence of a positive association between self-reported paraquat use and PD; however, the investigators reported somewhat conflicting findings for incident and prevalent PD cases. Specifically, the AHS Kamel et al. (2007) study reported a non-significant positive association with *prevalent* cases, but no association with *incident* cases. This is relevant to the evaluation of evidence because the prevalent cases are more likely to be subject to recall bias if self-reported pesticide use is not independent from their previous diagnosis of PD. For example, PD cases may be subject to recall bias if they recall past exposure more accurately or incorrectly self-report the use of paraquat relative to controls. The Tanner et al (2011) FAME study, nested within AHS, does not help clarify this issue because the investigators did not examine incident and prevalent PD cases separately in their statistical analysis. Moreover, FAME may also have introduced additional recall bias because a separate exposure assessment was conducted after cases and controls were enrolled in the study.

The Tanner et al (2011) FAME study results provide additional characterization of the potential relationship between paraquat exposure and PD in AHS. First, the investigators further stratified their analysis using median duration paraquat use and observed the OR increase from 2.4 (95% CI: 1.0-5.5, n = 10 exposed cases) in individuals reporting ≤ median duration of 8 lifetime days of paraquat use to 3.6 (95% CI: 1.6-8.1, n = 13 exposed cases) in individuals reporting > median lifetime days of paraquat use. However, this analysis does not constitute a formal analysis of the dose-response relationship between paraquat exposure and PD. Moreover, the number of exposed individuals in each category was relatively small and there is no rationale provided for using the median of 8 lifetime days of paraquat use as a cut-point for making comparisons. This latter consideration is relevant because it is unclear that 8 lifetime days of exposure is biologically meaningful in terms of the magnitude and frequency of exposure. Second, the FAME investigators examined several potential effect modifiers and reported that the OR for paraquat exposure increased when also considering (i) genetic susceptibility, (ii) decreased dietary intake of fats that may be protective of PD, and (iii) use of PPE (*i.e.,* gloves) when handling pesticides. However, any causal association with these factors has not been established, some factors may also be subject to recall bias (dietary intake and PPE), and the number of exposed study subjects was small. As such, further replication of results is needed in other study populations to have confidence in these findings.

AHS reported no evidence of an association between ever-never use of paraquat and dream enacting behavior in a more recent prospective study based on phase 4 follow-up of the AHS in cohort in 2013-2015 (Shrestha et al., 2018). This study did not evaluate PD directly and is not summarized in **Table 5** above, but was determined to be moderate quality and collected information on self-reported dream enacting behavior based on follow-up of the AHS cohort in 2013-2015. The relationship between dream enacting behavior and other non-motor symptoms is an area of active research in clinical and epidemiologic research. The AHS, for example, has more generally examined the association between non-motor symptoms and PD based on cross-sectional analysis of 191 men who reported physician-diagnosed PD during phase 4 follow-up (Shrestha et al., 2017). While this analysis was cross-sectional, a strong dose-response relationship between prevalence of PD and prevalence of dream-enacting behavior was observed amongst men in the AHS study cohort: specifically, using men reporting no dream-enacting behavior in the AHS cohort as a reference group, the ORs of reporting physician-diagnosed PD increased

with frequency of dream enacting behavior: < *3 times in life* – OR = 3.9 (1.7-8.9), n = 6 prevalent PD cases*; < once per month* – OR = 5.2 (3.1-8.5), n = 18 prevalent PD cases; *1 – 3 per month* – OR = 15.6 (9.2-26.4), n = 18 prevalent PD cases*; ≥ Once per week* – OR = 19.2 (11.0-33.5), n = 17 prevalent PD cases. This avenue of inquiry in the AHS may be useful to continue, but suggests at this time that there is no evidence of an association between paraquat exposure and prodromal PD symptom dream enacting behavior.

The two other agricultural study populations identified included the French AGRICAN cohort (Pouchieu et al., 2018) and Washington State Department of Public Health study population (Engel et al., 2001). Both studies reported no evidence of an association; however, they contributed less weight-of-evidence in OPP's assessment of the epidemiologic literature studies because they had important limitations (*e.g.,* cross-sectional design of Pouchieu et al., 2018, and 25% participation rate in Engel et al., 2001) and were both determined to be of low quality.

Eight hospital-based studies examined potential occupational paraquat exposure and PD. Five of these studies were low quality and contributed limited weight in OPP's assessment (Firestone et al. 2005 and 2010; Dhillon et al., 2008; and Hertzman et al., 1990 and 1994). Results of the remaining three studies, all rated moderate, were mixed and may be subject to recall bias, limitations in their exposure assessment approach, and potential selection bias. Liou et al.(1997) reported the strongest positive association based on individuals reporting ≥20 years of paraquat use in Taiwan. A similar association was observed for use of herbicides/pesticides more generally in the Liou et al.(1997) study, however, so it is unclear if the association is directly attributable to paraquat use, overall pesticide use considered more broadly, or another confounding factor correlated with reporting pesticide use. Tanner et al. (2009) also reported a non-significant positive association in their multicenter PD study. However, this reported association was based on only 9 exposed cases and was also similar to the reported associations for both other specific pesticides and pesticide use more generally. In contrast, Van der Mark et al. (2014) reported no association between occupational paraquat exposure and PD, based on self-reported crop activities and crop-exposure matrix. This approach is less likely to be subject to recall bias but may be subject to misclassification because exposure was determined by expert judgement and applied to all individuals for a particular job code/crop group.

Overall, there is limited, but insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between occupational paraquat exposure and PD. The conclusion that the overall evidence is limited, but insufficient is based on somewhat conflicting findings in the AHS cohort – with respect to incident and prevalent cases – and the potential for recall bias. The results of other studies outside AHS were also mixed and subject to limitations.

Studies of the AHS cohort, including Kamel et al. (2007) and the FAME studies from Tanner et al (2011), were determined to be the most relevant because of their focus on well-characterized agricultural populations in Iowa and North Carolina that are likely to experience agricultural exposure to pesticides. Kamel et al. (2007) reported a non-significant positive association with *prevalent* cases (OR = 1.8; 95% CI, 1.0-3.4, n = 14 paraquat exposed cases), but no association with *incident* cases (OR = 1.0; 95% CI, 0.5-1.9, n = 11 paraquat exposed cases). In contrast, the FAME study from Tanner et al. (2011) reported evidence of a moderately strong positive association for ever use of paraquat (OR = 2.5, 95% CI, 1.4-4.7, n = 23 exposed cases) considering prevalent and incident cases together (which makes interpretation difficult as both are subject to different limitations). Tanner et al. (2011) and the other FAME studies improved upon Kamel et al. (2007) by confirming PD diagnosis but were based on the same PD cases as the Kamel et al (2007) AHS study and share similar limitations, including the relatively small number of paraquat exposed PD cases (23 exposed cases) and the potential for recall bias. In addition, the Tanner et al. (2011) in the FAME study combined incident and prevalent PD cases in its statistical analysis and thus

does not provide additional clarification of the findings reported in Kamel et al. (2007). Finally, in a more recent prospective study based on follow-up of the AHS in cohort in 2013-2015, Shrestha et al. (2018) also reported no evidence of an association between ever-never use of paraquat and dream enacting behavior. Dream enacting behavior is a common precursor to PD and the lack of association between use of paraquat and dream enacting behavior as reported in Shrestha et al. (2018) provides additional characterization of potential PD risk within the AHS cohort.

No association between paraquat exposure and PD was observed in the other agricultural study populations that included the French AGRICAN cohort and the Washington State Department of Public Health Study, although these studies were given less weight in this assessment because they had important limitations (*i.e.,* cross-sectional design of Pouchieu et al., 2018, and 25% participation rate in Engel et al., 2001) and were determined to be of low quality. Finally, there were eight case-control studies that examined the potential association between occupational paraquat exposure and PD. Five of these eight case-control studies were low quality and given limited weight in OPP's assessment. Results of the remaining three case-control studies, all rated moderate, were mixed with one study reporting evidence of a positive association (Liou et al., 1997), one study reporting a non-significant positive association based on only 9 exposed cases (Tanner et al., 2009), and one study reporting no evidence of an association (Van der Mark et al., 2014). These studies may also be subject to recall bias, limitations in their exposure assessment approach, and potential selection bias that introduce additional uncertainty.

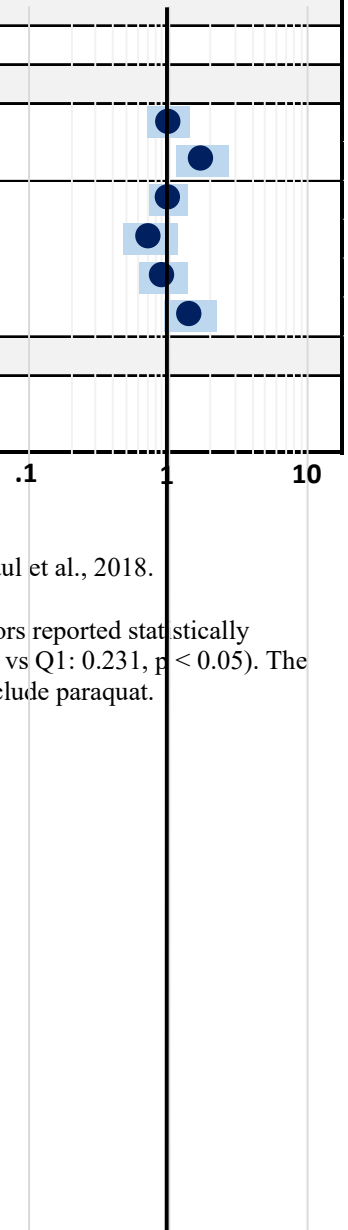
Non-Occupational Paraquat Exposure

The relationship between non-occupational paraquat exposure and PD was investigated in three study populations, including the PEG Study in California (eight articles), the Netherlands PD Study (one article), and a study of the Nebraska PD registry (one article). A summary of the primary findings on these study populations, including design, results, and assessment of quality, is provided in the **Table 6**. [14]

[14] Secondary articles further explore potential effect modification by environmental, dietary, and behavioral factors, but do not provide additional, independent information on the association between paraquat and PD. Secondary articles further expand upon, characterize, and extend the findings of primary articles and are summarized in *Summary of Reported PD Findings* **Figure 2** and **Appendix A, Table A-1**.

Table 6: Summary of the Primary PD Findings from Non-Occupational Study Populations, including Design Elements, Results, and Assessment of Quality, Grouped by Quality Rating.

Study Population	Primary Article	Design	Exposure	Outcome	Comparison	# Exposed Cases	Effect Estimate (OR, 95% CI)
High Quality							
Moderate Quality							
CA PEG [1]	Costello, et al. (2009)	Case-Control	GIS-based Assessment	Clinical Exam	Ever/Never	149	
					Ever/Never (Paraquat+Maneb)	88	
Netherlands	Brouwer, et al. (2017)	Case-Control	GIS-based Assessment	Clinical Exam	Ever/Never	181	
					First Tertile	44	
					Second Tertile	58	
					Third Tertile	79	
Low Quality							
Nebraska PD Registry [2]	Wan and Lin, 2016	Ecologic	GIS-based Assessment	PD Registry			



[1] Secondary articles included: Gatto et al., 2009; Ritz et al., 2009; Gatto et al., 2010; Wang et al., 2011; Lee et al., 2012; Sanders et al., 2017; Paul et al., 2018.

[2] Rate ratios were not calculated, but the investigators report their regression coefficients relative to quartile 1 for each pesticide. The investigators reported statistically significant coefficients for Quartile 3 and 4 of paraquat exposure, but not Quartile 2 (Q2 vs Q1: 0.343, $p > 0.05$); Q3 vs Q1: 0.255, $p < 0.05$; Q4 vs Q1: 0.231, $p < 0.05$). The investigators, however, only highlighted findings that exhibited an increase an PD incidence as quartile of exposure increased, which did not include paraquat.

The PEG Study was of moderate quality and first examined the association between paraquat exposure and PD in Costello et al. (2009). More broadly, the PEG investigators have included analysis of paraquat in a total of eight articles that examined various measures of exposure using a GIS-based approach (residential address, residential/ workplace address) and additional questionnaire information on residential well water. Results of PEG with respect to paraquat specifically are reported in five of these eight articles and are mixed, based on different measures of exposure and consideration of co-exposure to other pesticides. Briefly:

- Costello et al. (2009) reported no evidence of an association with residential address in analysis that stratified to paraquat-only exposure;
- Gatto et al. (2009) reported no evidence of an association with residential well water in analysis not stratified to paraquat-only exposure;
- Wang et al. (2011) reported no evidence of an association with either residential address or workplace address in an analysis that stratified to paraquat-only exposure; however, evidence of a positive association was reported for residential/occupational address combined in an analysis that was not stratified to paraquat-only exposure;
- Lee et al. (2012) reported evidence of a positive association was reported for residential/workplace address combined in an analysis that was not stratified to paraquat-only exposure; and
- Sanders et al. (2017), which recruited additional cases through 2013, reported a positive association when they considered residential/workplace address combined in an analysis not stratified to paraquat-only exposure.

Additional PEG studies examined potential effect modification between pesticide exposure and other factors, including TBI (Lee et al., 2012) and genetic susceptibility (Gatto et al., 2010; Sanders et al., 2017; Paul et al., 2018). These studies make use of the same general GIS-based exposure assessment approach and may have limited ability to investigate the relationship with paraquat if there is a strong degree of correlation across different pesticides. As such, these investigations may be unable to distinguish between factors associated with geographic proximity to agricultural land and living, pesticide use in general, and specific pesticides.

The other available study on non-occupational paraquat exposure and PD was the Netherlands PD Study (Brouwer et al., 2017). This study was of moderate quality and reported no evidence of an association between paraquat exposure in their primary analysis of ever/never exposure. The investigators further stratified their analysis by tertiles of paraquat exposure and reported the highest tertile of exposure, although not significant, had the highest risk estimate. The investigators examined the trend across these tertiles and reported no evidence of a significant trend. The Netherlands PD study shares many similarities with PEG Study conducted in California. PD cases were clinically confirmed and recruited from select clinics and the exposure assessment used a GIS-based approach that was not subject to recall bias potentially present in other studies identified for this review. An additional strength of their investigation was that controls were recruited from the same neurology clinics and are more likely to represent the same underlying study population. With regard to limitations, the study had a low participation rate (45% for cases and 35% in controls) and relied on a GIS-based exposure approach that lacked land-use data on pesticide application and instead estimated exposure more generically using spatial crop information and expert judgement on the frequency/probability of specific pesticide use of these crops.

The remaining Nebraska PD Registry Study by Wan and Lin (2016) was of low quality because its ecologic design does not provide individual-level information on either paraquat exposure or the PD

outcome. As such, the study contributed limited weight in OPP's evaluation of epidemiologic findings. While the study was more limited due to its ecologic design, the use of the Nebraska PD registry was a key strength that is not currently available in other U.S. states. This type of registry data is particularly helpful for characterizing the more general characteristics of PD incidence in the state of Nebraska. For example, Table 3 of Wan and Lin (2016) is excerpted below in **Table 7** and provides useful information on demographic characteristics that might be of interest when evaluating the relationship between paraquat exposure and PD. As shown, the unadjusted rate of PD incidence in Nebraska appears to be highest in counties with more poverty and greater rurality. While this rate is not adjusted for age and other factors, it suggests that rurality must be carefully considered in the design of studies that rely on GIS-based approaches.

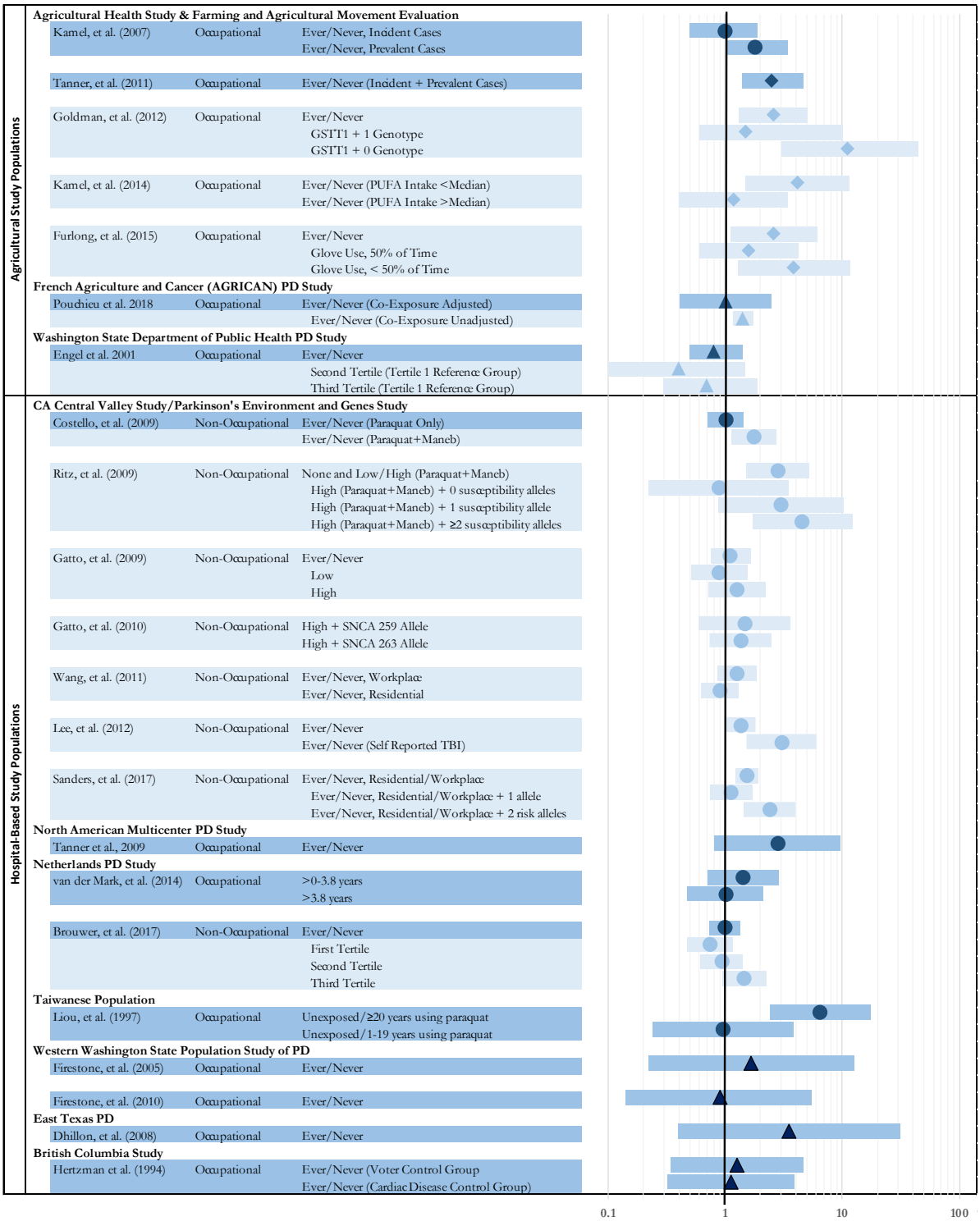
Table 7: Selected Characteristics of PD in Nebraska, 1997-2008 (Excerpted from Wan and Lin, 2016).

Variable	Case/Population	Rate (per Million)
Age		
Group 1 (40-64)	857/501,101	1,710
Group 2 (65-74)	1,494/115,699	12,912
Group 3 (≥75)	4,206/116,496	36,104
Poverty Rate		
Q1 (low)	3,836/1,111,956	3,450
Q2	1,414/370,492	3,817
Q3	438/87,492	4,978
Q4 (high)	869/140,831	6,171
Rurality		
Metropolitan	2,827/942,503	3,047
Micropolitan	2,561/576,660	4,441
Small town rural	66/19,450	3,393
More isolated rural	1,058/172,650	6,128

Overall, there is insufficient epidemiological evidence at this time to conclude there a clear associative or causal relationship between non-occupational paraquat exposure and PD. This conclusion was based on the limited number of studies on non-occupational populations, lack of consistent evidence of a positive association, and the potential for bias in the available studies. The PEG study reported evidence of positive association in some publications, for example, but reported no evidence of an association when restricting analysis to paraquat exposure only. The Netherlands PD study also reported no evidence of a positive association (Brouwer et al., 2017). Moreover, both the PEG and Netherlands PD studies relied on GIS-based approaches to estimate exposure which eliminated the potential for recall bias, but may have limited ability to distinguish with confidence between proximity to agricultural land, pesticide exposure in general, and specific pesticides as potential PD risk factors. The results of the ecologic Nebraska PD Registry Study (Wan and Lin, 2016) contributed limited weight to OPP's evaluation, but highlights the need to carefully account for rurality in the design and analysis of studies on paraquat exposure and PD.

Summary of Reported PD Findings

Figure 2: Summary of Odds Ratio Results for Epidemiologic Studies on Paraquat and Parkinson's Disease *(Primary study results highlighted in dark blue; Secondary study results focus on extending or further characterizing the primary study results and are highlighted in light blue). Diamond, Circle, and Triangular shapes represent the point estimates of high-, moderate-, and low-quality studies, respectively.*



3.2 Lung Function and Respiratory Effects (17 Articles)

The relationship between paraquat exposure and lung and respiratory effects was examined in 17 articles. Specific health outcomes evaluated in the epidemiologic literature included general lung function and respiratory symptoms, wheeze, allergic rhinitis, asthma, and chronic bronchitis. The literature for each of these outcome is summarized and evaluated in **Section 3.2.1** below. **Appendix A** also further summarizes all studies, organized by health outcome, with respect to their design, methods, results, and study quality.

3.2.1 Literature Review

General Lung Function and Respiratory Symptoms (Low Quality: Howard et al., 1981; Senanayake et al., 1993; Schenker et al., 2004; Cha et al., 2012; Castro-Gutierrez et al., 1997; Dalvie et al., 1999, Ames et al., 1993)

The association between paraquat exposure and lung function and respiratory symptoms was examined in 7 studies. The studies examined a range of different indicators of lung function and frequently used standardized clinical tests of lung function. This includes spirometry to measure Forced Vital Capacity (FVC) and Forced Expiratory Volume in 1 second (FEV1) and testing of lung gas transfer. One study also examined a range of non-specific respiratory symptoms that were ascertained through self-report by study participants. These studies are summarized below:

- Howard et al. (1981) conducted a cross-sectional study that investigated the relationship between use of paraquat and clinical indicators of health, including clinical measures of hematological, liver, renal, and lung function among palm oil and rubber plantation workers (n = 74) in Malaysia. The study population included 74 plantation workers, including 27 spraymen with at least 1,000 hours spraying paraquat and 2 comparison groups: (1) tappers, harvesters, and general plantation workers who had minimal exposure to paraquat due to working in areas which had recently been sprayed, and (2) factory workers where raw latex is initially processed and have no known occupational exposure to paraquat. All 3 groups resided in the same estate villages, worked 8-hour days, 6 days a week. Pesticide exposure assessment was based on personal interview and company records on the total amount of paraquat sprayed. Lung and respiratory function were assessed through analysis of blood samples and spirometry. Multiple linear regression was then used to assess the lung function parameters in spraymen relative to the 2 comparisons groups, controlling for ethnicity, smoking, age, and height. Based on this approach, the investigators reported no evidence of associations for the range of pulmonary functions, including FVC ($\beta = 0.139$, p-value = 0.48), FEV ($\beta = 0.141$, p-value = 0.51), FEV% ($\beta = 1.04$, p-value = 0.73), and CO diffusion ($\beta = -0.63$, p-value = 0.30).
- Ames et al. (1993) conducted a cross-sectional, community-based study that was part of a California Department of Health Services investigation into potential health consequences of paraquat exposure in a community located adjacent to agricultural fields. The community exposure occurred over 2 days in the Spring of 1991, resulting from drift following aerial application of diluted paraquat on agricultural fields adjacent to the community. Following complaints from community members, the CDHS conducted a survey of community residents and compared self-reported 2-week symptom prevalence among surveyed residents to those of 3 historical control communities. After collecting data on self-reported symptoms, the investigators calculated unadjusted prevalence estimates and compared symptom prevalence among the community respondents (n = 39) to historical controls from 3 comparison towns (n = 172) using a chi-squared test. Based on this approach, evidence of a positive association was reported for the following symptoms: breathing difficulty (prevalence ratio, PR: 2.2, $p < 0.01$), cough (PR: 2.6, $p < 0.001$), diarrhea (PR: 5.9, $p < 0.001$), eye irritation (PR: 2.5, $p < 0.001$), headache (PR: 1.7, p <

0.001), nausea (PR: 3.1, $p < 0.001$), rhinitis (PR: 2.5, $p < 0.001$), throat irritation (PR: 1.74, $p < 0.05$), unusual tiredness (PR = 2.9, $p < 0.001$), and wheezing (PR = 3.0, $p < 0.01$). Prevalence ratios for fever and vomiting were elevated among community members, relative to controls, but not statistically significant. The prevalence ratio for skin rash was near-null and not statistically significant. The prevalence of only 1 symptom – "asthma attacks" (evaluated only among respondents reporting pre-existing asthma) was observed to be lower among participating community members, relative to the historical control group (PR = 0.46), and the association was not statistically significant. Prevalence ratios for stomach cramping and skin irritation could not be calculated, as symptoms were not ascertained for members of the control population.

- Senanayake et al. (1993) conducted a cross-sectional study that investigated the relationship between use of paraquat and clinical indicators of health (hematological, liver, renal, and lung function health outcomes) among tea estate workers (n = 240) in Sri Lanka. The study population included 240 plantation workers including 85 spraymen, with at least 5 years of spraying paraquat. Two comparison groups: 1) 79 general estate workers who had minimal exposure to paraquat due to working in areas which had recently been sprayed, and 2) 76 tea factory workers who processed the freshly picked tea leaves and had no known occupational exposure to paraquat. All 3 groups resided in the same estate villages. The exposed group consisted of individuals that reported spraying paraquat on tea fields for a minimum of 5 years. Estate records provided the data to calculate the total number of spraying days and the total number of spraying days in the past 5 years. Full clinical examination. "Clinical examination. General Health - resting pulse, blood pressure; Hematology - hemoglobin concentration, packed cell volume; Renal - blood urea and creatinine; Liver - alkaline phosphatase, aspartate, alanine transferase, bilirubin, total protein, albumin; Respiratory - Morgan Transfer test model B for FVC, FEV, TLC, carbon monoxide transfer flow, chest x-rays. After collecting data on exposure and clinical examination, the investigators performed analysis of covariance to compare the 3 groups of workers. Based on this approach, the investigators reported no evidence of a significant positive association. Summary results on the exposed group and controls are provided in the **Table 8** below.

Table 8: Summary of lung function parameters reported in Senanayake et al. (1993).

	N	FEV_1	FEV_1/FVC (%)	Hemoglobin (g/dL)	Packed Cell Volume (%)
Control Group 1	76	3.42 (0.06)	80.37 (1.10)	14.28 (0.16)	44.87 (0.48)
Control Group 2	79	3.49 (0.06)	80.98 (1.03)	14.84 (0.16)	46.35 (0.50)
Exposed Group	85	3.48 (0.06)	80.89 (0.98)	15.50 (0.15)	45.37 (0.46)

- Castro-Gutierrez et al. (1997) conducted a cross-sectional study to evaluate the relationship between long-term occupational paraquat exposure and respiratory health among workers from 15 Nicaraguan banana plantations (n = 134 workers reporting more than 2 years of cumulative work applying paraquat, 152 non-exposed). The authors noted that personal protective equipment was unavailable to plantation workers, or is not used, due to the tropical heat. Participants completed a questionnaire interview to ascertain detailed exposure histories and presence of respiratory symptoms. Participants then underwent spirometry in order to objectively measure lung function parameters (FEV1 and FVC) and the presence of restrictive or obstructive pulmonary function deficits. The investigators performed logistic regression to assess the relationship between paraquat exposure and the respiratory outcomes dyspnea, chronic bronchitis, and abnormal spirometry, adjusting for age, gender, and smoking history. The investigators reported no evidence of a significant positive association between paraquat exposure and grade 1 or grade 2 dyspnea, but reported evidence of moderately strong and strong association for grade 3 dyspnea, based on comparison of low and intense exposed groups with a no exposure group (*Low*

vs. No Exposure – OR = 2.8, 95% CI: 1.4-5.6, n = 20 exposed individuals; *Intense vs. No Exposure* – OR = 4.6, 95% CI: 2.4-9.0, n = 30). The investigators also reported evidence of a moderately strong association for episodic dyspnea with wheezing based Intense vs. No Exposure groups (OR = 2.9, 95% CI: 1.4-6.3, n = 71 exposed individuals). For chronic bronchitis, no evidence of a significant positive association was reported (*Low vs. No Exposure* – OR = 1.0, 95% CI: 0.41-2.6, n = 8 exposed individuals; *Intense vs. No Exposure* – OR = 2.0, 95% CI: 0.92-4.4, n = 16). No evidence of a significant positive association was reported for abnormal spirometry (*Low vs. No Exposure* – OR = 0.93, 95% CI: 0.32-2.7, n = 5 exposed individuals; *Intense vs. No Exposure* – OR = 1.3, 95% CI: 0.51-3.4, n = 9).[15]

- Dalvie et al. (1999) conducted a cross-sectional study to evaluate the possible effects of paraquat spraying among workers on deciduous fruit farms in the Western Cape, South Africa. The study population included 126 study subjects (62 current herbicide sprayers and 70 controls not currently spraying herbicides) that were recruited from 41 fruit farms in Ceres district of the Western Cape Province, South Africa from January to March 1993. Paraquat exposure was based on a job exposure matrix that incorporated study subject questionnaire information and expert judgment to estimate lifetime exposure intensity. Information on respiratory outcomes was collected using a standardized questionnaire and clinical assessment of lung function and gas transfer were measured using spirometry and carbon monoxide gas transfer measurements, respectively. The relationship between paraquat exposure and the respiratory outcomes was evaluated using multiple linear regression. Based on this approach, the investigators reported no evidence of an association between long-term exposure to paraquat and reported symptoms, spirometry, gas transfer or chest radiography, although detailed statistical results are not reported in the publication. The investigators reported evidence of an association between exercise oxygen desaturation and long-term exposure to paraquat ($\beta = 0.0186$, $SE(\beta) = 0.0075$, p-value = 0.015, Partial $r^2 = 0.0611$). However, the coefficients of determination (R^2) in the models remained in the range 0.10-0.12, suggesting that exposure to paraquat and the other variables only account for a small proportion of the variability of the outcomes of interest. The investigators also evaluated the correlation between general herbicide exposure and paraquat exposure and reported correlation coefficient of greater than 0.78.

- Schenker et al. (2004) conducted a cross-sectional study among workers in banana, coffee and palm oil farms in Costa Rica. In order to recruit study subjects, 62 banana, coffee, and palm oil farms were identified throughout Costa Rica. After the initial contact, 11 farms were excluded because they no longer used paraquat, or had too few handlers to justify the expense and effort of data collection (25 farms). Among the remaining farms, 22 participated, 2 refused, and 2 were included in pilot study testing. Based on these participating farms, 338 Costa Rican farm workers were enrolled in the study and completed a questionnaire, spirometry, and a test of single-breath carbon monoxide diffusing capacity. Workers classified as handlers (n = 219) reported 6 months or more of work experience mixing, loading, or applying paraquat; non-handlers (n = 119) reported no experience with handling paraquat. A cumulative paraquat exposure index was created using urinary monitoring data and weights that incorporated information on work history, including the handling of paraquat in each job, the length of employment, the type of crop, and the use of protective equipment. Linear regression was used to evaluate the relationship between pulmonary function and exercise outcome measures and cumulative paraquat exposure. Logistic regression models were used to estimate the associations between exposure to pesticide with respiratory symptoms and lung function. Estimates were adjusted for age, height, weight and smoking status. Based on this approach, the investigators reported evidence of a positive association between cumulative exposure to paraquat and respiratory symptoms; specifically,

[15] Similar results reported for restrictive spirometry are not presented here.

each unit increase in the cumulative paraquat index was associated with a 1.8 increase in the odds of chronic cough (95% CI: 1.0- 3.1) and a 2.3 increase in the odds of shortness of breath with wheeze (95% CI: 1.2-5.1). Similarly, the investigators reported evidence of a positive association between paraquat exposure and ventilatory equivalent for CO_2 ($\beta = 0.49$, $p = 0.02$), based the total cumulative paraquat exposure index.

- Cha et al. (2012) conducted a cross-sectional study to examine the association of occupational paraquat exposure and lung/respiratory health effects among South Korean farmers. The study was based on a larger cross-sectional survey conducted in 2008-2009 among residents of Taean county, South Korea. Specifically, 9,246 out of 63,401 residents in the county enrolled in a voluntary health examination program study of potential health effects of an oil spill which occurred in 2007. A total of 2,882 full-time farmers who apply pesticides (2,508 paraquat-applying farmers and 374 non-paraquat-applying farmers) were selected for this analysis. Participants were self-employed farmers and described by the study authors as "approximately representative of full-time farmers in South Korea." Exposure data on 34 pesticides, including paraquat, was collected with a questionnaire and used to estimate exposure based on ever/never application, number of years of application, number of annual days of application, and lifetime days of application. Respiratory health effects, including COPD, asthma, wheeze, shortness of breath, and allergy rhinitis were assessed with an interviewer-administered questionnaire. Spirometry was also performed by trained nurses blinded to paraquat exposure status to assess pulmonary function. After collecting exposure and outcome data, logistic regression analysis was used to evaluate the relationship between paraquat exposure and respiratory health effects, adjusting for age, gender, distance to oil spill, smoking status, alcohol consumption, education, and cumulative exposure to 3 pesticides correlated with paraquat (carbofuran, imidacloprid, isoprothiolane. The model for wheeze was also examined with asthma (yes/no) as a covariate.

  With regard to pulmonary function based on spirometry, there was evidence of a positive association with paraquat exposure. In particular, a significantly lower ($p < 0.05$) FVC predicted percentage was observed in paraquat-applying male farmers (mean = 95.7) as compared to their non-paraquat-applying counterpart (mean = 102.5). No significant differences were observed among female farmers. Decreased FVC was also significantly associated with longer time (in years) of paraquat application ($\beta = -5.20$, $p < 0.001$) and with lifetime application (days) ($\beta = -22.19$, $p = 0.009$). Additionally, lower FEV_1 was associated with longer time of paraquat application ($\beta = -1.89$, $p = 0.010$). By gender, significant reductions in pulmonary functions were observed among male farmers (FVC years $\beta = -6.14$, $p < 0.001$; FVC days $\beta = -36.71$, $p < 0.001$; and FEV_1 $\beta = -2.30$, $p = 0.02$). Among females, only a marginally significant reduction in one of the pulmonary function measures was observed, FVC years $\beta = -3.12$, $p = 0.057$. The study also reported evidence of a positive association between the restrictive ventilatory defect in paraquat-exposed farmers vs non-applying farmers (OR = 1.89, 95% CI: 1.11- 3.24, n = 66 exposed cases). This finding was consistent when considering paraquat application years (p for trend = 0.015) and lifetime paraquat application days (p for trend = 0.007).

  With regard to self-reported respiratory health outcomes, the investigators reported no evidence of a positive association between paraquat exposure and wheeze (OR = 0.75, 95% CI: 0.52-1.08, n = 320 exposed individuals), shortness of breath (OR = 0.87, 95% CI: 0.54-1.40, n = 141 exposed individuals), and allergy rhinitis (OR = 1.16, 95% CI: 0.77-1.74, n = 305 exposed individuals) and no evidence of a significant positive association for COPD (OR = 1.44, 95% CI: 0.50-4.16, n = 54 exposed individuals), asthma (OR = 2.18, 95% CI: 0.99-4.82, n = 118 exposed individuals), and allergy rhinitis (OR = 1.16, 95% CI: 0.77-1.74, n = 305 exposed individuals). The results did not change meaningfully when stratified by gender.

Overall, there is insufficient epidemiological evidence at this time to conclude there a clear associative or causal relationship between occupational paraquat exposure and general lung function and respiratory symptoms. As summarized, 7 cross-sectional studies were identified that examined the association between paraquat and general lung function and respiratory symptoms using spirometry (6 studies), lung gas transfer (3 studies), and self-reported respiratory symptoms (1 study). Of the 6 studies that examined lung function using spirometry, 5 reported no evidence of an association with paraquat and more generally that lung function was generally within the normal adult rang. In contrast, 1 study by Cha et al. (2012) reported evidence of an association and observed significantly lower FVC and FEV1 in their cross-sectional study of paraquat-applying farmers in South Korea. Three of the available cross-sectional studies also examined lung function by measure lung gas transfer (an effect of interstitial or restrictive lung disease) and reported mixed findings. Schenker et al. (2004) measured carbon monoxide diffusing capacity, alveolar volume measured with single breath, and peak oxygen uptake during a maximal exercise test, and oxygen pulse peak and arterial oxygen desaturation from resting to peak exercise - all results showed no evidence of an association between paraquat exposure. Dalvie et al.'s study of 126 paraquat applicators in the Western Cape region of South Africa reported no evidence of an association of paraquat exposure and respiratory symptoms or carbon monoxide diffusing capacity, but they did report a positive association of chronic paraquat exposure and arterial oxygen desaturation during maximum exercise. However, 28% of the saturation traces were considered unreadable, and among those with readable traces the magnitude of the effect was small. Finally, Senanayake et al. (1993) found no difference in diffusion capacity in 85 Sri Lankan paraquat applicators compared with control factory and general workers.

In addition to the 6 studies that included clinical measures of lung function, there was 1 cross-sectional study that examined non-specific respiratory symptoms, based on an investigation of a potential drift event that was performed by the California Department of Health Services in 1991 (Ames et al., 1993). This study reported evidence of a strong positive association between paraquat and prevalence of the following 8 self-reported symptoms: cough, diarrhea, nausea, unusual tiredness, stuffy/runny nose, breathing difficulty, wheezing, and tearing eyes. This study focused on a 2-week period following a paraquat incident and has more limited relevance to this review of other identified epidemiologic studies.

In addition to the mixed results described above, all available studies had important limitations and were determined to be of low quality based on the study quality criteria outlined in the OPP framework. Most importantly, all available studies used cross-sectional designs and cannot evaluate the temporal association between paraquat exposure and lung function. OPP generally considers cross-sectional studies lower quality evidence for purposes of evaluation of epidemiologic literature in risk assessment. All studies also generally relied on questionnaires to characterize paraquat exposure in a wide range of agricultural settings outside the U.S. (*i.e.,* Malaysia, South Africa, Costa Rica, Taiwan, Nicaragua). In addition to the potential for exposure misclassification, it is unclear how the exposure levels in these studies relate to U.S. because the studies cannot be used to characterize how exposure levels in other countries and time periods relative to potential exposure levels in the U.S. The single study conducted in the U.S. (Ames et al., 1993) also relied on a cross-sectional design and was done in response to community concerns following a potential drift event. This study was also unable to quantify exposure and all outcomes were self-reported rather than clinically ascertained, and as a result may be subject to recall bias.

Wheeze (<u>Low Quality</u>: Hoppin et al. 2002; 2006a; 2006b; 2016)

The association between paraquat exposure and wheeze was examined in four studies conducted using the AHS study population (Hoppin et al. 2002; 2006a; 2006b; 2016).

- Hoppin et al. (2002) conducted a cross-sectional study using the AHS study population to examine the association between pesticide exposure to pesticides in the previous year and the prevalence of wheeze among pesticide applicators. Using data from the AHS prospective cohort, exposure and health outcomes were ascertained through participant self-administered questionnaires. Data were analyzed using logistic regression models, adjusting for age, state, past smoking, current smoking, and asthma/atopy. Of the 20,468 participants in the study, 3,838 reported wheeze and 16,630 participants did not report wheeze. Of the 3,838 cases, 192 (5%) reported exposure to paraquat. For the 16,630 participants who did not report wheeze, 832 (3.6%) reported exposure to paraquat. Based on analysis of these study subject, the investigators reported evidence of a positive association between wheeze and paraquat (OR = 1.27; 95% CI: 1.04-1.56 with a p-trend < 0.01,). Paraquat, as well as other pesticides, was then analyzed in an exposure-response model using the paraquat exposure categories: < 5 days, 5-9 days, > 10 days. In this analysis, there was no evidence of a significant exposure-response relationship and all OR estimates included the null value 1.0 (*< 5 days* – OR = 1.33, 95% CI: 0.99-1.78; *5-9 days* – OR = 1.12, 95% CI: 0.77-1.61; *> 10 days* – OR = 1.31, 95% CI: 0.92-1.86).
- In a separate cross-sectional study, Hoppin et al. (2006a) investigated potential associations between pesticides exposure and the prevalence of wheeze. Study participants were farmers (n = 17,920) and commercial pesticide applicators (n = 2,255) enrolled in the AHS between 1993 and 1997. Exposure and health outcomes were ascertained through participant self-administered questionnaires at enrollment. Cases were defined as participants who reported episodes of wheezing or whistling in the chest in the year before study enrollment. Exposure was defined as pesticide use in the year before enrollment ("current use"). Investigators explored the association between paraquat and wheeze using logistic regression models that adjusted for age, BMI, and smoking. State was also included as a potential confounder in the analyses for farmers; commercial applicator participants resided only in one state (Iowa). Among the total farmers and commercial applicators, the study authors reported 19% of farmers and 22% of commercial applicators reported wheeze in the past year. The authors noted that 3% of farmers and 7% of commercial applicators reported current use (defined as use within the past year) of paraquat. No evidence of a significant positive association was observed for wheeze among farmers (OR = 1.22; 95% CI: 0.98, 1.51) and no evidence of an association was observed among commercial applicators (OR = 0.93; 95% CI: 0.59, 1.47). The authors did not report the numbers exposed by case or non-case status for farmer applicators.
- Hoppin et al. (2006b) published an additional article that provides numeric details for commercial applicators: Of the 2,255 commercial applicant study participants, 486 reported wheeze in the last year, and 34 (7%) of those wheeze cases reported current use of paraquat. Of the 1,769 participants who did not report wheeze in the last year, 116 (7%) reported current use of paraquat. Study results suggested no evidence of a significant positive association between current paraquat use and wheeze (OR = 1.21; 95% CI: 0.78, 1.85).
- Hoppin et al. (2016) conducted a cross-sectional study in the AHS study population to examine the association between pesticide exposure and allergic and non-allergic wheeze among male farmers. The study population consisted of male participants in the AHS (n = 22,134) who completed a self-reported questionnaire detailing pesticide usage and symptoms of wheeze, which was defined as at least one episode of wheeze or whistling in the chest in the past year and a doctor diagnosis of hay fever for allergic wheeze, and at least one episode of wheeze or whistling in the chest in the past year without a diagnosis of hay fever for non-allergic wheeze. Survey information was used to assess paraquat exposure (current, past, or never-use) and to assess frequency and duration of use. Among the 1,310 allergic wheeze cases, 4% reported current use of paraquat, and among the 3,939 non-allergic wheeze cases, 2% reported current use of paraquat.

Of the 16,885 control subjects, 3% reported current use of paraquat. A polytomous logistic regression was used to determine the association between wheeze and pesticide exposure, and allergic and non-allergic wheeze were investigated separately. Models were adjusted for age, BMI, state, smoking, and current asthma, as well as for days applying pesticides and days driving diesel tractors. Analyses showed no evidence of a significant positive association between current paraquat use and allergic wheeze (OR = 1.10; 95% CI: 0.79, 1.55) and evidence of an association for non-allergic wheeze (OR = 0.91; 95% CI: 0.71-1.16).

Overall, there is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and wheeze. All available studies were cross-sectional and conducted using the AHS study population. While Hoppin et al. (2002) reported evidence of a significant positive association based on ever/never use of paraquat, there was no evidence of an exposure-response relationship. Moreover, the results of the remaining AHS studies are mixed and do not consistently provide evidence of an association even though all studies were done in the same study population and relied on similar methods. Hoppin et al. (2006) reported no evidence of a significant positive association for wheeze among farmers and no evidence of an association was observed among commercial applicators, based on an OR estimate for commercial applicators that was less than 1.0. Similarly, Hoppin et al. (2016) further investigated the AHS by examining allergic and non-allergic wheeze and reported no evidence of an association between paraquat use and either allergic or non-allergic wheeze. A general limitation of all 4 studies is that they relied on a cross-sectional design that assessed the relationship between prevalent cases of wheeze and pesticide exposure. As such, the available studies were unable to assess temporal association between paraquat exposure and wheeze and were determined to be of low quality based on the study quality criteria outlined in the OPP framework.

Allergic Rhinitis (<u>Low Quality</u>: Slager et al., 2009; Chatzi et al., 2007; Koureas et al., 2017)

The association between occupational paraquat exposure and allergic rhinitis was evaluated in 2 studies (Chatzi et al., 2007, Slager et al., 2009)). Both studies are summarized below; however, Chatzi et al. (2007) focused on the general class of herbicides, "all bipyridyl herbicides" so risk estimates are not specific to paraquat.

- Chatzi et al. (2007) conducted a cross-sectional study in Northern Crete, Greece to investigate the association of allergic rhinitis with the use of pesticides among grape farmers. The exposed group consisted of 150 randomly selected grape farmers with no other occupation besides grape farming. They were selected from 459 grape farmers in the age group of 25–70 years who were listed in the agricultural co-operative in the Malevisi region of Northern Crete. The non-exposed group consisted of a random sample of 150 employees in the tourist industry, aged 25–70 years, from the general population in the same region. The study was conducted from April to November 2002. The response rate was 80% and 67% in the exposed and non-exposed group, respectively. All participants completed a questionnaire during a face- to-face interview performed by the same trained physician. The questionnaire included questions on occupational history, such as the number of working hours per day, the number of years working in grape cultivations, the preventive measures used during working time (*e.g.,* gloves, mask, glasses), the use of pesticides and work-related symptoms. The questionnaire included a list of 50 commonly used pesticides (brand names), and grape farmers were asked to identify the pesticides they currently used. Grape farmers were also given the opportunity to add other pesticides that they had used and that were not included in the list. In order to assess health outcomes, the study included a questionnaire, skin prick tests for 16 common allergens, measurement of specific IgE antibodies against 8 allergens, and spirometry before and after bronchodilatation. After collecting exposure and outcome data, the investigators performed logistics regression to estimate ORs, adjusted for age, sex, and smoking status. Based on this approach, it was observed that grape

farmers who used pesticides had higher prevalence rates of allergic rhinitis symptoms (adjusted OR, 3.0; 95% CI, 1.4 to 6.2) compared with non-farmer control subjects. As compared to non-exposed farmers, adjusted analysis showed no evidence of a significant positive association between bipyridyl herbicides, which includes paraquat, and self-reported allergic rhinitis (OR = 2.2, 95% CI: 1.0-4.8) and evidence of a strong positive association between bipyridyl herbicides and the combination of allergic rhinitis with atopy (OR = 4.0, 95% CI: 1.4-11.2), based on 50 subjects reported use of bipyridyl herbicides.

- Slager et al. (2009) conducted a cross-sectional study using the AHS study population to examine the association between pesticides, including paraquat, and allergic rhinitis. A total of 2,245 commercial male pesticide applicators from Iowa completed self-administered questionnaires that assessed both exposure to pesticides and the outcome of current rhinitis. Logistic regression models were used to calculate ORs and 95% CIs to analyze the association between ever-use of a pesticide and current rhinitis, and models were adjusted for age, education, and growing up on a farm. Of the 1,664 cases of rhinitis reported in the study group, 117 (7%) reported exposure to paraquat; of the 581 respondents who reported no current rhinitis, 31 (5%) reported exposure to paraquat. Results showed no evidence of a significant positive association between exposure to paraquat and rhinitis based on ever-use (OR = 1.32; 95% CI: 0.68-2.01). The investigators further examined the exposure-response relationship by assessing the following exposure categories: 1-4 days per year, 5-9 days per year, and ≥ 10 days per year). Based on this approach, the investigators reported no evidence of an exposure-response relationship (*1-4 days per year* – OR = 1.29, 95% CI: 0.60-2.77; 5- 9 days per year – OR = 1.37, 95% CI: 0.54-3.50; and ≥ *10 days per year* – OR = 1.38, 95% CI: 0.76-2.50; p-trend = 0.207)
- Koureas et al. (2017) conducted a cross-sectional study in Thessaly, Greece to investigate the association between agricultural use of pesticides and the health outcomes rheumatoid arthritis and allergic rhinitis (see *Rheumatoid Arthritis* under **Section 3.4** on *page 75* for summary of results on rheumatoid arthritis). The study population included farm owners who identified through a list of owners available through the citizen's service center in the region of interest of Greece. 200 farm owners were contacted and 115 met the study eligibility criteria: (1) to personally apply pesticides systematically, (2) to have recently applied pesticides (no more than 7 days between last application and sampling) (Koreas et al., 2014). 80 of these eligible subjects agreed to participate in the study, resulting in a response rate of 70%. A control group of 90 male residents of the city of Larissa was recruited for the study. This group included urban males who were employed by the University of Larissa and recruited during voluntary blood donations. An additional group of older controls of volunteers from nursing homes was also enrolled in the study to enable age matching of subjects older than 65 years old. All study subjects were interviewed to obtain data on socio-demographics and lifetime pesticide exposure. Lifetime pesticide exposure was ascertained during this interview by asking subjects to recall total years of pesticide usage, the area and type of crop treated, the commercial names of the pesticides they have used and the frequency of application (per year) per pesticide. Description of outcome ascertainment is not described in any detail by the study authors, but the abstract suggests that medical history, including the outcomes rheumatoid arthritis and allergic rhinitis, was also collected during the interview. Descriptive statistics were calculated to characterize study subjects and multinomial logistic regression was used to calculate ORs between the farm owner group and the control group. Limited descriptive results are provided in the manuscript, but the investigators report there were only 6 cases of rheumatoid arthritis in the farm owner group and no cases in their control group. The number of farm owners with the outcome allergic rhinitis is not reported, but the investigators do report that 25 study subjects were allergic rhinitis cases. Based on the logistic regression model, the investigators reported no evidence of an association for rheumatoid

arthritis (OR = 0.69, 95% CI: 0.094-5.03) (findings on outcome evaluated in *Rheumatoid Arthritis* under **Section 3.4** on *page 75*) and evidence of a strong positive association for allergic rhinitis (OR = 9.10, 95% CI: 1.70-48.54).

There is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and allergic rhinitis. While Slager et al. reported a positive OR, it was not statistically significant and no exposure-response relationship was observed. The investigation by Chatzi et al. relied on a more limited exposure assessment approach and assessed exposure to bipyridyl herbicides, rather than paraquat specifically. More generally, Chatzi et al. focused on a study population of grape farmers in Crete that used multiple pesticides and may have been exposure to other factors that are associated with allergic rhinitis. As such, the investigators may have been unable to evaluate paraquat or other pesticides more specifically. This potential limitation is supported by the reported finding that all reported ORs – for 3 pesticide classes (herbicides, fungicides, and insecticides) and 12 individual pesticides – were greater than 1.0. Koureas et al. (2017) had many of the same study limitations. It is also important to highlight that all available studies relied on cross-sectional studies designs. As such, the available studies were unable to assess the temporal association between paraquat exposure and allergic rhinitis, and were determined to be low quality based on the study quality criteria outlined in the OPP framework.

Asthma (Low Quality: Hoppin et al., 2008, 2009)

Two studies were conducted to evaluate the association between paraquat exposure and asthma in the AHS study population. Hoppin et al. (2008) investigated adult-onset asthma in farm women and Hoppin et al. (2009) evaluated the association of atopic and non-atopic asthma in male farmers.

- Hoppin et al. (2008) conducted a cross-sectional study using the AHS study population to examine the association between adult-onset asthma among farm women and pesticide exposure including paraquat. The study population consisted of female participants in the AHS (n = 25,814) who completed a self-reported questionnaire or telephone interview at study enrollment (1993 – 1997), detailing pesticide usage and whether they had received a physician's diagnosis of asthma. This information was used to assess pesticide exposure, to determine lifetime total years of pesticide use, and to assess frequency of application. Asthma cases were then subdivided into atopic or non-atopic asthma based on self-reported eczema and/or hay fever. A polytomous logistic regression model was used to determine the association between asthma and pesticide exposure, controlling for age, state, smoking status, BMI, and whether or not the subject had grown up on a farm. A total of 702 adult-onset asthma cases were identified. Among the 282 atopic asthma cases in females, 6 (2%) reported ever use of paraquat. Among the 420 non-atopic asthma cases, 8 (2%) reported ever use of paraquat; of the 25,112 control subjects, 3,745 (15%) reported ever use of paraquat. The investigators reported no evidence of a significant positive association for paraquat exposure for either atopic (OR = 1.90; 95% CI: 0.83-4.34) or non-atopic asthma (OR = 1.60; 95% CI: 0.79-3.28), based on ever/never use.
- In a separate AHS study, Hoppin et al. (2009) conducted a cross-sectional study to examine the association between adult-onset asthma among male farmers and pesticides including paraquat. Cases included male AHS farmers, aged ≥ 20 years old, who reported having been diagnosed with asthma by a physician and completed the self-administered questionnaires used to assess individual pesticide exposure. Investigators used this questionnaire data to estimate intensity-adjusted lifetime days of use, and a polytomous logistic regression was used to calculate ORs and 95% CIs adjusting for age, state, smoking, BMI, and high pesticide exposure events (pesticide poisoning). Of the 19,704 private pesticide applicators who participated in this study, 127 reported atopic asthma and 314 reported non-atopic asthma. Of the 127 cases of atopic asthma, 28 (22%) cases indicated exposure to paraquat. Among the 314 cases of non-atopic asthma, 40

(13%) cases reported paraquat exposure. In the control group (n = 19,263) who reported no asthma, 3,068 (16%) reported exposure to paraquat. The investigators reported evidence of a significant positive association between ever-use of paraquat and atopic asthma (OR = 1.67; 95% CI: 1.05, 2.65) and no evidence of a positive association for non-atopic asthma (OR = 0.82, 95% CI: 0.58-1.18). These associations were further evaluated to examine the impact of excluding AHS participants who reported the co-morbidities chronic bronchitis or farmer's lung. Excluding study subjects with these co-morbidities weakened association for atopic asthma (OR weakened from 1.67 to 1.36 and became non-significant), but not for non-atopic asthma (OR strengthened from 0.82 to 0.68, but was non-significant in both analyses). The investigators also examined the association between intensity-adjusted lifetime days of paraquat use and atopic and non-atopic asthma and reported evidence of a significant positive association at or below the median no evidence of significant positive association above the median, respectively (1-79 days – OR = 1.88, 95% CI: 1.09-3.24); > 79 days – OR = 1.46, 95% CI: 0.73-2.89).

There is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and asthma. The 2 available AHS studies relied on cross-sectional study designs and were determined to be of low quality based on the OPP study quality criteria outlined in the OPP framework. The study of adult women by Hoppin et al. (2008) had a relatively small number of exposed cases, including 6 atopic asthma cases and 8 non-atopic asthma cases. While the study reported no evidence of a significant positive association, the results were imprecise due to the small number of exposed cases. A larger number of exposed cases were evaluated in the study of male farmers by Hoppin et al. (2009). This study reported evidence of a significant positive association with atopic asthma and no evidence of an association for non-atopic asthma. The association for atopic asthma did not display an exposure-response relationship, based on stratification using median intensity-adjusted lifetime days, and weakened when the investigators excluded cases with the co-morbidities for chronic bronchitis or farmer's lung. As such, the overall results from this study are mixed. It should also be emphasized that an important limitation of both studies was their cross-sectional study design. As such, the available studies were unable to assess temporal association between paraquat exposure and asthma and were low quality based on the study quality criteria outlined in the OPP framework.

Chronic Bronchitis (<u>Low Quality</u>: Hoppin et al., 2007; Valcin et al.,2007)

Two cross-sectional studies were conducted to evaluate the association between paraquat exposure and chronic bronchitis. Hoppin et al. (2007) investigated chronic bronchitis in male farmers, and Valcin et al. (2007) evaluated chronic bronchitis in farmers' wives.

- Hoppin et al. (2007) conducted a cross-sectional study using the AHS study population to examine the potential association between chronic bronchitis and exposure to pesticides including paraquat. The study population (n = 20,908) included applicators who lived in Iowa or North Carolina and participated in the AHS. Cases included private pesticide applicators (males only) who self-reported chronic bronchitis, were diagnosed at > 19 years of age, and had completed an initial and follow-up study questionnaire. A logistic regression model was used to calculate ORs and 95% CIs for chronic bronchitis and individual pesticides based on ever/never exposure, controlling for state, age, gender, and pack years smoking. Among the total 654 cases and 20,254 controls, 19% of cases and 16% of controls reported exposure to paraquat. The study results provide no evidence of a significant positive association between paraquat exposure and chronic bronchitis among male pesticide applicators (OR = 1.17; 95% CI: 0.94, 1.46).
- In another AHS study, Valcin et al. (2007) conducted a cross-sectional study to examine occupational risk factors for chronic bronchitis among women in the AHS. The study sample was limited to the 21,541 non-smoking female spouses who provided complete information on age,

smoking, and chronic bronchitis and were at least 20 years old at enrollment. All male spouses (n = 220), smokers (n = 8,503), those without smoking history data (n = 1,845), and those younger than 20 or missing age (n = 14) or missing age at diagnosis (n = 35) were excluded. Female pesticide applicators (n = 454) were also excluded because exposure information differed for applicators and spouses. Women who reported being diagnosed before age 20 (n = 189) were excluded to limit possible misreporting of disease. Participant-administered questionnaires determined the exposure (including paraquat), health outcome (self-report of physician-diagnosed chronic bronchitis), and potential confounders. A logistic regression was used to calculate individual ORs and 95% CIs for specific pesticides, adjusting for age and state. Of the 583 cases, 2% reported exposure to paraquat. Of the 20,958 controls, 1% reported exposure to paraquat. Results showed evidence of a positive association between chronic bronchitis and paraquat exposure (OR = 1.91: 95% CI: 1.02-3.55, n = 11 cases reporting paraquat use).

There is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and chronic bronchitis. Hoppin et al. (2007) reported no evidence of a significant positive association between paraquat exposure and chronic bronchitis among male pesticide applicators in the AHS. In contrast, Valcin et al. (2007) reported evidence of a positive association between chronic bronchitis and paraquat in their analysis of female spouses of AHS pesticide applicators, but based on only 11 cases reporting paraquat use. One important limitation for both studies was that the studies failed to ask their study participants about respiratory signs and symptoms during enrollment. Since respiratory signs and symptoms are helpful in diagnosing chronic bronchitis[16], this medical information could have provided increased confidence in the diagnosis, potentially. More generally, as with all other lung/respiratory outcomes, both studies used cross-sectional study designs. As such, the studies were unable to assess temporal association between paraquat exposure and chronic bronchitis and were of low quality based on the study quality criteria outlined in the OPP framework.

3.2.2 Evaluation of Findings

There were 17 published articles that examined the association between paraquat exposure and lung function and respiratory effects, including nine studies conducted using the AHS study population. The findings from these studies are summarized in **Table 9** below. Regarding study findings, there was generally mixed evidence for many of the health outcomes examined in the literature and the outcomes were examined in only a limited number of study populations. Moreover, apart from the more general study done by Ames et al. 1993, the only findings on a U.S. study population was from the AHS study population, with the remaining studies done in populations that may not be representative of U.S. agricultural practices. It is also important to emphasize that the identified literature had limitations with respect to study design, exposure assessment, and potential risk of bias. All identified studies used cross-sectional designs and were unable to evaluate the temporal association between paraquat exposure and the outcomes of interest. As such, all studies examined prevalent outcomes and cannot determine if exposure preceded potential onset of disease or reduction in lung function. For this reason, all identified studies were determined to be of low quality based on the study quality criteria outlined in the OPP framework.

[16] Ferris BG. 1978. Epidemiology Standardization Project (American Thoracic Society). Am Rev Respir Dis 118:1–120.

Table 9: Summary of Epidemiological Evidence on Paraquat Exposure and Respiratory Outcomes

Study	Study Population	Study Quality	General Lung Function			Wheeze	Allergic Rhinitis	Asthma	Chronic Bronchitis
			Spirometry	*Lung Gas Transfer*	*General*				
Ames et al., 1993	California Drift Event	L			🔴				
Howard et al., 1981	Malaysia Farmers	L	⊘	⊘					
Senanayake et al., 1993	Sri Lankan Farmers	L	⊘						
Schenker et al., 2004	Costa Rican Farmers	L	⊘	🔴	🔴				
Cha et al., 2012	South Korean Farmers	L	🔴		🔴				
Castro-Gutierrez et al., 1997	Nicaraguan Famers	L	⊘						
Dalvie et al., 1999	South Africa Famers	L	⊘	🔴	⊘				
Hoppin et al. 2002	AHS	L				🔴			
Hoppin et al. 2006a	AHS	L				⊙ *farmers* ⊘ *commercial*			
Hoppin et al. 2006b	AHS	L				⊙ *commercial*			
Hoppin et al. 2016	AHS	L				⊘			
Chatzi L et al., 2007 *(bipyridyl herbicides)*	Greek Farmers	L					⊙		
Slager et al., 2009	AHS	L					⊙		
Hoppin et al., 2009	AHS	L						⊙	
Hoppin et al., 2009 *(nonatopic)*	AHS	L						🔴	
Hoppin et al., 2007	AHS	L							⊙
Valcin et al., 2007	AHS	L							🔴

⊘ No evidence of an association between exposure and outcome (*e.g.,* OR ≤ 1.0).
⊙ No evidence of a significant association between exposure and outcome (*e.g.,* OR > 1.0 but not significant).
🔴 Evidence of an association between exposure and outcome (*e.g.,* OR > 1.0 and significant).

3.3 Cancer (8 Articles)

Eight studies examined the association between paraquat exposure and cancer, including all cancer, prostate cancer, breast cancer, bladder cancer, colorectal cancer, and glioma. A literature review and evaluation of the evidence for each type of cancer is provided below. An overall summary of study findings is provided in **Table 14** and at the end of this section and an additional summary of each study is provided in **Appendix A**.

3.3.1 Literature Review

All Cancers (High Quality: Park et al., 2009)

The associations between occupational paraquat exposure and incident cancer, including all cancers combined, cancers of the prostate, lung, colon, rectum, pancreas, kidney, and bladder, Non-Hodgkin's lymphoma (NHL), leukemia, and cutaneous melanoma, were all investigated in the AHS study population (Park et al., 2009).

Park et al. (2009) conducted a prospective study of the AHS cohort to investigate the relationship between paraquat exposure and cancer incidence. Paraquat exposure was determined using the enrollment questionnaire completed in 1993-1997 (n = 56,222). Take home questionnaires administered during the same time frame supplied data on the frequency and timing of use of paraquat for a subset of 24,655 pesticide applicators. Lifetime exposure and intensity weighted lifetime exposure were calculated from data on the take home questionnaire and were categorized into tertiles based on the distribution for all of the cancer cases. Cancer cases were ascertained through Iowa and North Carolina cancer registries. Incident cancers diagnosed from enrollment through December 31, 2004 were identified and coded using the International Classification of Diseases for Oncology (ICD-O-2). Poisson regression was used to calculate rate ratios, controlling for age at enrollment, education, cigarette smoking, alcohol consumption, family history of cancer, location (Iowa/NC), and five pesticides with the highest correlation with paraquat exposure. Based on this approach, the investigators reported no evidence of an association between ever use of paraquat and all cancers (RR: 0.95, 95% CI: 0.86-1.05, n = 667 exposed cases). The ever/never use results for all cancers are summarized in **Table 10** below, and are discussed in more detail later in this document under each of the specific cancers.

Table 10: Summary of Cancer Effect Estimates for Ever/Never Use of Paraquat Reported in Park et al. (2009)

Cancer Type	Non-exposed (N)	Exposed (N)	RR (95% CI)
All Cancers	**2,441**	**667**	**0.95 (0.86–1.05)**
Prostate cancer	1,002	252	0.95 (0.81–1.11)
Lung cancer	221	85	1.01 (0.76–1.34)
Colon cancer	193	46	0.88 (0.61–1.26)
Rectal cancer	87	27	1.12 (0.70–1.80)
Pancreatic cancer	38	14	1.32 (0.68–2.53)[b]
Kidney cancer	67	20	1.11 (0.63–1.95)
Bladder cancer	105	25	0.9 (0.56–1.46)
Non-Hodgkin's lymphoma	95	41	1.47 (0.97–2.23)[c]
Leukemia	77	20	0.98 (0.57–1.69)[b]
Cutaneous melanoma	88	23	0.98 (0.60–1.60)[b]

[a] Adjusted for age at enrollment, sex, race, education, research site, cigarette smoking, alcohol consumption, family history of cancers, and 5 pesticides that are correlated with paraquat.

[b] When the parameter estimator in the model was invalid or at a limit due to the small number of cancer cases, Park et al. (2009) calculated RRs and 95%CIs using the restricted model where the 5 pesticides that are correlated with paraquat were

Cancer Type	Non-exposed (N)	Exposed (N)	RR (95% CI)

excluded in the adjustment.
[c] $0.05 \leq p < 0.1$.

The investigators also examined lifetime exposure and intensity weighted lifetime days of paraquat exposure and similarly report no evidence of an association with any of the cancers examined in the study, including all cancers. The intensity weighted lifetime day results for all cancers are summarized in the **Table 11** below.

Table 11: Cancer Effect Estimates Reported for Intensity Weighted Lifetime Days of Paraquat in Park et al. (2009)

Cancer	Exposure Group	Exposed Cases	OR (95% CI)	P-trend
All Cancer	*0.1-36 Days*	88	1.02 (0.83-1.29)	*0.492*
	36.1-154 Days	90	0.96 (0.76-1.21)	
	154+ Days	91	0.92 (0.72-1.16)	
Prostate	0.1-36 Days	42	1.13 (0.81-1.57)	0.316
	36.1-154 Days	34	1.13 (0.81-1.57)	
	154.1+ Days	32	0.85 (0.57-1.24)	
Lung	0.1-154 Days	19	1.02 (0.62-1.70)	0.451
	154 Days+	10	0.71 (0.33-1.53)	
Colon	0.1-154 Days	15	1.40 (0.78-2.52)	0.235
	154 Days+	7	1.39 (0.61-3.17)	
Rectal	0.1-154 Days	4	0.88 (0.30-2.53)	0.743
	154 Days+	3	0.94 (0.40-5.15)	
Lymphoma	0.1-154 Days	8	1.16 (0.50-2.70)	0.396
	154 Days+	5	1.53 (0.50-4.71)	
Cutaneous Melanoma	0.1-154 Days	8	1.14 (0.53-2.44)	0.877
	154 Days+	4	1.03 (0.36-2.95)	

Based on the single study, there is no epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and all cancer. Park et al. (2009) reported no evidence of a positive association between all incident cancer and exposure to paraquat, based on ever-use. Analyses based on a lifetime exposure days of paraquat exposure metric similarly showed no evidence of a positive association for any of the stratified exposure categories; in addition, there was no evidence of an exposure-response trend between exposure category and incident cases. With regard to study quality, Park et al. (2009) was determined to be of high quality based on the study quality criteria outlined in the OPP framework. This determination is based on the general strengths of the AHS, including its prospective design, ability to identify cancer cases through linkage to cancer registries, and exposure assessment approach which examined cumulative lifetime exposure to paraquat.

Prostate Cancer (<u>High Quality</u>: Park et al., 2009; <u>Moderate Quality</u>: Cockburn et al., 2011)

The association between paraquat exposure and prostate cancer was evaluated in one study of the AHS study population and one non-occupational study population in California (Park et al., 2009; Cockburn et al., 2011).

- As further described in *All Cancers* under **Section 3.3** on *page 53,* Park et al. (2009) conducted a prospective study of the AHS cohort to examine the association between paraquat exposure and cancer, including prostate cancer. The study reported no evidence association between paraquat exposure and incident prostate cancer based on ever/never exposure (RR: 0.95, 95% CI: 0.88-

1.11, n = 252 exposed cases). The investigators also examined cumulative paraquat exposure based on both lifetime exposure days and intensity weighted lifetime exposure days and similarly reported no evidence of an association with prostate cancer (see **Table 11**).

- Cockburn et al. (2011) conducted a population-based case-control study in California's agricultural Central Valley (2005–2006) to investigate the association between prostate cancer and several pesticides, including paraquat. Cases (n = 670 eligible) were obtained from the California Cancer Registry, aged 60–74 years and diagnosed with histologically confirmed prostate cancer between August 2005 and July 2006 in Tulare, Fresno, and Kern counties. Case eligibility criteria included: 1) currently residing primarily in 1 of the 3 study counties; 2) having lived in California for at least 5 years prior to the study; and 3) ethnicity of non-Latino white or Latino white. After accounting for eligibility criteria and non-participation, 162 controls were recruited, of which 155 had complete data for analysis. Controls were recruited as part of the research group's study of Parkinson's disease conducted in the same study area. Controls aged 65 and older were identified from Medicare lists in 2001. Between 2004 and 2006, additional controls were recruited from randomly selected tax assessor residential units (parcels) in each of the 3 counties. They mailed recruitment materials to randomly selected parcels attempted to identify head-of-household names and telephone numbers using marketing companies and Internet searches. Eligibility criteria included: 1) currently residing primarily in 1 of the 3 study counties; 2) having lived in California for at least 5 years prior to the study; 3) ethnicity of non-Latino white or Latino white; 4) not having Parkinson's disease or prostate cancer; and 5) being at least 60 years of age. After accounting for eligibility criteria and non-participation, 173 controls were recruited, of which 150 had complete data for analysis. Historical ambient exposures to pesticides were derived from a combination of residential history and independently recorded pesticide and land-use data, using a GIS-based approach. Multivariable unconditional logistic regression was used to calculate odds ratios, adjusted for age (continuous), race/ethnicity (Latino white, non-Latino white), self-reported home pesticide use (ever/never), and occupational pesticide exposures derived from the job exposure matrix (not exposed, possibly exposed, or probably exposed). Based on this approach, the investigators reported no evidence of a significant positive association between prostate cancer and residential paraquat exposure (OR = 1.42, 95% CI: 0.87 to 2.31, n = 103 exposed cases).

Based on the two studies identified, there is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and prostate cancer. Park et al. (2009) reported no evidence of a positive association between prostate cancer and exposure to paraquat in the AHS cohort. Analyses of cumulative and intensity lifetime exposure days of paraquat exposure similarly showed no evidence of a positive association for any of the stratified exposure categories; in addition, there was no evidence of an exposure-response trend between exposure category and incident cases. As described previously in *All Cancers* under **Section 3.3** on *page 53*, this study was determined to be of high quality, based on its prospective design, ascertainment of cancer using established registries, and strengths of the AHS exposure assessment approach.

Cockburn et al. (2011) reported no evidence of a significant positive association in their case-control study that examined exposure based on proximity to agricultural land and pesticide use in California. This study was determined to be of moderate quality based on the study quality criteria outlined in the OPP framework. The main strengths of the study were the ascertainment of cancer cases using the California cancer registry and the assessment of exposure using a GIS-based approach that minimized the potential for recall bias. While GIS-based exposure assessment approach minimized recall bias, it has other limitations which are discussed in the review of the PEG study on *page 22*. Specifically, the approach may be more limited in its ability to investigate exposure to paraquat specifically, rather than general residential/workplace proximity to agricultural land in the 3 counties of interest. In addition, there is also

no published information on the measurement of paraquat residue levels in residential environments. Given that this approach has not been validated, it is unclear if being present at addresses within 500 m of agricultural land can provide a reliable estimate of true exposure.

Lung Cancer (High Quality: Park et al., 2009)

The association between paraquat exposure and lung cancer was evaluated in one prospective study involving the AHS study population (Park et al., 2009), which is further described in *All Cancers* under **Section 3.3** on *page 53.*

Park et al. (2009) reported no evidence of association between paraquat exposure and incident lung cancer based on ever/never exposure (RR: 1.01, 95% CI: 0.76-1.34, n = 85 exposed cases). The investigators also examined cumulative paraquat exposure based on both lifetime exposure days and intensity weighted lifetime exposure days and similarly reported no evidence of an association with lung cancer (see **Table 11**).

Based on this single study, there is no epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and lung cancer. The AHS investigation reported no evidence of a positive association between lung cancer and exposure to paraquat based on ever-use, and analyses based on a lifetime exposure days of paraquat exposure metric similarly showed no evidence of a positive association for any of the stratified exposure categories; in addition, there was no evidence of an exposure-response trend between exposure category and incident cases. As described previously in *All Cancers* **Section 3.3** on *page 53*, this study was determined to be of high quality, based on its prospective design, ascertainment of cancer using established registries, and strengths of the AHS exposure assessment approach.

Breast Cancer (Moderate Quality: Engel et al., 2005)

The association between paraquat exposure and breast cancer was evaluated in one study of the AHS study population (Engel et al., 2005).

Engel et al. (2005), as part of the AHS, evaluated the association between breast cancer incidence among farmers' wives and specific pesticides including paraquat. Pesticide exposure was assessed based on self-reported questionnaires completed by the AHS participants during study enrollment (1993 – 1997), and breast cancer cases were identified using cancer registries in Iowa and North Carolina. Of the 309 breast cancer cases identified within the cohort (n = 30,145) from study enrollment through 2000, fewer than 3 women reported paraquat exposure, so no paraquat-specific effect estimates were calculated for direct pesticide use by wives among all wives in the AHS cohort. The investigators performed an additional analysis that estimated exposure using husband's pesticide use. Based on this indirect measure of exposure, the investigators reported no evidence of a significant positive association between breast cancer and husband's pesticide use (RR = 1.3, 95% CI: 0.8-2.0, n = 30 exposed breast cancer cases).

Based on the AHS study identified, there is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and breast cancer. Engel et al. (2005) reported no evidence of a significant positive association among farmers' wives in the AHS. With regard to study quality, the study was determined to provide moderate quality evidence based on the study quality criteria outlined in the OPP framework. This determination was based on the general strengths of the AHS, including its prospective design and ability to identify cancer cases through linkage to cancer registries. An important limitation of the study, however was that only 3 woman reported direct use of paraquat. As a result, the investigators assessed indirect exposure based on

self-reported pesticide use data from wives' husbands. This approach has not been validated and may not be a reliable proxy for direct paraquat exposure by female spouses.

Colorectal Cancer (<u>High Quality</u>: Lee et al., 2007; Park et al., 2009)

The association between paraquat exposure and colorectal cancer was evaluated in two studies of the AHS study population that used similar methods and overlapping study subjects (Park et al., 2009; Lee et al., 2007).

- Lee et al. (2007) conducted a prospective cohort study to investigate the association between colorectal cancer incidence and pesticide exposure, including paraquat, in the AHS study population. The study population (n = 56,813) consisted of male pesticide applicators and their spouses living in Iowa and North Carolina who were enrolled in the AHS cohort. Cases were identified using cancer registry files from Iowa and North Carolina, and identified through the International Classification of Diseases for Oncology (ICD-0-2) code and controls included pesticide applicators (males only) who had not been previously diagnosed with colorectal cancer. Vital status was confirmed through the state death registries and the National Death Index annually. Incident cases were determined beginning at study enrollment (1993-1997) through December 31, 2002. Exposure was assessed through an initial enrollment questionnaire, and followed by a more detailed self-administered questionnaire filled out at home as part of initial enrollment. The questionnaires were used to determine pesticide usage of 50 different pesticides including paraquat. Exposure intensity values for individual pesticides were calculated using data collected from the questionnaire completed at enrollment as well as information obtained from previous published literature on pesticides. An unconditional logistic regression was used to calculate ORs and 95% CIs for individual pesticide exposures, and was adjusted for age, smoking status, state, and total days of pesticide application among all enrolled study participants. Of the 305 colorectal cancer cases, 60 cases reported ever having exposure to paraquat. The study authors reported no evidence of a positive association between colorectal cancer and exposure to paraquat, based on ever-use (OR = 0.9; 95% CI: 0.7-1.3). Similar results were observed when stratifying the analysis by cancer type, with no evidence of a positive association for colon cancer (OR = 0.7, 95% CI: 0.5-1.1) and no evidence of a significant positive association for rectal cancer (OR = 1.5, 95% CI: 0.8-2.6).
- As further described in *All Cancers* under **Section 3.3** on *page 53,* Park et al. (2009) conducted a prospective study of the AHS cohort to examine the association between paraquat exposure and cancer, including colorectal cancer. The study reported no evidence of an association between ever/never paraquat exposure and colon cancer (OR = 0.88, 95% CI: 0.61-1.26, n = 46 exposed cases) and no evidence of a significant positive association for rectal cancer (OR = 1.12, 95% CI: 0.7-1.8, n = 27 exposed cases). The investigators also examined cumulative paraquat exposure, based on both lifetime exposure days and intensity weighted lifetime exposure days and reported no evidence of an association with either colon or rectal cancer (see **Table 11**).

Based on the two AHS studies identified, there is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and colorectal cancer. Neither AHS investigation reported evidence of a significant positive association between colorectal cancer and exposure to paraquat based on ever-use, and analyses based on a lifetime exposure days of paraquat exposure metric similarly showed no evidence of a positive association for any of the stratified exposure categories; in addition, there was no evidence of an exposure-response trend between exposure category and incident cases (see **Table 11**). Similarly, Lee et al. (2007) also analyzed the AHS cohort and reported no evidence of an association. Both studies were determined to be of high

quality based on their prospective design, ascertainment of cancer using established registries, and strengths of the AHS exposure assessment approach.

Pancreatic Cancer (<u>High Quality</u>: Park et al., 2009)

The association between paraquat exposure and pancreatic cancer was evaluated in one prospective study of the AHS study population (Park et al., 2009), which is further described in *All Cancers* under **Section 3.3** on *page 53.*

Park et al. (2009) reported no evidence of a positive association between paraquat exposure and pancreatic cancer, based on ever/never exposure (OR = 1.32, 95% CI: 0.68-2.53, n = 14 exposed cases). The investigators were unable to assess cumulative paraquat exposure because too few exposed cases completed the take-home questionnaire needed to estimate lifetime exposure days and intensity weighted lifetime exposure days.

Based on the single study identified, there is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and pancreatic cancer. Park et al. (2009) reported no evidence of a significant positive association between pancreatic cancer and exposure to paraquat based on ever-use and were unable to assess cumulative paraquat exposure. As described previously in *All Cancers* under **Section 3.3** on *page 53*, this study was determined to be of high quality, based on its prospective design, ascertainment of cancer using established registries, and strengths of the AHS exposure assessment approach.

Kidney Cancer (<u>High Quality</u>: Park et al., 2009)

The association between paraquat exposure and kidney cancer was evaluated in one study of the AHS study population (Park et al., 2009), which is further described in *All Cancers* under **Section 3.3** on *page 53.*

Park et al. (2009) reported no evidence association between paraquat exposure and pancreatic cancer, based on ever/never exposure (OR = 1.11, 95% CI: 0.63-1.95, n = 20 exposed cases). The investigators were unable to assess cumulative paraquat exposure because too few exposed cases completed the take-home questionnaire needed to estimate lifetime exposure days and intensity weighted lifetime exposure days.

Based on the single study identified, there is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and kidney cancer. Park et al. (2009) reported no evidence of a positive association between pancreatic cancer and exposure to paraquat based on ever-use. As described previously in *All Cancers* under **Section 3.3** on *page 53*, this study was determined to be of high quality, based on its prospective design, ascertainment of cancer using established registries, and strengths of the AHS exposure assessment approach.

Bladder Cancer (<u>High Quality</u>: Koutros et al., 2016; Park et al., 2009)

The association between paraquat exposure and bladder cancer was evaluated in two studies of the AHS study population (Koutros et al., 2016, Park et al., 2009).

- Koutros et al. (2016) conducted a prospective cohort study to investigate the association between bladder cancer incidence and pesticide exposure, including paraquat, in the AHS study population. The study population consisted of male pesticide applicators, with incident bladder cancer cases identified through cancer registry files in North Carolina and Iowa and through 2010

and 2011, respectively. Pesticide exposure was assessed via 2 self-administered questionnaires, one administered during study enrollment (1993 – 1997) and a second follow-up questionnaire administered 5 years after enrollment. Investigators used this questionnaire data to estimate cumulative lifetime days of use and intensity-weighed lifetime days of use, and a Poisson regression analysis was used to calculate RRs controlling for age, race, state of residence, pack-years of cigarettes, and pipe smoking. Among the study population (n = 54,344), 321 bladder cancer cases were reported from study enrollment through follow-up in 2010 (in North Carolina) and 2011 (in Iowa), with 71 of the cases reporting exposure to paraquat. The investigators observed no evidence of an association between ever/never use of paraquat exposure and bladder cancer (RR: 0.86, 95% CI: 0.61-1.20). The investigators further analyzed the association using cumulative intensity-weighted days of paraquat exposure, stratified by smoking status, and similarly reported no evidence of an association (*Exposure Tertile 1* – OR = 0.96, 95% CI: 0.49-1.89, n = 10 exposed cases; *Exposure Tertile 2* – OR = 1.64, 95% CI: 0.91-2.96, n = 13 exposed cases; *Exposure Tertile 3* – OR = 1.29, 95% CI: 0.69-2.40, n = 12 exposed cases; *p-trend* = 0.65).

- As further described in *All Cancers* under **Section 3.3** on *page 53,* Park et al. (2009) conducted a prospective study of the AHS cohort to examine the association between paraquat exposure and cancer, including bladder cancer. The study reported no evidence association between paraquat exposure and incident bladder cancer based on ever/never exposure (OR = 0.9, 95% CI: 0.56-1.46, n = 25 exposed cases). The investigators were unable to assess cumulative paraquat exposure because too few exposed cases completed the take-home questionnaire needed to estimate lifetime exposure days and intensity weighted lifetime exposure days.

Based on the two AHS studies identified, there is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and bladder cancer. Neither AHS investigation reported evidence of a positive association between bladder cancer and exposure to paraquat based on ever-use, and analyses based on lifetime exposure days of paraquat exposure metric similarly showed no evidence of a positive association for any of the stratified exposure categories; in addition, there was no evidence of an exposure-response trend between exposure category and incident cases. Both studies were determined to be of high quality based on their prospective design, ascertainment of cancer using established registries, and strengths of the AHS exposure assessment approach.

Lymphoma (<u>High Quality</u>: Park et al., 2009; <u>Moderate Quality</u>: Ferri et al., 2017)

The association between paraquat exposure and lymphoma was evaluated in two studies. This included one study of NHL in the AHS study population (Park et al., 2009) and one study of both NHL and HL subtypes (Ferri et al., 2017).

- As further described in *All Cancers* under **Section 3.3** *on page 53,* Park et al. (2009) conducted a prospective study of the AHS cohort to examine the association between paraquat exposure and cancer, including NHL. The study reported no evidence of a significant positive association between paraquat exposure and NHL, based on ever/never exposure (RR: 1.47, 95% CI: 0.97-2.23, n = 41 exposed cases). The investigators further investigated lifetime exposure and intensity weighted lifetime days of paraquat exposure and reported no evidence of an association based on 13 exposed cases that completed the follow-up take-home questionnaire (see **Table 11**).
- Ferri et al. (2017) conducted a case-control study to investigate the association between occupational exposures, including paraquat, and major B-cell lymphoma subtypes in the provinces of Bari and Taranto in Southern Italy. 158 cases (30 HL and 128 NHL) were recruited from the hematology divisions of the University Hospital of Bari "Moscati" Hospital of Taranto during the years 2009-2014. 76 controls were from hospitals (departments of the

ophthalmological/orthopedic clinics of Bari and Tara) and a population-based regional register. No matching was performed because of the small number of controls enrolled into the study. After recruiting cases and controls, study subjects were interviewed using a semi-structured questionnaire to obtain information on demographic, socioeconomic, and lifestyle factors. The questionnaire was also used to ascertain exposure by asking questions on job activities and assigning qualitative exposure scores using the Carcinogen Exposure (CAREX) job-exposure matrix. CAREX assigns exposure scores to specific job titles and is based on professional judgement; specifically, CAREX assigns scores to different job sectors, based on the categories: no exposure, low exposure, and medium/high exposure. For each job activity, the duration was recorded and used to assess cumulative exposure for each study subject. The investigators then performed univariate analysis to examine the distribution of the ORs by occupational titles and multivariable logistic regression to assess the relationship between cumulative exposure to paraquat and lymphoma, adjusting for sister cancer familiarity, age at diagnosis, province, sex, smoking (pack/years) and level of education. Based on this approach, the investigators reported the results presented in **Table 12** below. While evidence of a significant positive association was reported for all lymphomas in the investigators' low exposed group, more specific analysis of HL and HLS, stratified by low and medium-high paraquat exposure, did not provide evidence of a significant positive association in analysis of all lymphomas or stratifying by HL and NHL.

Table 12: Summary of Effect Estimates Reported in Ferri et al. (2017)

Paraquat Exposure	Cases	Controls	OR (95% CI)
All lymphomas			
No	123	66	*Reference*
Low	28	6	2.91 (1.03-8.2)
Medium-high	7	4	1.1 (0.26-4.59)
Overall	158	76	1.51 (0.8-2.87)
Hodgkin lymphomas			
No	24	66	*Reference*
Low	6	6	1.95 (0.38-10.04)
Medium-high	-	-	-
Overall	30	76	1.52 (0.35-6.58)
Non-Hodgkin's lymphoma			
No	99	66	*Reference*
Low	22	6	2.83 (0.96-8.37)
Medium-high	7	4	1.27 (0.3-5.41)
Overall	128	76	1.52 (0.79-2.94)

Estimates were adjusted by sister cancer familiarity, age at diagnosis, province, sex, smoking (packs/years), years and level of education

Based on the two studies identified, there is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and lymphoma, including NHL and HL. As described previously in *All Cancers* under **Section 3.3** on *page 53*, Park et al. (2009) was determined to be of high quality based on its prospective design, ascertainment of cancer using established registries, and strengths of the AHS exposure assessment approach. The ever/never results are based on only 41 exposed cases who reported paraquat use when enrolled in AHS. Only 18 of these exposed cases completed the more detailed follow-up take-home questionnaire so the lifetime/cumulative exposure effect estimates were less stable and had wider confidence internals. Park et al. also examined multiple cancer outcomes. As such, they acknowledge that their findings may be due to chance and suggest that they warrant re-evaluation in AHS when more incident cases have accumulated. Ferri et al.'s investigation used a more limited case-control design that relied on retrospective exposure assessment. This retrospective exposure assessment could have been subject to recall bias, but more importantly relied on very broad job categories and generic assessment of occupations that could use

paraquat. This approach may be less reliable for estimating paraquat-specific exposure because there may be considerable variability in pesticide use practices with agriculture, depending on job responsibilities, crop type, and other factors. Due to these limitations, Ferri et al. (2017) was determined to be of moderate quality.

Childhood Leukemia (Moderate Quality: Monge et al., 2007)

The association between paraquat exposure and childhood leukemia was evaluated in a single Costa Rican population-based case-control study (Monge et al., 2007).

Monge et al. (2007) conducted a population-based case-control study in Costa Rica to investigate the relationship between parental exposure to pesticides and the risk of leukemia in offspring. The study population for investigating paraquat included 300 cases of childhood leukemia (age 0 to 14 years at diagnosis) in Costa Rica diagnosed between 1995 and 2000, and 579 population-based controls, who were drawn from the National Birth Registry and frequency-matched by birth year to cases. Exposure to paraquat and other pesticides was assessed through interview during 2001-2003. Pesticide-related interview questions included occupational, environmental, and home exposures of both parents. Those in agriculture reported use of pesticides, agricultural tasks, frequency of exposure (# applications/month and hours/day), determinants of exposure (task technology, PPE, field reentry, storing of pesticides, personal hygiene). Data were collected on 25 specific pesticides. The procedure for assessment included a prompted list of pesticides. Interview data were combined with external data on application rates for 14 crops, 21 calendar years, and 14 geographic regions. Childhood leukemia cases were ascertained using the Costa Rica Cancer Registry and confirmed at the Children's Hospital of Costa Rica. A total of 334 cases were identified. 34 of those cases either refused to participate or could not be located. After obtaining data on exposure and outcome, logistic regression was used to calculate ORs for total leukemia and acute lymphocytic leukemia. The researchers evaluated the correlation between pesticide exposure and a number of factors among the controls in order to select covariates. Most models included urban/rural residence. Other factors considered, but which showed little correlation among the controls with pesticide exposure (thus were not included) were: maternal age at conception, infectious disease of the child during the first year, x-ray exposure, mother's tobacco and alcohol use during pregnancy, father's smoking, history of newborn jaundice, and vaccination of the child. Based on this approach, the investigators examined maternal and paternal exposure and stratified exposure by year before conception and first year of life.

These results are summarized in **Table 13** below. With respect to maternal exposure, there were only 7 exposed cases overall, so the effect estimates are less stable and no evidence of a significant positive association was reported for either total leukemia or acute lymphocytic leukemia. With respect to paternal exposure, there was evidence of a positive association between paraquat exposure and total leukemia based on stratification by high vs. low exposure and year before conception as the exposure window of interest. However, other paternal results were not statistically significant for total leukemia acute and lymphocytic leukemia and provide no evidence of a positive association.

Table 13: Summary of Effect Estimates Reported in Monge et al. (2007)

Comparison	Comparison	OR (95% CI, number exposed cases)	
		Exposed/Unexposed	High /Low Exposure
Total Leukemia			
Father	Year Before Conception	1.1 (0.7, 1.7) n = 39	2.3 (1.1, 5.2) n = 14 (low), 25 (high)
	First Year of Life	1.5 (1.0, 2.3) n = 45	1.9 (0.9, 4.1) n = 18 (low), 27 (high)
Mother	Year Before Conception	3.4 (1.0, 11.8) n = 7	7.5 (0.5, 122.7) n = 1 (low), 3 (high)
	First Year of Life	7.8 (0.9, 7.06) n = 4	Not Reported
Acute Lymphocytic Leukemia			
Father	Year Before Conception	1.0 (0.6, 1.5) n = 30	1.67 (0.7, 4.1) n = 12 (low), 18 (high)
	First Year of Life	1.4 (0.9, 2.2) n = 36	1.7 (0.7, 4.0) n = 15 (low), 21 (high)
Mother	Year Before Conception	3.5 (1.0, 12.7) n = 6	6.0 (0.4, 101.6) n = 2 (low), 4 (high)
	First Year of Life	9.5 (1.1, 85.5) n = 4	Not Reported

Based on this single study, there is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and childhood leukemia. While the study ascertained cases using a Costa Rican Cancer Registry, the study was determined to be moderate quality because of limitations in its design and exposure assessment approach. For example, the investigators relied on a questionnaire to retrospectively assess exposure. This approach may be subject to misclassification because participants were asked to remember their pesticide use and other exposure up to ten years prior to the interview. More importantly, this approach may be subject to recall bias if cases recall their past exposure differently than controls. In addition, the study had only small number of paraquat exposed cases, particularly for the assessment of mother's exposure and childhood leukemia, which included a total of 4 exposed leukemia cases and 6 acute lymphocytic leukemia cases, respectively.

Glioma (Low Quality: Lee et al., 2005)

The association between occupational pesticide exposure and adult glioma was evaluated in one study of an agricultural population in Nebraska (Lee et al., 2005*).*

Lee et al. (2005) conducted a case-control study to investigate the association between farming and agricultural pesticide use in a study population of adults in eastern Nebraska. Cases were histologically-confirmed primary adult glioma cases diagnosed between 1 July 1988 and 30 June 1993. Cases were identified from the Nebraska Cancer Registry, or from 11 participating hospitals in Lincoln and Omaha covering more than 94% of adult glioma cases in the study population. Controls for the current study were randomly selected from the controls from the previous study covering the same base population and frequency matched by age, sex, and vital status to the combined distribution of the glioma, stomach, and esophageal cancer cases. The data were collected using telephone interviews with men and women diagnosed with glioma (n = 251) between 1988 and 1993 and controls (n = 498) randomly selected from the same geographical area. Unconditional logistic regression was used to calculate ORs for farming and for use of individual and chemical classes of insecticides and herbicides, including pesticides classified as nitrosatable (able to form N-nitroso compounds upon reaction with nitrite). With regard to paraquat, the investigators reported evidence of a strong positive association between paraquat use and risks of glioma

(OR = 11.1, 95% CI: 1.2- 101); however, this association was based on only 5 exposed cases and had very wide confidence intervals.

Based on this single study, there is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and glioma. While Lee et al. (2005) reported evidence of a strong positive association, the study was determined to be of low quality based on the study quality criteria provided in the OPP framework. The study had several important limitations related to its design, exposure assessment approach, statistical analysis, and ability to control for confounding. With regard to study design, Lee et al. used a case-control approach and may have introduced selection bias when recruiting their control group. Differences between the results for the self-reporting respondents and the proxy respondents illustrate the possible problem, as the control groups for each of these respondents were constructed differently and each could be biased in a different way. In the analysis, the reference group for the statistical tests is non-farmers, even though the pesticide use questions were not asked of non-farmers. As a result, the results for pesticides are confounded with farmer versus non-farmers and control groups with different proportions of farmers will result in different statistical results. The use of respondent-reported paraquat use to ascertain exposure introduced further uncertainty because it is not possible to attribute the increased odds of glioma to paraquat exposure alone. In particular, the self-reporting and proxy respondents have different levels of knowledge about pesticide use and possibly different motives for responding. Moreover, self-reported exposure assessment is likely to be subject to differential misclassification because study participants may incorrectly recall previous pesticide usage. In addition to these limitations, findings on paraquat are based on only 5 exposed cases and do not provide reliable effect estimates.

Cutaneous Melanoma (<u>High Quality</u>: Park et al., 2009)

The association between paraquat exposure and cutaneous melanoma was evaluated in one study of the AHS study population (Park et al., 2009), which is further described in *All Cancers* under **Section 3.3** on *page 53.*

Park et al. (2009) reported no evidence association between paraquat exposure and cutaneous melanoma, based on ever/never exposure (OR = 0.98, 95% CI: 0.60-1.60, n = 23 exposed cases). The investigators also examined cumulative paraquat exposure based on both lifetime exposure days and intensity weighted lifetime exposure days and similarly reported no evidence of an association with cutaneous melanoma (see **Table 11**).

Based on this single study, there is no epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and cutaneous melanoma. Park et al. (2009) reported no evidence of an association between cutaneous melanoma and exposure to paraquat based on ever-use, and analyses based on lifetime exposure days of paraquat exposure metric similarly showed no evidence of a positive association for any of the stratified exposure categories; in addition, there was no evidence of an exposure-response trend between exposure category and incident cases. As described previously in *All Cancers* under **Section 3.3** on *page 53*, this study was determined to be of high quality, based on its prospective design, ascertainment of cancer using established registries, and strengths of the AHS exposure assessment approach.

3.3.2 Evaluation of Findings

A total of eight studies were identified that investigated the association between paraquat exposure and cancers and are summarized in **Table 14** below. Five of the eight studies relied on the AHS cohort and the remaining three relied on registries or hospitals to identify cases in Costa Rica, Nebraska, and Southern Italy. Within AHS, Park et al. (2009) examined the largest number of cancer types and reported no

evidence of an association for most cancer outcomes and no evidence of a significant positive association for NHL. Ferri et al. (2007) also examined the association with NHL, as well as other lymphomas, but relied on a limited exposure assessment approach that may not reliably capture paraquat-specific exposure. As such, OPP determined there is *insufficient epidemiological evidence* at this time to conclude that there is a relationship between paraquat exposure and lymphoma, including NHL and HL. The association reported in Park et al. (2009), while not statistically significant, may warrant re-evaluation in AHS and further investigation in other study populations that may experience chronic exposure to paraquat.

For the remaining cancer types investigated, OPP has determined there is *no epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and cancer. Studies generally did not report positive findings and individual types of concern have only been investigated in a single study population, typically AHS, so the available epidemiologic literature does not enable a robust weight-of-evidence determination.

Table 14: Summary of Epidemiological Evidence on Paraquat Exposure and Cancer Outcomes

Study	Study Population	Study Quality	All Cancer	Prostate	Lung	Colon	Rectum	Pancreas	Kidney	Bladder	Lymphoma - All	NHL	HL	Leukemia	Melanoma	Breast	Child Leukemia	Glioma	Melanoma
Cockburn et al. (2011)	AHS	M		⊙															
Engel et al., 2005	AHS	M														⊘			
Ferri et al. (2017)	Southern Italy	M									⊙	⊙	⊘						
Koutros et al. (2015)	AHS	H								⊘									
Lee et al. (2007)	AHS	H				⊘	⊘												
Lee et al., (2005)	Nebraska	L																●	
Monge et al. (2015)	Costa Rica	M															⊙		
Park et al. (2009)	AHS	H	⊘	⊘	⊘	⊘	⊙	⊙	⊙	⊘		⊙		⊘	⊘				⊘

⊘ No evidence of an association between exposure and outcome (*e.g.,* OR ≤ 1.0).

⊙ No evidence of a significant association between exposure and outcome (*e.g.,* OR > 1.0 but not significant).

● Evidence of an association between exposure and outcome (*e.g.,* OR > 1.0 and significant).

3.4 Other Health Outcomes (25 Articles)

The remaining epidemiologic literature examined a broad range of adverse health outcomes and is summarized in this section. **Table 15** at the end of this section provides a summary of the study findings and quality ratings. For most of these health outcomes, only a single study was available on relationship with paraquat exposure. Many of these studies were of lower quality and/or only conducted in a single study population. These outcomes included:

- General Mortality
- Injury Mortality
- Renal/Liver Function and Hematology
- Thyroid Disease
- Myocardial Infarction
- Oxidative Stress
- Abnormal Skin Pigmentation
- Rheumatoid Arthritis
- Actinic Keratosis
- Male Reproduction
- Suicide
- Infant Birth Weight
- Aplastic Anemia

For a smaller number of health outcomes, more than one study was available and they were of higher quality based on the study quality criteria provide in the OPP framework. These outcomes included:

- End Stage Renal Disease
- Diabetes
- Eye Disorders
- Depressive Symptoms

The remainder of this section reviews the literature for these health outcomes, but provides more in-depth evaluation of positive findings from higher quality studies that warrant greater characterization for purposes of the OPP's Human Health Risk Assessment. In addition, **Appendix A** further summarizes the studies described in each section and provides the OPP's study quality assessment for individual article.

3.4.1 Literature Review

General Mortality (Moderate Quality: Tomenson and Campbell, 2011)

A single study evaluated the association between paraquat exposure and mortality in a cohort of paraquat production workers (Tomenson and Campbell, 2011).

Tomenson and Campbell (2011) reported on an update of a retrospective cohort study of mortality among workers at 4 paraquat production plants in Widnes, in the northwest of England. The aim of the study was to evaluate the mortality risk from Parkinson's Disease and other major causes among workers manufacturing paraquat between 1961 and 1995. During the late 1970s, several workers who had worked in one or more of the paraquat production plants operating in Widnes were diagnosed with skin lesions, including keratosis, squamous-cell carcinoma, and Bowen's disease, among others. As part of a subsequent investigation, a cohort of paraquat production workers was identified. The cohort included all workers who had ever been associated with the production of 4,49-bipyridyl or its subsequent conversion

to paraquat, or the packaging of paraquat. The cohort in the study included most of participants of the original cohort and an additional 227 employees (217 males and 10 females) from a subsequent cohort study of paraquat production plant workers established in 1983. Twenty males from the original cohort were excluded because they were determined to not have had exposure to paraquat (n = 8) or had insufficient identifying or demographic information to be included (*e.g.,* missing date of birth, n = 12). The final cohort evaluated in this study consisted of 926 male employees and 42 female employees. All cohort members were considered occupationally exposed to paraquat. However, only very limited industrial hygiene sampling was conducted to assess workers' paraquat exposures, and the authors determined that the available information was insufficient to conduct a quantitative exposure assessment. The investigators obtained cohort members' vital status at the end of June 2009 from the Medical Research Information Service of the National Health Service. Underlying cause of death and other causes of death mentioned on death certificates were coded by the U.K. Office of Population Censuses and Surveys using International Classification of Diseases (ICD) codes.

Standardized mortality ratios (SMR) were calculated as the ratio of the observed to the expected deaths, and presented as percentages, along with 95% confidence intervals. Based on this approach the investigators reported no evidence of an association with mortality generally or PD-related mortality. Specifically, there was no relative increase in mortality observed among the 926 male paraquat plant workers compared to the national mortality rate (SMR for all-cause mortality: 88%, 95% CI: 78%-98%) or local mortality (SMR: 66%, 95% CI: 68%-86%). Working in the paraquat production plants was also not associated with PD-related mortality (SMR comparing Parkinson's disease mortality among paraquat plant workers to national mortality rate: 31% (95% CI: 1%-171%); SMR comparing PD-related mortality among paraquat plant workers to local PD-related mortality: (32% (1%-176%). Standardized mortality ratios for specific causes were all below 100%, indicating lower mortality among workers relative to national and local mortality rates, except for the SMR for external causes of death, which was 100% (i.e. parity between paraquat plant workers and reference populations).

There is no epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between non-occupational paraquat exposure and mortality. Tomenson and Campbell (2011) found no evidence of positive associations between working in a paraquat production plant and mortality or Parkinson's disease-specific mortality using either national or local reference populations. Overall, the study was determined to be of moderate quality based on the study quality criteria provided in the OPP framework. With regard to strengths, the investigators used national and local reference populations, and SMRs estimated using the 2 reference groups were similar to each other. The investigators used administratively collected age- and period-specific mortality data from national and local sources in order to estimate expected deaths and calculate standardized mortality ratios. This study design ensures that exposure pre-dates outcome, which was a strength of the study. A quantitative exposure assessment was not conducted, and the authors assumed that all workers included in the study were exposed to paraquat and its precursors. Although mortality from many causes was evaluated, the authors focused on Parkinson's disease; however, only 1 case of Parkinson's disease-specific mortality was observed among the paraquat plant workers. The study included all workers, but is still susceptible to selection bias due to the healthy worker effect – meaning that an alternative explanation for the lower mortality observed among paraquat plant workers is that the workers are generally healthier, and have lower mortality than the general populations used for comparison.

Injury Mortality (Low Quality: Waggoner et al., 2013)

The association between occupational pesticide exposure and injury mortality was evaluated in one study using the AHS study population (Waggoner et al., 2013).

Waggoner et al. (2013) investigated the association between specific pesticides including paraquat and fatal injury among farmers using data from the prospective cohort AHS. The study population consisted of male farmers (n = 51,035) in Iowa and North Carolina that were enrolled in AHS in 1993-1997 and followed-up through 2008. Individual pesticide exposure for 49 specific pesticides was assessed through the enrollment and follow-up questionnaires. Fatalities among the participants were ascertained through state death registries and the National Death Index, and cases were defined as any mortality that occurred in an occupational setting, including motor vehicle accidents, from enrollment until the end of follow-up (1993-December 31, 2008). The control group included farmers who did not suffer from a deadly injury during the study, regardless of vital status. A Cox proportional hazards model was used to calculate HRs and 95% CIs for fatal injuries and individual pesticides based on ever/never exposure, adjusted for age and state. Of the total study population (n = 51,035), 11,161 (25%) farmers reported ever exposure to paraquat. Among the total fatal injuries reported (n = 338), 91 (31%) reported exposure to paraquat. The investigators reported evidence of a positive association between risk of fatal injury and paraquat exposure among male farmers in the AHS, based on ever/never use (HR: 1.35; 95% CI: 1.05-1.74). The investigators also further examine the exposure-response for 18 select herbicides; however, paraquat was not included in this exposure-response analysis and no rationale was provided for its exclusion.

Based on this single study, there is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between occupational paraquat exposure and injury mortality. Overall, the study was determined to be low quality based on the study quality criteria provided in the OPP framework. While Waggoner et al. (2013) leveraged the AHS's prospective design and mortality data available through the National Death Index, it has important methodological limitations. The original aim of AHS was to examine the association between chronic pesticide exposure and cancer outcomes. In contrast to cancer, fatal injury is an acute event so it is unclear if self-reported pesticide use at enrollment is a valid measure of exposure during the time interval that preceded fatal injury. The investigators also indicate that frequency of pesticide use may be an "indicator" of other activities that could increase the risk of fatal injury. For example, individuals who use more pesticides may also use more complex farm equipment more frequently, increasing the chance of an occupational accident that could lead to death. As such, more definitive information is needed on cause of fatal injury and the contributing events that lead to accidents before any conclusions can be drawn from the AHS study population.

End Stage Renal Disease (<u>High Quality</u>: Lebov et al., 2016; <u>Moderate Quality</u>: Lebov et al., 2015)

The association between paraquat exposure and end stage renal disease (ESRD) was evaluated in 2 AHS studies, one of female spouses of pesticide applicators and the other of male pesticide applicators (Lebov et al., 2015, 2016, respectively).

- Lebov et al. (2015) conducted a prospective study using the AHS study population to examine the association of ESRD and pesticides in the wives of pesticide applicators. The study population consisted of <u>female spouses of pesticide applicators</u> enrolled in the AHS, an ongoing, prospective cohort study, and ESRD cases were ascertained through linkage with the U.S. Renal Data System. Of the 31,142 study participants who were enrolled in the study in 1993-1997, a total of 98 ESRD cases were identified. Pesticide exposure was assessed by information obtained via self-administered questionnaires completed at enrollment and at home, with this information used to assess both direct exposure (wives' personal use of paraquat) and indirect exposure (husbands' use of paraquat). A Cox proportional hazards model was then used to calculate HRs for ESRD, adjusting for age. The investigators examined direct exposure to some pesticides, but this information was not available for paraquat. For the indirect exposure analysis (husbands' use of pesticides among wives' who reported no personal use of pesticides), 64 confirmed cases of renal

disease were identified among study participants, and 21 (40.4%) of those cases reported husbands' ever use of paraquat. Among the 13,653 non-cases, 10,010 (75.6%) controls reported husbands' ever use of paraquat. Results suggested evidence of a positive association between indirect paraquat exposure and ESRD (HR = 1.99; 95% CI: 1.14-3.47). A further analysis considered husbands' cumulative exposure and provided no evidence of a significant positive association (*1.0-15.4 lifetime exposure days* – HR: 1.36, 95% CI: 0.43-4.30; > *15.4-102.8 Lifetime Days* – HR: 1.78, 95% CI: 0.56-6.62), but was based on only 6 of 21 exposed cases that completed the take-home questionnaire information needed to assess cumulative exposure.

- Lebov et al. (2016) evaluated the association of ESRD and pesticides among male pesticide applicators (as opposed to the wives, above) enrolled in the AHS during 1993-1997. ESRD cases were identified through linkage of the AHS cohort data with the US Renal Data System. Pesticide exposure was assessed via self-administered questionnaires completed at enrollment and at home, and this information was used to calculate lifetime pesticide usage for 39 pesticides. Exposure values were further modified by an intensity factor to account for the variation in pesticide application practices to produce an estimate of intensity-weighted lifetime days of exposure. The Cox proportional hazards model was used to calculate HRs for ESRD, controlling for state of study enrollment. Of the 24,429 study participants, 320 confirmed cases of ESRD were identified, including 33 reporting use of paraquat. Based on these study subject, the investigators assessed tertiles of exposure and reported evidence of a positive association using the non-exposed as the referent category: Low Exposure Tertile (< 708.75 days): HR = 1.05, 95% CI: 0.56, 1.97, n = 11 exposed cases); Middle Exposure Tertile (≥ 708.75 to ≤ 2,334.5 days): HR = 2.3, 95% CI: 1.2-4.41, n = 11 exposed cases);); High Exposure Tertile (≥ 2,334.5 days): 2.15, 95% CI: 1.11-4.15, n = 11 exposed cases);), with p for trend = 0.0164.

Based on the two AHS studies, there is limited but insufficient evidence at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and end stage renal disease. Overall, Lebov et al. (2015) was determined to be of moderate quality and Lebov et al. (2016) was determined to be of high quality based on the study quality criteria provided in the OPP Framework. The general strengths of both studies were the underlying prospective design of AHS, focus on U.S. agricultural populations, and availability of a U.S. registry to comprehensively identify ESRD cases. Lebov et al. (2016) was also able to direct assess paraquat exposure based on the AHS survey instrument. In contrast, Lebov et al. (2015) indirectly assessed pesticide exposure of applicator wives using husband use information as a surrogate. This approach has not been validated and may not be a reliable proxy for direct paraquat exposure by female spouses. Based on the study limitation, Lebov et al. (2015) was rated moderate even though the two studies share many of the same design elements.

Both studies reported evidence of a positive association between paraquat exposure and ESRD, based on husbands' ever use of paraquat among applicator wives (Lebov et al., 2015) and the upper 2 tertiles of paraquat exposure among applicators (Lebov et al., 2016). While positive associations were reported, there were only a small number of paraquat cases in both studies (21 and 33, respectively), so the ability to assess the exposure-response relationship was limited. As such, while both AHS studies reported positive findings, further investigation is needed to replicate the results in studies with a larger number of cases and other study populations that may experience chronic paraquat exposure.

Renal/Liver Function and Hematology (Low Quality: Howard et al., 1981; Senanayake et al., 1993)

Two studies examined the association between general health and occupational paraquat exposure (Howard et al., 1981; Senanayake et al., 1993). These studies also assessed lung and respiratory outcomes, so general information on their design is provided in **Section 3.2.1**. With respect to renal and liver and hematology, the authors report the following:

- As described in **Section 3.2.1**, Howard et al. (1981) conducted a cross-sectional study that investigated the relationship between use of paraquat and clinical indicators of health, including clinical measures of hematological, liver, renal, and lung function among palm oil and rubber plantation workers (n = 74) in Malaysia. Blood samples were analyzed to assess liver function (ALT, AST, ALKP), renal function (blood urea nitrogen, serum creatinine), and hematology (red and white cell counts, PCV, MCHC, MCH, MCV and white cell differential) and urine albumen was also measured. The investigators analysis focused on comparison of 27 paraquat exposed spraymen with 2 unexposed groups: (1) tappers, harvesters, and general plantation workers who had minimal exposure to paraquat due to working in areas which had recently been sprayed, and 2) factory workers where raw latex is initially processed and have no known occupational exposure to paraquat. Based on this comparison, the investigators reported no evidence of an association for the renal, liver and hematological parameters. The investigators further reported that group means fell within the normal range of the laboratory performing the analysis and some lung and liver measurements were actually higher in the unexposed groups.[17]
- As described in **Section 3.2.1**, Senanayake et al. (1993) conducted a cross-sectional study which investigated the relationship between use of paraquat and clinical indicators of health (hematological, liver, renal, and lung function health outcomes) among tea estate workers (n = 240) in Sri Lanka, including 85 spraymen, with a at least 5 years of spraying paraquat. Two comparison groups: 1) 79 general estate workers who had minimal exposure to paraquat due to working in areas which had recently been sprayed, and 2) 76 tea factory workers who processed the freshly picked tea leaves and have no known occupational exposure to paraquat. After collecting data on exposure and clinical examination, the investigators performed analysis of covariance to compare the 3 groups of workers. Based on this approach, the investigators reported no evidence of an association for the parameters hemoglobin and packed cell volume. Paraquat sprayers had a mean hemoglobin of 14.50 g/dl and packed cell volume of 45.37%, whereas factory and general workers had a mean hemoglobin of 14.28g/dl and 14.84g/dl, respectively, and mean packed cell volume of 44.87% and 46.35%, respectively.

Based on the two available studies, there is no epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between non-occupational paraquat exposure and renal/liver function and hematology. The available studies were determined to be of low quality based on the study quality criteria in the OPP framework. The primary limitation of both studies is that they relied on cross-sectional designs and were unable to assess the temporal association between paraquat exposure and the parameters examined. They were also conducted in countries that may not be generalized to the U.S. because of differences in agricultural practices, as well occupations practices in their reference populations, and other lifestyle and demographic factors.

Diabetes (<u>Moderate Quality</u>: Montgomery et al., 2008, Starling et al., 2014; Juntarawijit and Juntarawijit, 2018)

Three studies investigated the association between paraquat exposure and diabetes, including two AHS studies (Montgomery et al., 2008; Starling et al., 2014) and one study of Thai farmers (Juntarawijit and Juntarawijit, 2018).

[17] Reported regression coefficients and p-values - Hb: -0.34 (p-value = 0.21); PCV: -1.90 (p-value = 0.13); RBC: -0.262 (p-value = 0.16); MCV: 0.43 (p-value = 0.96); MCH: 0.71 (p-value = 0.52); log10WBC: -0.0186 (p-value = 0.053); log10AST: -0.0300 (p-value = 0.51); log10ALT: 0.4302 (p-value < 0.0001); log10ALKP: -0.0889 (p-value = 0.003); log10Creatinine: -0.0383 (p-value = 0.034); log10BUN: -0.0757 (p-value = 0.028).

- Montgomery et al. (2008) investigated the association between diabetes and paraquat exposure among pesticide applicators in a nested case-control study. The study population consisted of participants in the AHS (n = 33,457)[18], and incident diabetes was identified via self-report at either enrollment, on the take-home questionnaire and during a follow-up interview completed 5 years after enrollment in the AHS (1999-2003). A questionnaire detailing pesticide usage was used to determine lifetime exposure. Logistic regression was used to determine the association between diabetes and paraquat exposure. Among the 1,176 diabetic cases, 313 (32%) reported ever use of paraquat. Among the 30,611 non-diabetic controls with complete data, 6,509 (24%) reported ever use of paraquat. Reported unadjusted results provide evidence of a positive association between ever use of paraquat and diabetes (OR = 1.45; 95% CI: 1.26, 1.66); however, there was no evidence of an association when also adjusting for BMI and state of residence in addition to age (OR = 1.01; 95% CI: 0.87, 1.18).
- In another study, diabetes incidence among female spouses was reviewed by Starling et al. (2014) in a cohort study to investigate its potential association with paraquat and other pesticides. Using data from the AHS, an ongoing prospective cohort, the study population included female spouses (n = 13,637) of farmers who resided in Iowa and North Carolina, and incident cases included farmers' wives who self-reported a physician-diagnosis of diabetes between study enrollment (1993-1997) and follow-up interviews conducted an average of 12 years after enrollment. Pesticide exposure was assessed via self-report during study enrollment for 50 individual pesticides including paraquat based on ever-use. Two follow-up interviews conducted approximately every 5 years collected health information including incident diabetes, also via self-report. Cox proportional hazard regression models were used to estimate HRs and 95% CIs to analyze the association between ever-use of a pesticide and incident diabetes in women, adjusting for BMI and state. Of the total 688 cases, 19 (3%) reported exposure to paraquat, and of the total 12,949 non-cases, 264 (2%) reported paraquat exposure. Reported study results provide no evidence of a significant positive association between paraquat use and incident diabetes in women based on ever-use (HR = 1.07; 95% CI: 0.67, 1.71).
- Juntarawijit and Juntarawijit (2018) conducted a case-control study of the Bang Rakem district of Thailand. Cases were recruited from 7 randomly selected hospitals from 21 sub-district hospitals in Bang Rakem. Of 2,832 potential cases identified from outpatient service information, 1,000 were randomly selected for initial interview. Controls were close neighbors of cases and were the same gender and with 5 years of age. 866 cases and 1021 controls provided demographics information and completed an exposure questionnaire derived from the AHS. Multivariable logistic regression was used to calculate ORs for 35 individual pesticides, including paraquat, adjusting for gender, age, BMI, smoking, alcohol, family history of diabetes, and occupation. The investigators evaluated ever/never exposure, but indicate that they could not evaluate cumulative exposure-days because the number of subjects using individual pesticides was small. Based on this approach, the investigators reported no evidence of a significant positive association between paraquat exposure and diabetes (OR = 1.31, 95% CI: 0.97-1.79, n = 115 paraquat exposed cases).

Overall, there is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and diabetes. Montgomery et al. (2008) reported no evidence of a positive association between ever-use of paraquat and diabetes among pesticide applicators. Similarly, Starling et al. (2014) reported no evidence of a significant positive association between paraquat use and incident diabetes in women based on ever-use. Self-reported diagnosis of diabetes among the study participants and the inability to control for diet and exercise were considered study limitations in both studies and may have resulted in misclassification of some of the observed

[18] Note: The study population includes only applicators who completed questionnaires at enrollment and follow-up.

results and/or errors induced by confounding, respectively. The potential for selection bias was also present in both studies since a large number of participants who did not complete a follow-up questionnaire might have been diabetic at study enrollment. Juntarawijit and Juntarawijit (2018) also reported no evidence of significant positive association in their study in Thailand. This study was also determined to be of moderate quality based on the study quality criteria provided in the OPP framework. Study strengths included clinically ascertainment of diabetes cases and recruitment of both cases and controls that were recruited from similar neighborhoods. The study, however, relied on a more limited questionnaire to ascertain only ever/never exposure.

Eye Disorders (Low Quality: Kirrane et al., 2005; Moderate Quality: Montgomery et al., 2017)

Two AHS studies investigated the association between paraquat exposure and eye disorders, including a cross-sectional study conducted by Kirrane et al. (2005) and a nested case-control study by Montgomery et al. (2017).

Kirrane et al. (2005) conducted a cross-sectional study using the AHS study population to investigate the association of paraquat and other pesticide exposures and retinal degeneration and other eye disorders among wives of farmer pesticide applicators. A total of 31,173 women self-reported eye disorders and pesticide use through mailed questionnaires that were completed and returned by study participants; however, telephone interviews were used for the subjects who did not return their mailed questionnaire. Logistic and hierarchical logistic regression modeling were used to obtain ORs and 95% CIs for individual pesticides including paraquat, controlling for age and state of residence. Of the 281 cases who reported retinal or macular degeneration among the study participants, 0.4% reported exposure to paraquat, and among the controls, 1.2% reported exposure to paraquat. Results showed no evidence of a positive association between paraquat exposure and retinal degeneration (OR = 0.7; 95% CI: 0.3, 1.7).

- In a follow-up study to Kirrane et al. (2005), Montgomery et al. (2017) conducted a case-control study nested in the AHS to determine if new cases of age-related macular degeneration (AMD) were associated with previous pesticide exposure including paraquat. Using data from the AHS follow-up interviews, cases included AHS study participants (men and women) who self-reported either an AMD diagnosis during 1994 to 2007 or reported early signs of AMD. These cases were ascertained by physicians with supporting pathology or retinal photographs obtained from the cases. Cases were compared to a control group, consisting of AHS members who did not have AMD. Exposure was assessed at enrollment and follow-up via self-report, and a logistic regression was run to determine ORs and 95% CIs for individual pesticides including paraquat, controlling for age, gender, and smoking. Among the total 161 cases and 39,108 controls, 30 (20%) exposed cases and 5,542 (15%) exposed controls reported exposure to paraquat. The results indicated no evidence of a significant positive association between paraquat and AMD based on ever/never exposure (OR = 1.5; 95% CI: 0.9-2.3). The analysis of cumulative days of use also indicated no evidence of a significant positive association between paraquat and AMD (> 0-10 Cumulative Days of Paraquat Use – OR = 1.2, 95% CI: 0.5-2.6, n = 7 exposed cases; > 10 Cumulative Days of Paraquat Use – OR = 1.4, 95% CI: 0.6-3.2, n = 6 exposed cases; p-trend = 0.413).

There was insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between paraquat and either AMD or retinal degeneration. Kirrane et al. (2005) reported no evidence of an association in their cross-sectional study of the AHS. This study was determined to be of low quality based on the OPP framework study quality criteria. The primary reason for this determination is that the study relied on a cross-sectional design and was unable to assess the temporal association between paraquat exposure and the eye disorders of interest. Montgomery et al.

(2017) also reported no evidence of an association. This study used a stronger case-control design and was determined to be of moderate quality because the study prospectively identified potential eye disorder cases, clinically confirmed diagnosis, and assessed both ever/never exposure and cumulative lifetime exposure.

Thyroid Disease (Low Quality: Goldner et al., 2010)

One study investigated the association of thyroid disease relative to paraquat exposure in the AHS study population (Goldner et al., 2010).

Goldner et al. (2010) investigated the association between thyroid disease and paraquat and other pesticides in a cross-sectional analysis using data from the AHS. Pesticide exposure among female spouses of male farmers in the AHS was reported through 2 self-administered questionnaires (at enrollment and follow-up), and prevalent thyroid disease status was ascertained through self-report during follow-up interviews. Prevalent thyroid disease was further classified into 3 subgroups: hypothyroidism, hyperthyroidism, and 'other' thyroid disease. Pesticide exposure (ever/never) was assessed via a self-administered questionnaire. Polytomous logistic regression analysis was used to analyze the association between ever-use of a pesticide and the occurrence of thyroid disease, adjusting for BMI, age at enrollment, smoking status, hormone replacement therapy (ever/never), and education. Of the 2,043 total cases of thyroid disease reported, 5 (1.4%) hyperthyroid cases, 21 (1.9%) hypothyroid cases, and 8 (1.4%) 'other' thyroid cases reported ever-use of paraquat. The authors reported that the number of exposed cases was too small to assess the paraquat association with hyperthyroid. The authors reported evidence of a significant positive association for hypothyroid (OR = 1.9; 95% CI: 1.1-2.8) and no evidence of a significant positive association for other thyroid disease (OR = 1.4; 95% CI: 0.73-3.1).

There was insufficient evidence at this time to conclude that there is a clear associative or causal relationship between paraquat and thyroid disease. The single available study was conducted using the AHS study population and reported no evidence of significant positive association among female spouses of male farmers. The study was determined to be of low quality based on the OPP framework study quality criteria. The primary limitation of the study is that it relied on a cross-sectional design and was unable to assess the temporal association between paraquat exposure and thyroid disease. Other study limitations included ascertainment of thyroid disease based on self-report, rather than clinical diagnosis. Additionally, the investigators were only able to assess ever/never exposure and did not have more detailed exposure information to assess the dose-response relationship between paraquat exposure and thyroid disease.

Myocardial Infarction (Moderate Quality: Mills et al., 2009)

The association between occupational paraquat exposure and fatal and non-fatal myocardial infarction (MI) was evaluated in the AHS study population.

Mills et al. (2009) conducted a prospective study using the AHS cohort to investigate the association between myocardial infarction (MI) and pesticide exposure. The study population consisted of AHS male pesticide applicators living in Iowa and North Carolina, and pesticide exposure was assessed through 2 self-reported questionnaires completed at study enrollment and again at the 5-year follow-up. MI included both fatal and non-fatal myocardial incidents which were analyzed separately due to different follow-up times. The study population for MI mortalities (n = 54,609) was more inclusive relative to the non-fatal MI group (n = 32,024), as the non-fatal MI group included the 5-year follow-up period. For MI mortalities, cases included pesticide applicators involved in the AHS who died from a fatal MI between the time of study enrollment to follow-up (1993-2004), and these were ascertained using state and national death databases. Non-fatal MI incident cases were identified during follow-up (1999-2003) and

included AHS participants who self-reported the occurrence of MI. The Cox proportional hazard regression model was used to calculate HRs and 95% CIs for fatal and non-fatal MI risk for individual pesticides, adjusted for age, smoking, and state for the fatal MI analysis, and adjusted for state, age, smoking, and BMI for the non-fatal MI analysis. Among the 476 fatal MI cases, 27% reported exposure to paraquat, and of the 839 non-fatal MI cases, 32% reported paraquat exposure. No evidence of an association was reported for fatal MI and ever/never paraquat exposure (fatal MI: HR= 0.90; 95% CI: 0.71-1.15) and no evidence of a significant positive association was reported for non-fatal MI and ever/never paraquat exposure (non-fatal MI: HR = 1.09; 95% CI: 0.97-1.30).

There is no epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and fatal and non-fatal MI in male pesticide applicators. The single available study was conducted using the AHS study population and reported no evidence of a positive association among male pesticide applicators. The study was determined to be to be moderate quality based on the OPP framework study quality criteria. Study strengths include the prospective design of AHS and exposure assessment approach. With respect to limitations, myocardial infarction mortality and nonfatal myocardial infarction incidence were ascertained using state/national death registries and self-report during phase 1 follow-up in 1999-2003, respectively. The use of registry data on mortality allowed the investigators to evaluate fatal MI in the entire AHS cohort, where non-fatal MI could only be evaluated in 32,024 of the total 54,609 participants enrolled in AHS (58%). The follow-up period for non-fatal MI was only a median time of 5 years, whereas the median follow-up time for fatal MI was 11.8 years. An additional limitation in the evaluation of non-fatal MI is that ascertainment relied on self-report and has not been validated. The investigators acknowledge this in the discussion of their findings and suggest that this approach may result in misclassification, most likely non-differential, because studies in other populations suggest that only 60-68% of self-reported MI cases could be validated based on medical chart review.

Oxidative Stress (<u>Low Quality</u>: Ranjbar et al., 2002)

The association between paraquat exposure and oxidative stress based on plasma measurement of lipid peroxidation, antioxidant capacity, and total thiol groups was evaluated in one study of paraquat production workers in Tehran, Iran.

Ranjbar et al. (2002) conducted a cross-sectional study to investigates oxidative stress in 30 workers at a paraquat–formulating factory (exposed) and in 30 volunteers from Tehran University (unexposed). The 30 cases were male workers at a paraquat-formulating factory who were in the profession at least for 1 year and ranged in age between 25 and 57 years. These workers' main work was formulating paraquat. The 30 controls were age and gender-matched volunteers of medical sciences employees from the Tehran University who based on their socio-economic and nutrition status were not directly exposed to pesticides. Plasma samples were obtained from each subject. The 3 measures of oxidative stress were lipid peroxidation, antioxidant capacity, and total thiol groups. Lipid peroxidation was measured from plasma samples mixed with trichloroacetic acid (20%) and the precipitate was dispersed in H2SO4 (0.05 M). Thiobarbituric acid was added and heated. Thiobarbituric acid reactive substances were extracted by n-butanol and absorbance was measured in nmol/ml. Antioxidant capacity of blood was determined by measuring the ability of plasma to reduce Fe3+ to Fe2+. The ferric reducing ability of plasma was measured in µmol/ml. Total thiol (SH) groups of plasma was measured spectrophotometrically in units mM. Two sample t-tests were used to compared cases and controls for each of the outcomes. Based on comparison between the paraquat factory workers and unexposed volunteers from Tehran University, the investigators reported evidence of an association. Each of these group comparisons was statistically significant ($p < 0.001$) and is summarized below:

- **Mean lipid peroxidation** for cases was 11.46 nmol/ml (95% confidence interval (CI) 10.86 – 12.06) and for controls was 10.11 nmol/ml (95% CI: 9.68 – 10.53)
- **Mean antioxidant capacity** for cases was 1.35 µmol/ml (95% CI: 1.32 – 1.38) and for controls was 1.54 µmol/ml (95% CI: 1.51 – 1.57
- **Mean total (SH) groups** for cases was 0.16 mM (95% CI: 0.15 – 0.17) and for controls was 0.21 mM (95% CI: 0.19 – 0.22)

Based on the single study available, there is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and oxidative stress. The study reported evidence of a positive evidence, but was determined to be low quality based on the OPP framework study quality criteria. Most importantly, the study used a cross-sectional design and was unable to assess the temporal association between paraquat exposure and the measures of oxidative stress examined. The study was also relatively small and included only 30 workers and 30 university employees. While information is not available, it seems likely that these 2 groups may have systematic differences in other factors, such as health and socioeconomic status, that could introduce selection bias into the study.

Abnormal Skin Pigmentation (Low Quality: Jee et al. 1995)

The association between paraquat exposure and abnormal skin pigmentation was evaluated in one study of Taiwanese paraquat production workers.

Jee et al. (1995) conducted a cross-sectional study in tandem with a histopathologic case-series study with the objective of characterizing the pathologic features of workers in paraquat manufacturing plants with a focus on the role of occupational exposure to bipyridine. Paraquat exposure *per se* was not evaluated. Potentially bipyridine-exposed workers (n = 242) from 28 paraquat production factories in Taiwan were examined and interviewed between 1983 and 1991. Exposure characterization was based on job classification; workers were classified as "bipyridine exposed" if their job included centrifugation and crystallization processing of bipyridine in open tanks. Photographs of suspicious lesions corresponding to 156 workers were taken for subsequent objective characterization and evaluation of severity; 86 workers did not have suspicious skin lesions. Of the 156 workers, 133 had skin lesions which were graded for severity on a 1-to-3 scale. Severity of abnormal skin changes was strongly associated with exposure to bipyridines (p-trend = 0.0001). Eleven workers considered to be representative of the affected workers provided skin biopsy specimens (n = 23) which were evaluated by a dermato-pathologist. The severity of skin lesions was ranked by severity and analyzed in conjunction with worker reported occupational exposure histories. Pathology specimens showed various degrees of solar damage including early actinic changes, solar lentigo, actinic keratosis, squamous cell carcinoma, and actinic keratosis coexisting with squamous cell carcinoma.

There is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and abnormal skin pigmentation. Jee et al. (1995) assessed abnormal skin pigmentation and skin lesions among Taiwanese paraquat factory workers but did not evaluate associations with paraquat exposure specifically and therefore did not report any evidence of a positive association between paraquat and any health endpoint. The study was very limited overall and appears to be a *post hoc* assessment of an association rather than a conventional epidemiologic study design implemented to test an *a priori* hypothesis. For example, subject selection was not well detailed in the report, but it appears that a convenience sample of subjects was enrolled in the study. As such, the study may be more appropriately considered a hypothesis-generating study. The researchers presented a single cross-tabulation of skin lesion severity grade by bipyridine exposure category (which was only crudely defined). Again, paraquat exposure *per se* was not evaluated. Misclassification of exposure (false

positives and false negatives) was likely in this study but to an unknown extent. The authors presented little evidence to reassure the reader that these errors were independent of skin lesion severity grade. Selection bias due to the healthy worker effect may be present as the study included only workers present and employed at the paraquat plants, though this is unlikely to have induced the positive association observed between occupational exposure and skin lesion severity. The investigators also made no attempt to adjust for potential confounders.

Rheumatoid Arthritis (Low Quality: Koureas et al., 2017)

The association between paraquat exposure and rheumatoid arthritis was evaluated in one study of farm owners in Greece.

Koureas et al. (2017) conducted a cross-sectional study in Thessaly, Greece to investigate the association between agricultural use of pesticides and the health outcomes rheumatoid arthritis and allergic rhinitis. A summary of the study's design and methods is available in *Allergic Rhinitis* under **Section 3.2** *(see page 47*). As summarized, limited descriptive results are provided in the manuscript, but the investigators report that 25 study subjects were allergic rhinitis cases. Based on the logistic regression model, the investigators reported no evidence of an association for rheumatoid arthritis (OR = 0.69, 95% CI: 0.094-5.03).

Based on this single study, there is no epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and rheumatoid arthritis. This study determined to be of low quality and had several important limitations. It is likely that selection bias is present because exposed and unexposed study subjects were distinct populations. The investigators also did not consider co-exposure to pesticide or agricultural risk factors so it is not clear that the study had the ability to distinguish between farming in general and specific risk factors in an agricultural setting. Furthermore, it relied on a cross-sectional design and was unable to evaluate the temporal association between paraquat exposure and rheumatoid arthritis.

Actinic Keratosis (Low Quality: Cooper et al., 1994)

The association between occupational paraquat exposure and actinic keratosis was evaluated in one study of paraquat product workers in Texas.

Cooper et al. (1994) conducted a cross-sectional study of keratoses among workers at a paraquat production plant in Texas which was motivated by earlier reports of excess keratoses occurring among paraquat production workers in England and Taiwan. The aim of this study was to evaluate whether occupational exposures related to work in a paraquat production plant are associated with the prevalence of keratosis. To evaluate the association, they compared keratosis prevalence among current workers (n = 112) to that among a sample of the workers' friends who never worked at the paraquat production plant (n = 232). Odds of keratosis among 2 levels of plant exposure were also assessed. Non-exposed friends of plant workers were frequency-matched to workers on age, race, and sex. The study, which took place in 1990, was based on occupation (worker vs. friend), employment records, self-reported exposures. Paraquat exposure specifically was not evaluated in relation to the outcome, apart from "cumulative plant exposure". The prevalence of actinic keratoses was 40% among workers determined to have high cumulative plant exposure; the prevalence among workers with low cumulative plant exposure was 20%. The unadjusted prevalence of the primary actinic keratosis outcome among plant workers (prevalence: 30%) and matched friends (prevalence: 28%) were qualitatively similar and not significantly different. Actinic keratosis prevalence was not associated with worker status (versus friend) in multivariable models.

There is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and actinic keratosis. Cooper et al. (1994) found no evidence of a significant positive association between working in a Texas paraquat production plant and prevalence of actinic keratosis. The study, however, had several important limitations and was determined to be of low quality based on the OPP framework study quality criteria. Most importantly, the cross-sectional design is unable to assess the temporal association between occupational work and keratosis risk. Paraquat exposure specifically was not evaluated in relation to the keratosis outcome. The corresponding measures of keratosis frequency and association (prevalence and prevalence ratios) mix incident outcomes with prevalent ones. The use of a non-occupational comparison group raises the question of non-comparability, though the authors considered use of a "friend" comparison group to be an improvement on previously published assessments of actinic keratosis among paraquat plant workers.

Male Reproduction (Hormone Levels and Semen Quality) (Low Quality: Hossain et al., 2010; Cremonese et al., 2018)

The association between occupational pesticide exposure and semen quality was evaluated in two studies of Malaysian farmers and rural men in Brazil, respectively (Hossain et al., 2010; Cremonese et al., 2018).

- Hossain et al. (2010) conducted a cross-sectional study to investigate the relationship between use of paraquat and/or malathion and semen quality among farmers (n = 152) in 3 farming communities in rural Sabah, Malaysia. The date of data collection is not provided in the article. Pesticides exposure assessment was based on self-report and included history of pesticide exposure, and exposure pattern (type of pesticide, duration of use, spraying and cleaning of pesticide cans). The outcome of interest was assessed through analysis of semen samples which were processed and analyzed by qualified personnel based on WHO guidelines.[19] Specific semen quality parameters included semen volume, pH, morphology, motility, WBC count, and sperm concentration. Subjects were asked to abstain from sex for 2-3 days prior to providing the sample. The researchers used chi-square tests and calculated odds ratios. The researchers looked for differences in semen quality by smoking status, alcohol consumption, marital status, and those with children vs. those without children and did not find any significant differences at $p < 0.05$. Based on analysis of 90 unexposed subjects and 62 exposed subjects (of those 62 exposed, 39 were exposed to paraquat and 15 to malathion), the investigators reported evidence of a positive association between self-reported use of paraquat and/or malathion and several semen quality parameters. Odds ratios and 95% CIs for exposure to paraquat and/or malathion (not separated in analyses) for risk of abnormal results compared to normal: *Semen Volume* – 6.5 (2.7, 15.2); *Semen pH* – 2.66 (0.1-0.9); *Concentration* – 8.77 (4-19); *Sperm Motility* – 5.18 (2.5-10.5); *Sperm Morphology* – 4.96 (1.6-14.6); and *Semen WBC* – 4.51 (1.5-13.4).
- Cremonese et al. (2018) conducted a cross-sectional study to investigate the relationship between pesticides, including paraquat, and reproductive hormones, semen quality, and genital measures in rural and urban men in Brazil. Study subjects were recruited between 2012-2013 and consisted of a random sample of rural and urban males aged 18-23 living in Farroupilha in Rio Grande do Sul. Rural males were identified from a list of rural households from the municipal agriculture office. 180 rural males were identified from this list of which 80 were randomly selected for the study. An additional 30 rural males were identified, resulting in a total rural male group of 110. The group of urban males, defined as living in urban area of Farroupilha, served as a reference

[19] WHO, 1992. Laboratory Manual for the Examination of Human Semen and Sperm—Cervical Mucus Interaction. Cambridge University Press. 3rd ed.
WHO, 1999. Laboratory Manual for the Examination of Human Semen and Sperm-Cervical Mucus Interaction (Paperback). 4th ed.

population and consisted of 50 males that were randomly selected from the same military service list. Urban males were excluded if they reported use of pesticides or a history of working in agricultural (n = 5). A final sample of 99 rural men and 36 urban men entered the study. A questionnaire was used to obtain information on demographics, occupation, health, and lifestyle factors. The same questionnaire was also used to ascertain pesticide exposure and included questions on years of agricultural work, years of mixing/applying pesticides, and frequency of mixing/applying pesticides. Subjects were also asked to recall specific pesticides, based on a list of product trade names that were common to the study area. Male reproductive function was examined by collecting blood to assess hormone levels (testosterone, LH, FSH, SHBG, prolactin, FAI, and Testosterone:LH), semen samples to assess semen quality, and measuring genitals (width, length, height, and anogenital distance) by a urology specialist. After collecting data on study subjects, multivariable regression was performed to assess several different exposure variables, including paraquat exposure. Based on this approach, the investigators reported evidence of a significant association for LH (*1-5 Years Paraquat Use:* β = 0.96, 95% CI: 0.75-1.29; ≥ *6 Years Paraquat Use*: β = 0.83, 95% CI: 0.69-0.99; p-trend = 0.05); and sperm motility (*1-5 Years Paraquat Use:* β = 0.90, 95% CI: 0.66-1.21; ≥ *6 Years Paraquat Use*: β = 0.66, 95% CI: 0.48-0.92; p-trend = 0.02). For other reproductive factors examined, the investigators reported no evidence of an association. These factors included the hormone levels testosterone (FSH, SHBG, prolactin, FAI, and Testosterone:LH), semen quality (concentration and motility), and testicular volume. The same 2 factors, LH and sperm motility, had significant association with most other pesticide exposure variables investigated in the study, including all pesticides, fungicides, herbicides, OP insecticides, dithiocarbamate fungicides, other chemical classes, mancozeb, and glyphosate.

There is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and male reproductive factors. While the two studies identified some evidence of an association for some factors, both relied on cross-sectional study designs. As such, they are unable to assess the temporal association between paraquat exposure and male reproductive function and were determined to be low quality based on the study quality criteria provided in the OPP framework. The studies also have several other important limitations. For example, they were conducted in Malaysia and Brazil and may not be representative of the U.S. because of differences in U.S. agricultural practices and population characteristics. Both studies also had limitations in the exposure assessment approach and relied on self-report through study questionnaire. The associations reported by Cremonese et al. (2017) were also observed for other exposure variables, including most other pesticide exposure categories and their analysis of rurality. As such, the observed associations may not be due to a specific exposure variable, but rather systematic differences in rural and urban males in the study area in Brazil.

Depressive Symptoms (<u>Moderate Quality</u>: Beard et al., 2013, Beard et al., 2014; <u>Low Quality</u>: Kim et al., 2013)

The association between occupational pesticide exposure and depressive symptoms was evaluated in one study of male South Korean farmworkers and two studies of the AHS study population (Beard et al., 2013, Beard et al., 2014).

- Kim et al. (2013) conducted a cross-sectional study to investigate the association between occupational pesticide exposure and depressive symptoms among male farmers in South Korea. A nationwide sampling survey of male farmers was conducted in South Korea, involving a total of 1,958 male farmers interviewed in 2011. Severity of occupational pesticide poisoning was based on symptoms, types of treatment, and number of pesticide poisonings per individual.

Twenty-one symptoms and signs were used to identify pesticide poisoning based on a pilot study and reference reviews. These symptoms and signs included nausea, vomiting, diarrhea, sore throat, runny nose, dyspnea, headache, dizziness, hyperactivity, profuse sweating, blurred vision, paranesthesia, slurred speech, paralysis, chest pain, syncope, muscle weakness, skin irritation, eye irritation, lacrimation and fatigue. If respondents reported suffering any of the symptoms or signs and it had occurred within 48 hours of occupational pesticide use, it was defined as an acute occupational pesticide poisoning. Characteristics of pesticide poisoning included: any exposure, severity of exposure, number of exposures, treatment for exposure, lifetime hospitalization for exposure (any and number), lost workdays for exposure, type of pesticide used, and causative pesticides of acute occupational poisoning (class and name, including paraquat). The Geriatric Depression Scale was used to assess depressive symptoms. Survey logistic regression was used to estimate ORs and 95% CIs, adjusted for age, marital status, income, smoking, perceived health status and comorbidity. After controlling for potential confounders, there was evidence of a positive association between acute occupational pesticide poisoning and subsequent depressive symptoms (OR = 1.61; 95% CI: 1.10 to 2.34). Among 431 farmers with acute occupational pesticide poisoning in 2010, the investigators reported evidence of a strong positive association between acute paraquat occupational poisoning and depressive symptoms (OR = 2.25, 95% CI: 1.14 to 4.44), based on 15 farmers with depression and 61 farmers without depression.

- Beard et al. (2013) conducted a prospective cohort study to investigate the association between pesticide exposure, including paraquat, and self-reported depression among farmers' wives in the AHS. The study population consisted of female spouses (n = 16,893) in the AHS living in Iowa and North Carolina, and pesticide exposure was assessed during study enrollment for 50 different pesticides including paraquat using self-administered questionnaires. Cases included farmers' wives who self-reported incident depression between the time of study enrollment (1993-1997) to study follow-up (2005-2010), and cases were ascertained through responses to questions during the telephone follow-up interview. The controls included study participants who did not report incident depression. RRs and 95% CIs were calculated using a log-binomial regression model to determine if an association between ever-use of a pesticide and depression existed. Inverse probability weights were applied to adjust for education level, age at enrollment, ever diagnosed with diabetes, state of residence, and drop out, as well as account for the substantial number of study subjects (n = 10,639) who did not complete the follow up interview (1,342 due to death). Of the 1,054 cases, 14 (1%) reported exposure to paraquat. No evidence of a positive association was observed between paraquat exposure and incident depression among farmer's wives (RR = 1.08; 95% CI: 0.64, 1.83) based on ever/never use. A further analysis considered husbands' use of specific pesticides based on ever/never use and the risk of depression among their wives who had reported never using pesticides; no evidence of a significant positive association was reported for paraquat exposure (RR = 1.22; 95% CI: 0.95-1.56 with n = 101 exposed cases).
- In a separate study, Beard et al. (2014) conducted a prospective cohort study to investigate the association between pesticide exposure, including paraquat, and self-reported depression among male pesticide applicators. Participants self-reported physician diagnoses of depression prior to enrollment only (defined as 'PRE-E' in the study), at both enrollment and follow-up (defined as 'PRE-B' in the study), or at follow-up only (defined as 'POST' in the study). Pesticide exposure (ever / never) was assessed via 2 self-administered questionnaires, one during study enrollment and a second follow-up questionnaire administered 5 years after enrollment. Polytomous logistic regression was used to calculate ORs and 95% CIs for individual pesticides. Inverse probability weighting adjusted for confounders including age, diabetes diagnosis, education level, and state of residence as well as missing covariate data for subjects and study drop-outs. Among the study population (n = 21,208), 1,702 (8%) reported receiving a diagnosis of depression (cases). Of

those 1,702 cases, 474 reported depression diagnoses at enrollment but not follow-up, and 120 (26%) of those cases reported exposure to paraquat. A total of 540 individuals of the 1,702 cases reported depression diagnosis at both enrollment and follow-up, and 123 (25%) of those cases reported exposure to paraquat. Finally, 688 individuals of the 1,702 cases reported depression diagnosis at follow-up only, and 158 (24%) of those cases reported exposure to paraquat. There were 19,506 study participants who reported no physician diagnosis of depression (controls), and 15,371 (79%) of those controls reported exposure to paraquat. Results suggested no evidence of a significant positive association between paraquat exposure and risk of depression for those who reported depression at enrollment only (OR = 1.20; 95% CI: 1.0, 1.5); for those who reported depression at both enrollment and follow-up (OR = 1.1; 95% CI: 0.9, 1.4); and for those who reported depression at follow-up only (OR = 1.1; 95% CI: 0.9, 1.3). A Wald chi-square tests found no significant difference in the ORs between these groups for paraquat exposure (p = 0.77).

Overall, there is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and depression. While Kim et al. (2013) reported evidence of a positive association with acute paraquat poisoning, the study has limitations related to its design and exposure assessment approach and was determined to be of low quality based on the OPP framework study quality criteria. Most importantly, Kim et al. (2013) used a cross-sectional design that was unable to assess temporal association between exposure and subsequent depression. Assessment of paraquat exposure by self-report introduced additional uncertainty and may be subject to recall bias.

With regard to findings from AHS, no evidence of an association was reported in the Beard et al. (2013) assessment of farmers' wives that focused specifically on their paraquat use and no evidence of a significant positive association was observed among pesticide applicators in Beard et al. (2014). Beard et al. (2013 and 2014) were determined to be moderate quality based on the study quality criteria provided in the OPP framework. Both studies were done prospectively as part of the AHS study but relied on self-report using the AHS questionnaire at enrollment and follow-up to ascertain study subjects with depression. Both studies also relied on the AHS questionnaire to ascertain exposure. However, Beard et al. (2014) focused on male pesticide applicators and was able to directly assess pesticide exposure based on information provided on their past use of paraquat. Beard et al. (2013) assessed the paraquat use of female spouses of pesticide applicators, but also assessed paraquat exposure indirectly using the paraquat use information provided by their husbands. This indirect approach has not been validated and may introduce exposure misclassification.

Suicide (Moderate Quality: Beard et al., 2011)

One study investigated the association between paraquat exposure and suicide in the AHS study population (Beard et al., 2011).

Beard et al. (2011) conducted a prospective cohort study to investigate the association pesticide exposure and suicide mortality among AHS commercial applicators and farm owners/operators. Pesticide exposure was assessed via a self-administered questionnaire at enrollment. Cases (suicides after enrollment) were identified by linking the AHS cohort to state mortality files and the National Death Index through 2009. The Cox proportional hazards model was used to analyze the association between pesticide exposure and suicide risk and calculate HRs and 95% CIs, adjusting for age, sex, number of children, frequency of alcohol consumption within the past year, and smoking. Among the study population (n = 81,998), 43,444 reported paraquat exposure. There were 110 suicides (cases) occurring between enrollment in the AHS (from 1993 to 1997) and May 2009. The study results suggested no evidence of an association between suicide and paraquat exposure (HR = 0.70; 95% CI: 0.42, 1.16 with n = 19 exposed cases, and 43,376 unexposed cases) based on ever/never use.

There is no epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between paraquat exposure and suicide. The single available study was conducted using the AHS study population and reported no evidence of an association. This study was determined to be of moderate quality based on the OPP framework study quality criteria. Study strengths include the prospective design of AHS and exposure assessment approach. The study was also able to identify suicide cases using the National Death Index. This approach may be comprehensive for suicide cases resulting in mortality, but provides incomplete characterization of suicidal behavior because cases of suicide attempt and ideation cannot be identified using the National Death Index.

Infant Birth Weight (Low Quality: Sathyanarayana et al., 2010)

One study investigated the association between paraquat exposure and infant birth weight in the AHS study population (Sathyanarayana et al., 2010).

Sathyanarayana et al. (2010) investigated in a cross-sectional study the potential association between maternal exposure to pesticides including paraquat during the first trimester of pregnancy and subsequent birth weight using data from the AHS. The study population consisted of female spouses of pesticide applicators enrolled in the AHS who had given a singleton birth[20] within 5 years of study enrollment and had complete information on all covariates (n = 2,246). Self-administered questionnaires were used to collect information from the female spouses on specific pesticide use and activities as well as demographic and lifestyle characteristics, health conditions, and pregnancy details including history, complications, and pregnancy outcomes. Ever/never exposure to paraquat and other specific pesticides did not distinguish exposure at any particular period in a participant's life including pregnancy, and was based on the participant's answer to the question "Have you ever personally mixed or applied this (pesticide)?". The outcome, the birth weight of the participant's most recent live singleton birth, was considered as a continuous dependent variable. Linear regression was used to estimate change in birth weight relative to pesticide exposure controlling for maternal BMI at study enrollment, maternal height, parity, whether the birth was preterm or not, state of residence, and maternal smoking status during pregnancy. In analyses of individual pesticides, the authors reported no evidence of a significant association between mother's ever use of paraquat and a change in offspring's birth weight (regression coefficient = -0.2 g; 95% CI: -212, 212 g with 21 women reporting ever use and 2,202 women reporting never use.

There is no epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between maternal paraquat exposure and infant birth weight. The single available study was conducted in the AHS study population and reported no evidence of an association. The study, however, relied on a cross-sectional design and was unable to assess the temporal association between maternal paraquat exposure and infant birth weight. As such, the study was determined to be of low quality based on the OPP framework study quality criteria.

Aplastic Anemia (Moderate Quality: Prihartono et al., 2011)

The association between occupational pesticide exposure and aplastic anemia was evaluated in one study in Thailand (Prihartono et al., 2011).

Prihartono et al. (2011) conducted a clinic-based case-control study in Thailand to evaluate associations between occupational exposures to pesticides and industrial chemicals, including exposure to paraquat. Study subjects consisted of residents of the 3 regions in Thailand (Bangkok, Khonkaen, and Songkla) who, if they were to have aplastic anemia, would be eligible to be cases in the study. Cases were aplastic

[20] Singleton birth defined as a birth event that resulted in a single, live born child.

anemia patients identified by physicians practicing in these regions, who met inclusion/exclusion criteria, and whose diagnoses were confirmed by study hematologists. Control participants were selected from among patients of the same hospitals as the cases. Diagnoses among controls included trauma, acute infections (*e.g.,* pneumonia), acute abdominal emergencies, and other conditions. Four or more controls were matched to each case based on gender, age at diagnosis of the case, and region. Exposure to the pesticides paraquat and the organophosphate, the carbamate, and the organochlorine classes was assessed using 2 complementary approaches: by participant self-reporting using a questionnaire and by expert assessment. The questionnaire was administered by trained health care providers. Information on work history included job title, type of industry, and duration of work. For the expert-assignment of exposure – termed a "semi-quantitative methodology" in the report – 3 Thai industrial hygienists assigned exposure estimates to all jobs reported by the cases and controls. The experts were blinded to case/control status. For each job, the 3 experts assigned levels of probability of exposure, frequency, and intensity of exposure, as well as an overall confidence rating for their estimates, using a standardized instrument.

Aplastic anemia was diagnosed if potential cases met at least 2 of the following criteria: white blood cell count of 3.5×10^9/L or lower; a platelet count of 50×10^9/L or lower; a hemoglobin level of 100 g/L or lower; or a hematocrit of 30% or lower. Diagnoses were confirmed by a bone marrow biopsy that characterized hypocellularity without marrow fibrosis or infiltration by leukemic, lymphomatous, or carcinoma cells. The biopsies were reviewed by study hematologists to determine final eligibility. Cases undergoing chemotherapy or radiotherapy and cases with other systemic diseases associated with pancytopenia were excluded.

Multivariable logistic regression modeling was used to estimate covariate-adjusted odds ratios for paraquat exposure and aplastic anemia. Potential covariates included age, gender, region of residence, as well as household pesticides and drugs including thiazide, sulfonamide, chloramphenicol, tetracyclines, penicillin, ampicillin/ amoxicillin, other named antibiotics, and unspecified antibiotics. The investigators examined the association between paraquat exposure and aplastic anemia using both self-report and expert assignment exposure assessment methods. Based on self-reported exposure, the investigators reported no evidence of a significant positive association between ever use of paraquat and aplastic anemia (OR = 1.68, 95% CI: 0.92-3.05, n = 17 exposed cases). The investigators further examined exposure probability based on expert consensus and reported no evidence of an association in their low/medium paraquat exposed categories (OR = 0.83, 95% CI: 0.63-1.09, n = 76 exposed cases) and evidence of a positive association was observed in the "high/very high" paraquat exposed category (OR = 1.71, 95% CI: 1.32-2.22, n = 141 exposed cases). In their further analysis of expert assignment of exposure that also adjusted for all other pesticide use, the investigators reported no evidence of a significant positive association (OR = 1.62, 95% CI: 0.59-4.45, n = 141 exposed cases); however, the reported effect estimate was similar in magnitude to their analysis based on self-reported exposure.

Based on the single study identified, there is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between maternal paraquat exposure and aplastic anemia. Prihartono et al. (2011) was determined to be of moderate quality based on the OPP framework study quality criteria. The study had several important limitations related to its design and exposure assessment approach. The clinic-based case-control design used in their investigation is efficient for studying a relatively rare disease like aplastic anemia, but it is also susceptible to bias, selection bias in particular. It is possible that the prevalence and duration of paraquat exposure among the clinic-based control subjects is not representative of the exposure in the study base. If paraquat exposure is not independent of the control subjects' diagnoses, then the control selection would result in biased association estimates. Non-differential exposure misclassification is likely if study subjects recalled their past exposures with error, and if the expert-based exposure assignments were performed imperfectly. Some degree of differential exposure misclassification and consequent recall bias is possible, and would

be present if cases were more prone to misreport their exposures because of their diagnosis. Such information bias was mitigated by their use of an objective, semi-quantitative exposure assignment procedure. The known suspected risk factors that may be associated with pesticide use were appropriately considered by the study investigators.

3.4.2 Evaluation of Findings

For the majority of these health outcomes, only a single study was available on the relationship with paraquat exposure. Many of the studies on these health outcomes examined multiple different exposures, were of lower quality, and/or reported no evidence of a positive association in their analysis of pesticide exposure. These outcomes included:

- General Mortality
- Injury Mortality
- Renal/Liver Function and Hematology
- Eye Disorder
- Thyroid Disease
- Myocardial Infarction
- Oxidative Stress
- Abnormal Skin Pigmentation
- Rheumatoid Arthritis
- Actinic Keratosis
- Male Reproduction
- Suicide
- Infant Birth Weight
- Aplastic Anemia

For a smaller number of health outcomes, there were more than one study and the study quality were moderate or high. These outcomes included:

- Diabetes
- End Stage Renal Disease
- Depressive Symptoms

Overall, OPP concluded there was *no evidence* of an association for the health outcomes general mortality, diabetes, eye disorders, thyroid disease, myocardial infarction, suicide, and infant birth weight. For health outcomes with a single study with positive findings (OR > 1.0 and significant), OPP generally concluded there was *insufficient evidence* of an association for health outcomes. This included the health outcomes injury mortality, renal/liver function, oxidative stress, abnormal skin pigmentation, actinic keratosis, depressive symptoms, and aplastic anemia.

OPP concluded there was *limited, but insufficient evidence* of a clear associative or causal relationship for end-stage renal disease, based on AHS studies on male farmers (Lebov et al., 2016) and their spouses (Lebov et al., 2015) that both reported evidence of a positive association. While positive associations were reported, there were only a small number of paraquat cases in both studies (21 and 33, respectively) so the ability to assess the exposure-response relationship and perform sensitivity analysis was limited. As such, while both AHS studies reported positive findings, further investigation is warranted to replicate the results in studies with a larger number of cases and other study populations that may experience chronic paraquat exposure.

Table 15: Summary of Epidemiological Findings on Paraquat Exposure and Other Health Outcomes Other than Parkinson's Disease, Lung/Respiratory, and Cancer

Outcome	Low	Moderate	High
General Mortality		⦸ Tomenson and Campbell, 2011	
Injury Mortality	● Waggoner et al., 2011		
End Stage Renal Disease			● Lebov et al., 2015 *(Female Spouses)* ● Lebov et al., 2016 *(Male Applicators)*
Renal and liver function and hematology	⦸ Howard et al., 1981 ⦸ Senanayake et al., 1993		
Diabetes		⦸ Montgomery et al., 2008 ⦿ Starling et al., 2014 ⦿ Juntarawijit and Juntarawijit, 2018	
Eye Disorders		⦸ Kirrane et al., 2005; ⦿ Montgomery et al., 2017	
Thyroid disease	● Goldner et al., 2010 *(Hypothyroid)* ⦿ Goldner et al., 2010 *(Other thyroid diseases)*		
Myocardial Infarction		⦸ Mills et al., 2009 *(Fatal)* ⦿ Mills et al., 2009 *(Non-Fatal)*	
Oxidative Stress	● Ranjbar et al., 2002		
Abnormal Skin Pigmentation	● Jee et al. 1995		
Rheumatoid Arthritis	⦸ Koureas et al. (2017)		
Actinic keratosis	⦸ Cooper et al., 1994		
Male Reproduction	● Hossain et al., 2010 ● Cremonese et al., 2018		
Depressive Symptoms	● Kim et al., 2013	⦿ Beard et al., 2013 ⦿ Beard et al., 2014	
Suicide		⦸ Beard et al., 2011	
Infant Birth Weight		⦸ Sathyanarayana et al., 2010	
Aplastic anemia		● Prihartono et al., 2011	

⦸ No evidence of an association between exposure and outcome (*e.g.,* OR ≤ 1.0).

⦿ No evidence of a significant association between exposure and outcome (*e.g.,* OR > 1.0 but not significant).

● Evidence of an association between exposure and outcome (*e.g.,* OR > 1.0 and significant).

4 CONCLUSIONS

OPP performed a systematic review of the epidemiologic literature on paraquat exposure and identified 74 articles that investigated a range of health outcomes, including Parkinson's Disease, lung function and respiratory effects, cancer, and 17 other health outcomes. OPP's conclusions on the available evidence for these outcomes are summarized below.

- **Parkinson's Disease** had the most comprehensive body of epidemiologic literature with a total of 13 study populations, including three agricultural cohorts, nine hospital-based populations, and one Parkinson's Disease registry in Nebraska (26 articles). Based on the findings from these studies, it was concluded:
  - There *is limited, but insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between occupational paraquat exposure and Parkinson's Disease. This conclusion is based on mixed findings reported in the AHS study population and FAME – with respect to incident and prevalent cases – and the potential for recall bias (Kamel et al., 2009; Tanner et al., 2011). In examination of evidence from other occupational studies, no association between paraquat exposure and PD was observed in either the French AGRICAN cohort or the Washington State Department of Public Health Study. Similarly, mixed evidence was reported in the remaining three case-control studies, with one study reporting evidence of a positive association (Liou et al., 1997), one study reporting a non-significant positive association based on only nine exposed cases (Tanner et al., 2009), and one study reporting no evidence of an association (Van der Mark et al., 2014). However, these case-control studies contributed less weight in OPP's determination because of their weaker study designs, more limited exposure assessment approach, and potential for recall bias.
  - There is *insufficient epidemiological evidence* at this time to conclude that there is a clear associative or causal relationship between non-occupational paraquat exposure and PD. This conclusion was based on the limited number of studies on non-occupational populations, lack of consistent evidence of a positive association, and the potential for bias in the available studies. The PEG study reported evidence of a positive association between paraquat exposure and PD in some publications, for example, but reported no evidence of an association when restricting analysis to paraquat exposure only. The Netherlands PD study also reported no evidence of a positive association (Brouwer et al., 2017). Moreover, both the PEG and Netherlands PD studies relied on GIS-based approaches to estimate exposure which eliminated the potential for recall bias but may have limited ability to distinguish between proximity to agricultural land, pesticide exposure in general, and specific pesticides as potential PD risk factors with confidence. The results of the ecologic Nebraska PD Registry Study (Wan and Lin, 2016) contributed limited weight to OPP's evaluation, but highlights the need to carefully account for rurality in the design and analysis of studies on paraquat exposure and PD.

  In order to strengthen the available evidence, future epidemiologic studies should aim to minimize recall bias and more systematically evaluate paraquat exposure specifically using an approach that addresses co-exposure to other pesticides and evaluates other factors that may be associated with rural living.

- **Lung function and respiratory effects** were examined in nine study populations (17 articles) that included general lung function, wheeze, allergic rhinitis, asthma, and chronic bronchitis. Based on the findings from these studies, it was determined that there is *insufficient epidemiological evidence* to conclude that there is a clear associative or causal relationship between occupational paraquat exposure and the health outcomes investigated, including: general lung function and respiratory symptoms, wheeze, allergic rhinitis, asthma, and chronic bronchitis. While 17 articles were identified, all studies were determined to be low quality because they used cross-sectional designs and could not evaluate the temporal association between paraquat exposure and onset of the health outcomes of interest. Additionally, some studies were conducted outside the United States and may not be generalizable because they focused on regions with different agricultural practices and study populations with different demographic and lifestyle characteristics.
- **Cancer outcomes** were only examined in four study populations (8 articles), with most cancer outcomes investigated in a single study, typically AHS. OPP concluded there was *no epidemiological evidence* of a clear associative or causal relationship for the cancer outcomes: all incident cancer and lung cancer. The conclusion on these outcomes was based on the AHS reporting no evidence of an association. OPP concluded there was *insufficient epidemiological evidence* of a clear associative or causal relationship for the cancer outcomes: bladder cancer, breast cancer, childhood leukemia colorectal cancer, glioma, kidney cancer, pancreatic cancer, prostate cancer, and lymphoma. Many of these cancer outcomes were only investigated in a single study population.
- **17 other health outcomes** (25 articles) were investigated in the literature primarily examined occupational paraquat exposure. Most outcomes were only investigated in a single study population. OPP concluded there was *no epidemiological evidence* of an association for the health outcomes general mortality, suicide, and infant birth weight. For health outcomes with a single study with positive findings (OR > 1.0 and significant), it was generally concluded there was *insufficient evidence* of an association between the health outcomes and paraquat exposure. This included the health outcomes diabetes, myocardial infarction, eye disorders, injury mortality, renal/liver function, oxidative stress, abnormal skin pigmentation, actinic keratosis, depressive symptoms, thyroid disease, and aplastic anemia. OPP concluded there was *limited, but insufficient epidemiological evidence* of a clear associative or causal relationship for end-stage renal disease based on AHS studies on male farmers (Lebov et al., 2016) and their spouses (Lebov et al., 2015) that both reported evidence of a positive association. While positive associations were reported, there were only a small number of paraquat cases in both studies (21 and 33, respectively), so the ability to assess the exposure-response relationship was limited. As such, while both AHS studies reported positive findings, further investigation is warranted to replicate the results in studies with a larger number of cases and other study populations that may experience chronic paraquat exposure.

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Appendix A: SUMMARY OF EPIDEMIOLOGIC STUDIES AND STUDY QUALITY ASSESSMENT

Table A-1: Summary of Epidemiologic Studies on Parkinson's Disease (PD).

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
Agricultural Study Populations							
Kamel et al. (2007)	1993-1997 (Enrollment) to 1999-2003 (Phase 2 Follow-up)	Agricultural Health Study (AHS)	Cohort Cross-sectional n = 84,738 enrolled, 57,251 Phase 2 Follow-up	AHS Survey Instrument – Ever/Never Paraquat Use	AHS Survey Instrument At enrollment and follow-up, ''Has a doctor ever told you that you had been diagnosed with Parkinson's disease?'	No evidence of a significant positive association with prevalent PD (OR = 1.8; 95% CI, 1.0-3.4, n = 14 paraquat exposed cases). No evidence of an association with incident PD (OR = 1.0; 95% CI, 0.5-1.9, n = 11 paraquat exposed cases).	Moderate
Tanner et al. (2011)	1993-1997 (Enrollment) to 1999-2003 (Phase 2 Follow-up)	Farming and Agricultural Movement Evaluation (FAME) study (nested within AHS)	Nested Case-Control n = 110 cases, 358 controls	FAME Survey Instrument – Ever/Never Paraquat Use and Cumulative Lifetime Use	Agreement of 2 neurologists after independent review of all available diagnostic information (medical records, in-person examination records, and videotaped examination)	Evidence of a moderately strong positive for ever use of paraquat (OR = 2.5, 95% CI, 1.4-4.7, n = 23 exposed cases). Investigators examined the cumulative lifetimes days of paraquat exposure and reported that the effect estimate increased from an OR of 2.4 (95% CI: 1.0-5.5, n = 10 exposed cases) in individuals reporting ≤ median paraquat use of 8 lifetime days to an OR of 3.6 (95% CI: 1.6-8.1, n = 13 exposed cases) in individual reporting > median paraquat use of 8 lifetime days.	High

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
Goldman et al. (2012)	1993-1997 (Enrollment) to 1999-2003 (Phase 2 Follow-up)	Farming and Agricultural Movement Evaluation (FAME) study (nested within AHS)	Cohort Nested Case-Control n = 87 cases, 343 controls	FAME Survey Instrument – Ever/Never Paraquat Use and Cumulative Lifetime Use Genetic profile: Genotyping of study subject's glutathione S-transferase M1 (GSTM1) and T1 (GSTT1).	PD case status was determined by agreement of 2 movement disorder specialists following established criteria for PD (Gelb et al. 1999) and information from medical records, in-home examination, and videotaped movement evaluation	Glutathione S-transferase T1 (GSTT1) genotype significantly modified the association between paraquat and Parkinson's disease (P interaction: 0.027): **Ever/Never (GSTT1):** OR = 1.5, 95% CI: 0.6–3.6. relative to subjects that reported no paraquat use and had functional GSTT1; **Ever/Never (homozygous deletion of GSTT1):** OR = 11.1, 95% CI: 3.0–44.6, relative to subjects that reported no paraquat use and had functional GSTT1 No interaction was observed between paraquat exposure and glutathione S-transferase M1 (GSTM1) genotype; corresponding odds ratio estimates were not included in the report.	High
Kamel et al. (2014)	1993-1997 (Enrollment) to 1999-2003 (Phase 2 Follow-up)	Farming and Agricultural Movement Evaluation (FAME) study (nested within AHS)	Nested Case-Control n = 89 cases, 336 controls	FAME Survey Instrument – Ever/Never Paraquat Use and Cumulative Lifetime Use Food intake: Diet History Questionnaire v I, a self-administered 144-item food frequency questionnaire developed by National Cancer Institute. Total energy and dietary fats estimated using Diet*Calc, z1.4.3. Daily intakes of total fat, saturated fat, monounsaturated fatty acids	Agreement of 2 neurologists after independent review of all available diagnostic information (medical records, in-person examination records, and videotaped examination	The OR for paraquat was 4.2 (95% CI: 1.5-12) in individuals with low PUFA intake but 1.2 (95% CI: 0.4-3.4) in those with high PUFA intake (p-interaction = 0.10). The OR for paraquat was 4.0 (95% CI: 1.5-10.9) in individuals with low N-6 PUFA intake but 1.2 (95% CI: 0.4-3.3) in those with high N-6 PUFA intake (p-interaction = 0.08). The OR for paraquat was 3.8 (95% CI: 1.4-10.3) in individuals with low linoleic acid intake	High

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
				(MUFAs), polyunsaturated fatty acids (PUFAs), and individual PUFAs were expressed as a percentage of total energy (nutrient density).		but 1.2 (95% CI: 0.4-3.3) in those with high linoleic acid intake (p-interaction = 0.09).	
Furlong et al. (2015)	1993-1997 (Enrollment) to 1999-2003 (Phase 2 Follow-up)	Farming and Agricultural Movement Evaluation (FAME) study (nested within AHS)	Nested Case-Control n = 69 cases, 267 controls)	FAME Survey Instrument – Ever/Never Paraquat Use and Cumulative Lifetime Use; Structured CATI on demographics, lifestyle, medical history, a complete occupational history including details of all farm jobs, and information on PPE and hygiene practices.	PD case status determined by agreement of 2 movement disorder specialists following established criteria for PD (Gelb et al. 1999) and information from medical records, in-home examination, and videotaped movement evaluation	No evidence of significant positive association between paraquat exposure and PD among protective glove users (OR = 1.6, 95% CI: 0.6-4.2). Evidence of a strong positive association among non-glove users, defined as report of using gloves less than 50% of the time (OR = 3.9, 95% CI: 1.3-11.7).	High
Pouchieu et al. (2018)	2005-2007 (Enrollment)	French AGRIculture and CANcer (AGRICAN) PD Stud	Cross-Sectional n = 149,810 subjects (1,732 subjects reported doctor-diagnosed PD)	AGRICAN Enrollment Questionnaire – survey responses on livestock/crop activities combined with the French crop-exposure matrix PESTIMAT.	AGRICAN Enrollment Questionnaire - 'Has a doctor ever told you that you had PD?' Subjects were also asked if they suffered from any of 3 parkinsonian symptoms: (i) tremor in hands or feet; (ii) rigidity of arms or legs, and (iii) slowness or tightening in activities of daily living, walking or speaking.	No evidence of an association in adjusted analysis of Ever/Never Paraquat Use (OR = 1.01, 95% CI: 0.41-2.49). No evidence of an association for cumulative paraquat use (1-25 years paraquat exposure – OR = 1.05, 95% CI: 0.40-2.76; 26-46 years paraquat exposure – OR = 0.94, 95% CI: 0.37-2.41).	Low
Engel et al. (2001)	1972-1976 (Enrollment)	Washington State Department of Public Health PD Study	Cohort n = 238 subjects reporting pesticide use, 72 subjects unexposed	Subject also completed a self-administered question to ascertain pesticide use information, including years of farming, crops grown, acres for each crop, pesticide use practices, application methods, and use of personal protective equipment.	Each study subject received a physical examination to confirm the presence of clinical symptoms of PD.	No evidence of an association was reported for ever/never use (OR = 0.8, 95% CI: 0.5 – 1.3, n = 20 exposed cases) or tertiles of years exposure (Tertile 2 vs Tertile 1 – OR = 0.4, 95% CI: 0.1- 1.4; Tertile 3 vs Tertile 1 – OR = 0.9, 95%	Low

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
						CI: 0.4- 2.4). Similar results were also reported for tertiles of acre-years of exposure.	
Shrestha et al. (2018)	1993-1997 (Enrollment) to 2013-2015 (Phase 5 Follow-up)	Agricultural Health Study (AHS)	Prospective Cohort n = 23,478 subjects completing Phase 5 Questionnaire	AHS Survey Instrument – Ever/Never Paraquat Use	AHS Survey Instrument – , "Have you ever been told, or suspected yourself, that you seem to 'act out dreams' while sleeping?" If they answered yes, they were prompted to answer additional questions on the frequency of symptoms.	No evidence of an association between ever-never use of paraquat and dream enacting behavior (OR = 1.1, 95% CI: 0.9-1-3, n = 339 exposed cases).	Moderate
Hospital-Based Study Populations							
Costello et al. (2008)	1998-2007	California Central Valley/Parkinson's Environment and Genes Study (PEG)	Case-Control n = 368 cases, 341 controls	GIS-based Exposure Assessment - California Pesticide Use Report data combined with data from California's Public Land Survey System. Maneb and paraquat exposure categorized as no exposure, paraquat only exposure, maneb only exposure, and both paraquat and maneb exposure, for time windows 1974-1999, 1974-1989, and 1990-1999.	Confirmed as having clinically probable or possible PD by a University of California–Los Angeles (UCLA) movement disorder specialist.	No evidence of a positive association for paraquat only exposure (OR = 1.01, 95% CI: 0.71-1.43, n = 149 exposed cases) or maneb only exposure (OR = 3.04, 95% CI: 0.30 – 30.86, n = 3 exposed cases). Evidence of a positive association for both paraquat and maneb exposure combined (OR = 1.75, 95% CI: 1.13- 2.73, n = 88 exposed cases).	Moderate
Gatto et al. (2009)	1998-2007	California Central Valley/Parkinson's Environment and Genes Study (PEG)	Case-Control n = 368 cases, 341 controls	GIS-based Exposure Assessment - California Pesticide Use Report data combined with data from California's Public Land Survey System. Self-reports of private wells as drinking water sources at a residential address	Confirmed as having clinically probable or possible PD by a University of California–Los Angeles (UCLA) movement disorder specialist.	No evidence of a significant positive association between paraquat exposure from well water (OR = 1.10, 95% CI: 0.75-1.63, n = 79 exposed cases).	Moderate

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
Ritz et al. (2009)	1998-2007	California Central Valley/Parkinson's Environment and Genes Study (PEG)	Case-Control n = 324 cases, 334 controls	GIS-based Exposure Assessment - California Pesticide Use Report data combined with data from California's Public Land Survey System. Dopamine transporter (DAT) polymorphisms.	Confirmed as having clinically probable or possible PD by a University of California–Los Angeles (UCLA) movement disorder specialist.	The study examined paraquat/maneb combined exposure and did not specifically report results on paraquat exposure alone	Moderate
Gatto et al. (2010)	1998-2007	California Central Valley/Parkinson's Environment and Genes Study (PEG)	Case-Control n = 333 cases, 336 controls	GIS-based Exposure Assessment - California Pesticide Use Report data combined with data from California's Public Land Survey System.	Confirmed as having clinically probable or possible PD by a University of California–Los Angeles (UCLA) movement disorder specialist.	No evidence of a significant positive association between high exposure and PD, stratified by the presence of specific SNCA genotype variants (SNCA 259 Allele – OR = 1.45, 95% CI: 0.59-3.59; SNCA 263 Allele – OR = 1.35, 95% CI: 0.74-2.46, n = 31 exposed cases No evidence of a significant positive association in subjects with PD onset ≤68 years (OR = 3.15, 95% CI: 0.74-13.37, n = 13 exposed cases) and no evidence of an association in subjects with PD onset > 68 years (OR = 0.84, 95% CI: 0.27-2.62, n = 18 exposed cases).	Moderate
Wang et al. (2011)	1998-2007	California Central Valley/Parkinson's Environment and Genes Study (PEG)	Case-Control n = 362 cases, 341 controls	GIS-based Exposure Assessment - California Pesticide Use Report data combined with data from California's Public Land Survey System.	Confirmed as having clinically probable or possible PD by a University of California–Los Angeles (UCLA) movement disorder specialist.	Evidence of a positive association between paraquat exposure and PD (OR = 1.50, 95% CI: 1.03-2.18, n = 162 exposed cases, combined analysis of workplace/residential address, that did not exclude exposure to maneb and ziram).	Moderate

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
Lee et al. (2012)	1998-2007	California Central Valley/Parkinson's Environment and Genes Study (PEG)	Case-Control n = 362 incident cases, 341 controls	GIS-based Exposure Assessment - California Pesticide Use Report data combined with data from California's Public Land Survey System.	Confirmed as having clinically probable or possible PD by a University of California–Los Angeles (UCLA) movement disorder specialist.	Evidence of a positive association between self-reported TBI and PD (OR = 2.00, 95% CI: 1.28-3.14) and paraquat exposure (OR = 1.36, 95% CI: 1.02-1.81). Evidence of a positive interaction between paraquat exposure and TBI. Specifically, odds ratio of 3.01 (95% CI: 1.51-6.01) was reported in participants reporting a TBI and exposure to paraquat (21 cases, 19 controls) relative to those exposed to neither risk factor (167 cases, 419 controls).	Moderate
Sanders et al. (2017)	2001-2007 and 2010-2015	California Central Valley/Parkinson's Environment and Genes Study (PEG)	Case-Control n = 362 cases, 341 controls	GIS-based Exposure Assessment - California Pesticide Use Report data combined with data from California's Public Land Survey System.	Confirmed as having clinically probable or possible PD by a University of California–Los Angeles (UCLA) movement disorder specialist.	Evidence of a positive association between paraquat residential/workplace exposure and PD (OR = 1.54, 95% CI: 1.23-1.93, n = 245 exposed cases). No evidence of a significant positive association between paraquat exposure in subjects with no more than 1 risk alleles (OR = 1.13, 95% CI: 0.75-1.70, n = 48 exposed cases). Strong positive association in subjects with 2 risk alleles (OR = 2.38, 95% CI: 1.44-3.95, n = 22 exposed cases).	Moderate
Paul et al. (2018)	2001-2007 and 2010-2015	California Central Valley/Parkinson's Environment and Genes Study (PEG)	Case-Control n = 472 cases, 532 controls	GIS-based Exposure Assessment - California Pesticide Use Report data combined with data from	Confirmed as having clinically probable or possible PD by a University of California–Los Angeles	No paraquat-specific results reported.	Not Applicable-No paraquat-specific

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
				California's Public Land Survey System.	(UCLA) movement disorder specialist.		results reported.
Tanner et al. (2009)	July 2004 to May 31 2007	North American Multicenter PD Study	Case-Control n = 519 cases, 511 controls	Standardized computer-assisted phone interview to collect information on potential risk factors, including questions on the use tobacco, caffeine, and alcohol, head injury, and occupational history. Subjects reporting pesticide use were asked about the 8 specific pesticides: 2,4-D, paraquat, permethrin, dieldrin, mancozeb, rotenone, maneb, and diquat.	Cases clinically evaluated using the following inclusion criteria: (1) parkinsonism of no known cause, defined as 2 or more signs (resting tremor, bradykinesia, rigidity, and postural reflex impairment), 1 of which must be resting tremor or bradykinesia; (2) diagnosis within 8 years to minimize the risk of survival bias; and (3) absence of dementia.	Evidence of a positive association between pesticide use in general and parkinsonism (OR = 1.90, 95% CI: 1.12-3.21, based on 44 cases). No evidence of a significant positive association between paraquat and parkinsonism (OR = 2.80, 95% CI: 0.81-9.72, based on 9 exposed cases). While not statistically significant, the OR estimate was greater than 2.0.	Moderate
van der Mark et al. (2014)	2010-2012	Netherlands PD study	Case-control n = 444 cases 444, 876 controls	CATI: Occupational history, conducted by trained interviewers. Exposure algorithm based on crops and crop-pesticide exposure matrix: Exposure estimated by summing chance of paraquat use at farm x frequency of use, for all years working on farms	Diagnosis of Parkinson's disease from 5 hospitals in 4 different areas in the Netherlands	No evidence of a significant positive association (> 0-3.8 years Exposure OR = 1.42, 95% CI: 0.71-2.85, n = 18 exposed cases; > 3.8 years (OR = 1.01, 95% CI: 0.48-2.12, n = 15 exposed cases).	Moderate
Brouwer et al. (2017)	2010-2013	Netherlands PD study	Case-Control n = 352 cases 352, 607 controls 607	Spatio-temporal model (based on agricultural crops around residential addresses from 1961 to 2010)	Medical files reviewed by a neurologist to confirm case diagnosis	No evidence of an association when comparing subjects ever exposed and not exposed (OR 1.00, 95% CI: 0.73 - 1.36). In further analysis based on tertiles, there was no evidence of a significant positive association among subjects in the highest exposure tertile and those not	Moderate

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
						exposed (OR 1.46, 95% CI: 0.95 – 2.23) and no association in the middle exposure tertile (OR 0.93, 95% CI: 0.61 – 1.40) or low exposure tertile (OR 0.74, 95% CI: 0.47 – 1.16). A test of trend among the tertiles was not statistically significant (p = 0.19).	
Liou et al. (1997)	1993-1995	Taiwanese population	Case-Control n = 120 cases, 240 controls	Self-reported history of paraquat exposure by standardized interview. Paraquat exposure classified into the 3 groups; duration of exposure: 0 yrs, 1-19 yrs, > 20 yrs.	Diagnosis of Parkinson's disease in PD patients at Movement Disorder Clinic at National Taiwan University Hospital were confirmed by neurologists, requiring at least 2 cardinal symptoms of PD	Evidence of a strong positive association for the ≥20 years paraquat use category (OR = 6.44, 95% CI: 2.41-17.2, n = 24 exposed cases). Participants reporting use of paraquat and other herbicides/pesticides had twice the odds of PD, compared with those who had been exposed to herbicides/ pesticides other than paraquat (OR = 2.0, p-value < 0.01)	Moderate
Firestone et al. (2005)	1992-2002	Western Washington State population study of PD	Case-Control n = 250 cases, 388 controls	Face-to-face structured interview conducted by nurse practitioner: Demographics, medical and occupational history (job duration, 6 months), occupational and home-based pesticide use, drinking water source, residential history, and smoking history. Subjects reported first and last year of use and frequency of exposure (number exposed days per year). Cumulative exposures categorized as ordinal	Trained neurologist confirmed PD diagnoses by medical chart review, requiring at least 2 of 4 cardinal signs of PD (bradykinesia, resting tremor, cogwheel rigidity, and postural reflex impairment), one of which had to be bradykinesia or resting tremor	No evidence of an association (OR = 1.67, 95% CI: 0.22-12.76, based on 2 exposed cases)	Low

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
				variables (low/high or low/medium/high), based on product of duration and frequency of use			
Firestone et al. (2010)	1992-2006	Washington State population study of PD	Case-Control n = 404 cases, 526 controls	Same as Firestone et al. (2005)	Same as Firestone et al. (2005)	No evidence of an association (OR = 0.9, 95% CI: 0.14-5.43, based on 2 exposed cases)	Low
Dhillon et al. (2008)	Not specified	East Texas Parkinson's disease study	Case-Control n = 100 cases, 84 controls	Structured interview using standardized questionnaire on recent and lifetime pesticide exposure (Rotenone and a variety of herbicides, insecticides, fumigants, fungicides), any lifetime use of other pesticides (*e.g.,* Paraquat, Maneb, DDT), as well as occupational and military history, medical history, demographic information diet, and lifestyle behaviors.	Diagnosis by standard clinical/lab diagnostic criteria by a neurologist specializing in movement disorders	No evidence of a significant positive association between ever having personally used, mixed, or applied paraquat and odds of Parkinson's disease among a study base of East Texas residents (OR = 3.5, 95% CI: 0.4, 31.6, n = 4 exposed cases)	Low
Hertzman et al. (1990)	1988	British Columbia study	Case-Control n = 57 cases, 122controls 122	Questionnaire, Paraquat exposure categorized as "ever" versus "never" contact.	Cases were identified by physicians practicing in the region. Diagnoses confirmed by examination by study neurologist.	Hertzman et al. (1990) only had 4 exposed cases and no exposed controls so the study population, so the study could not calculate an effect estimate or adjust for confounding.	Low
Hertzman et al. (1994)	Not specified	Okanagan Valley of British Columbia	Case-Control n = 142 cases, 124 Voter Controls, 121 Cardiac Disease Controls	All cases and controls were interviewed to obtain information on personal, occupational, and chemical exposure. This included 79 different pesticides that were used in the orchard industry in the region.	PD cases were identified by contacting physicians in the region, including 160 general practitioners, 3 neurologists, and 25 internal medicine specialists (6 doctors refused to participate).	No evidence of a significant positive between paraquat exposure and PD, based on either control group (PD Cases vs. Voter Control Group – OR = 1.25, 95% CI: 0.34-4.63; PD Cases vs Chronic Cardiac Disease Controls – OR = OR = 1.11, 95% CI: 0.32-3.87, n = 6 exposed cases. However,	Low

First Author (Pub Year)	Study Period	Description of study population	Study Design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
						there were only 6 exposed cases, so paraquat exposure appears to be very limited in the investigator's study population.	

Table A-2: Summary of Epidemiologic Studies on Lung and Respiratory Outcomes

First Author (Pub Year)	Study Period	Description of Study population	Study Design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
General Lung and Respiratory Symptoms							
Howard et al. (1981)	Not Reported	Malaysia rubber and oil palm estates study	Cross-sectional n = 24 plantation workers, 23 unexposed factory workers	Total amount of paraquat sprayed calculated from Interviews and company records.	Full clinical examination: Respiratory - spirometry and transfer factor; Liver - blood samples (ALT, AST, ALKP); Renal - blood samples (blood urea nitrogen, serum creatinine); Urine albumen; Hematology – Cyanmethemoglobin, red and white cell counts, PCV, MCHC, MCH, MCV and white cell differential	No evidence of an associations for the range of pulmonary functions, including FVC (β = 0.139, p-value = 0.48), FEV (β = 0.141, p-value = 0.51), FEV% (β = 1.04, p-value = 0.73), and CO diffusion (β = -0.63, p-value = 0.30)	Low
Ames et al. (1993)	1991	Hollister, CA (Case De Fruta community)	Cross-sectional n = 60 residents, 172 historical controls	1. External comparison: Living in the community affected by the pesticide drift. 2. Internal comparison: Survey-based self-report.	Survey questionnaire administered 14 days after first day of pesticide spraying resulting in the drift. Developed by CDHS. No information regarding validation. Included breathing difficulty, cough, diarrhea, eye irritation, headache, nausea, rhinitis, throat irritation, tiredness, and wheezing.	Evidence of a positive association was reported for the following symptoms: Breathing difficulty (prevalence ratio, PR: 2.2, $p < 0.01$), cough (PR: 2.6, $p < 0.001$), diarrhea (PR: 5.9, $p < 0.001$), eye irritation (PR: 2.5, $p < 0.001$), headache (PR: 1.7, $p < 0.001$), nausea (PR: 3.1, $p < 0.001$), rhinitis (PR: 2.5, $p < 0.001$), throat irritation (PR: 1.74, $p < 0.05$), unusual tiredness (PR: 2.9, $p < 0.001$), and wheezing (PR: 3.0, $p < 0.01$).	Low
Senanayake et al. (1993)	Not Reported	Dickoya, Sri Lanka Study	Cross-sectional n = 85 spraymen (exposed), 76 tea factory workers (unexposed), and 79 general	Interview and company record review.	Clinical examination. General Health - resting pulse, blood pressure Hematology - hemoglobin concentration, packed cell volume; Renal - blood urea and creatinine; Liver - alkaline phosphatase,	No evidence of a significance positive association for the factors FEV1, FEV1/FVC (%), Hemoglobin (g/dL), and Packed Cell Volume (%)	Low

First Author (Pub Year)	Study Period	Description of Study population	Study Design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
			workers (unexposed)		aspartate, alanine transferase, bilirubin, total protein, albumin; Respiratory - FVC, FEV, TLC, carbon monoxide transfer flow, chest x-rays		
Castro-Gutierrez et al. (1997)	1987-1988	Nicaraguan banana plantation workers (age >= 24 years)	Cross-sectional n = 134 exposed, 152 unexposed	Self-report of 2-plus years of work/exposure to paraquat. More intense exposure defined as 2-plus years of work applying paraquat and self-reported prior history of rash or skin burns attributed to paraquat exposure.	Lung function (FEV1 and FVC); Respiratory symptoms; and non-respiratory outcomes: history of nail damage or loss of nails, bloody nose, splashes in eyes).	Evidence of moderately strong and strong association for grade 3 dyspnea (Low vs. No Exposure – OR = 2.8, 95% CI: 1.4-5.6, n = 20 exposed individuals; Intense vs. No Exposure – OR = 4.6, 95% CI: 2.4-9.0, n = 30). Evidence of a moderately strong association for episodic dyspnea with wheezing (OR = 2.9, 95% CI: 1.4-6.3, n = 71 exposed individuals). No evidence of a significant positive association For chronic bronchitis (Low vs. No Exposure – OR = 1.0, 95% CI: 0.41-2.6, n = 8 exposed individuals; Intense vs. No Exposure – OR = 2.0, 95% CI: 0.92-4.4, n = 16). No evidence of a significant positive association for abnormal spirometry (Low vs. No Exposure – OR = 0.93, 95% CI: 0.32-2.7, n = 5 exposed individuals; Intense vs. No Exposure – OR = 1.3, 95% CI: 0.51-3.4, n = 9)	Low
Dalvie et al. (1999)	Last 2 weeks of May 1994	South Africa agrochemical neurotoxicity study	Cross-sectional n = 62 herbicide sprayers, 70	Questionnaires administered by trained interviewers. Extensive exposure data collected for each agricultural job performed. A paraquat	Lung function (Spirometry, carbon monoxide gas transfer measurement, arterial oxygen saturation)	Evidence of an association was reported for measures of long-term exposure to paraquat and arterial oxygen desaturation during exercise,	Low

First Author (Pub Year)	Study Period	Description of Study population	Study Design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
			unexposed workers	job exposure matrix developed for different application activities.		independently of short-term exposure (beta coefficients of magnitude 0.019). Evidence of an association between several metrics of exposure to paraquat and mean value of predicted exercise oximetry (Cumulative exposure to paraquat β = 0.00114; Intensity of exposure to paraquat β = 0.01941; Absolute cumulative exposure to paraquat β = 0.00126; Absolute intensity of exposure to paraquat β = 0.01984).	
Schenker et al. (2004)	2000	Study of Agricultural Lung Disease (SALUD)	Cross-sectional n = 338	cumulative paraquat exposure index created using biological monitoring data and included weighting for the type of crop and use of protective equipment. The cumulative exposure index was calculated based upon work history reported by each worker, including the handling of paraquat in each job, the length of employment, the type of crop, and the use of protective equipment	Respiratory symptoms Lung function (Spirometry and single-breath carbon monoxide diffusing capacity)	Evidence of a positive association between cumulative exposure to paraquat and respiratory symptoms. Each unit increase in the cumulative paraquat index was associated with a 1.8 increase in the odds of chronic cough (95% CI: 1.0-3.1) and a 2.3 increased in the odds of shortness of breath with wheeze (95% CI: 1.2-5.1). Evidence of a positive association between paraquat exposure and ventilatory equivalent for CO2 (β= 0.49, p = 0.02)	Low
Cha et al. (2012)	2008-2009	2007 Hebei Spirit oil spill cohort (Farmers)	Cross-Sectional n = 2,882 farmers	Interviewer-administered questionnaire asked about 34 individual pesticides commonly used in study area, use of personal	Interviewer-administered questionnaire: COPD, asthma, Wheeze, Exertional wheeze.	Evidence of a positive association with paraquat exposure and spirometry. No evidence of a positive association between paraquat	Low

First Author (Pub Year)	Study Period	Description of Study population	Study Design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
				protective equipment and pesticide application method.	Spirometry: Best FVC and FEV1 among a minimum of 3 acceptable forced expirations.	exposure and wheeze (OR = 0.75, 95% CI: 0.52-1.08, n = 320 exposed individuals), shortness of breath (OR = 0.87, 95% CI: 0.54-1.40, n = 141 exposed individuals), and allergy rhinitis (OR = 1.16, 95% CI: 0.77-1.74, n = 305 exposed individuals) No evidence of a significant positive association for COPD (OR = 1.44, 95% CI: 0.50-4.16, n = 54 exposed individuals), asthma (OR = 2.18, 95% CI: 0.99-4.82, n = 118 exposed individuals), and allergy rhinitis (OR = 1.16, 95% CI: 0.77-1.74, n = 305 exposed individuals).	
Wheeze							
Hoppin et al. (2002)	1994-1997 (Enrollment)	Agricultural Health Study (AHS)	Cross-sectional n = 20,468	AHS Survey Instrument – Ever/Never Paraquat Use and Cumulative Lifetime Use	AHS Survey Instrument: "How many episodes of wheezing or whistling in your chest have you had in the past 12 months?"	Evidence of a positive association between wheeze and ever/never paraquat use (OR = 1.27; 95% CI: 1.04-1.56 with a p-trend = 0.46,). No evidence of a significant positive exposure-response relationship (< 5 days – OR = 1.33, 95% CI: 0.99-1.78; 5-9 days – OR = 1.12, 95% CI: 0.77-1.61; > 10 days – OR = 1.31, 95% CI: 0.92-1.86).	Low
Hoppin et al. (2006a)	1993-1997 (Enrollment)	Agricultural Health Study (AHS)	Cross-sectional n = 20,175 (17,920 farmers and 2,255 commercial applicators)	AHS Survey Instrument – Ever/Never Paraquat Use	AHS Survey Instrument: "How many episodes of wheezing or whistling in your chest have you had in the past 12 months?"	No evidence of a significant positive association was observed for wheeze among farmers (OR = 1.22; 95% CI: 0.98, 1.51). No evidence of an association was observed	Low

First Author (Pub Year)	Study Period	Description of Study population	Study Design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
						among commercial applicators (OR = 0.93; 95% CI: 0.59, 1.47).	
Hoppin et al. (2006b)	1993-1997 (Enrollment)	Agricultural Health Study (AHS)	Cross-sectional n = 2,255 IA commercial applicators	AHS Survey Instrument – Ever/Never Paraquat Use	AHS Survey Instrument: "How many episodes of wheezing or whistling in your chest have you had in the past 12 months?"	No evidence of a significant positive association between reported current paraquat use and wheeze (OR = 1.21; 95% CI: 0.78, 1.85).	Low
Hoppin et al. (2016)	1993-1997 (Enrollment) through 2005-2010 (Phase 3 Follow-up)	Agricultural Health Study (AHS)	Cross-sectional n = 22,134 men	AHS Survey Instrument – Ever/Never Paraquat Use	AHS Survey Instrument: "How many episodes of wheezing or whistling in your chest have you had in the past 12 months?" "Allergic status based on a history of doctor-diagnosed hay fever".	No evidence of a significant positive association between current paraquat use and allergic wheeze (OR = 1.10; 95% CI: 0.79, 1.55) No evidence of an association between current paraquat use and non-allergic wheeze (OR = 0.91; 95% CI: 0.71-1.16).	Low
Allergic Rhinitis							
Chatzi L et al. 2007	April to November, 2002	Northern Crete grape farmers	Cross-sectional n = 120 exposed, 100 unexposed	Questionnaire on occupational history (number of working hours per day, number of years working in grape cultivation, preventive measures used during working time, use of pesticides) and work-related symptoms. Grape farmers asked to identify pesticides they currently used from a list of 50 commonly used pesticides (brand names and pictures).	Allergic rhinitis and Asthma (Face- to-face interview performed by the same trained physician)	No evidence of a significant positive association between bipyridyl herbicides, which includes paraquat, and self-reported allergic rhinitis (OR = 2.2, 95% CI: 1.0 -4.8). Evidence of a strong positive association for the combination of allergic rhinitis with atopy (OR = 4.0, 95% CI: 1.4- 11.2), based 50 subjects reported use of bipyridyl herbicides.	Low
Slager et al. 2009	1993-1997	Agricultural Health Study (AHS)	Cross-Sectional n = 2,245 IA commercial applicators	AHS Survey Instrument – Ever/Never Paraquat Use and Cumulative Lifetime Use	AHS Survey Instrument: Current rhinitis – ''During the past 12 months have you	No evidence of a significant positive association between exposure to paraquat and rhinitis based on ever-use	Low

First Author (Pub Year)	Study Period	Description of Study population	Study Design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
					had a stuffy, itchy, or runny nose?"	(OR = 1.32; 95% CI: 0.68-2.01).	
					Rhinitis severity – ''How many episodes of stuffy, itchy, or runny nose have you had in the past 12 months?''	No evidence of an exposure-response relationship (1-4 days per year – OR 1.29, 95% CI: 0.60-2.77; 5- 9 days per year – OR = 1.37, 95% CI: 0.54-3.50; and ≥ 10 days per year – OR = 1.38, 95% CI: 0.76-2.50; p-trend = 0.207)	
Koureas et al. (2017)	June to August, 2010	Thessaly, Greece famers	Cross-sectional n = 80 farm owners, 90 urban males employed by University of Larissa	Lifetime pesticide exposure was ascertained in interview by asking subjects to recall total years of pesticide usage, the area and type of crop treated, the commercial names of the pesticides they have used and the frequency of application (per year) per pesticide.	Medical history, including the outcomes rheumatoid arthritis and allergic rhinitis, was also collected during the interview.	Evidence of a strong positive association for allergic rhinitis (OR = 9.10, 95% CI: 1.70-48.54), based on 25 study subjects reporting allergic rhinitis.	Low
Asthma							
Hoppin et al. (2008)	1993-1997 (Enrollment)	Agricultural Health Study (AHS)	Cross-Sectional n = 25,814 farm women	AHS Survey Instrument – Ever/Never Paraquat Use	AHS Survey Instrument: Self-report of a doctor's diagnosis of asthma after age 19 years and atopic status based on a self-reported history of doctor-diagnosed eczema or hay fever.	No evidence of a significant positive association for paraquat exposure for either atopic (OR = 1.90; 95% CI: 0.83-4.34) or non-atopic asthma atopic (OR = 1.60; 95% CI: 0.79-3.28), based on ever/never use.	Low
Hoppin et al. (2009)	1993-1997 (Enrollment)	Agricultural Health Study (AHS)	Cross-Sectional n = 19,704 male farmers (127 adult-onset, allergic cases and 314 adult-onset, non-allergic cases)	AHS Survey Instrument – Ever/Never Paraquat Use and Cumulative Lifetime Use	AHS Survey Instrument: Self-report of a doctor's diagnosis of asthma after age 19 years and atopic status based on a self-reported history of doctor-diagnosed eczema or hay fever.	Evidence a significant positive association between ever-use of paraquat and atopic asthma (OR = 1.67; 95% CI: 1.05, 2.65). No evidence of an association for non-atopic	Low

First Author (Pub Year)	Study Period	Description of Study population	Study Design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
						asthma (OR = 0.82, 95% CI: 0.58-1.18). In intensity-adjusted lifetime days of paraquat use for atopic and non-atopic asthma, evidence of a significant positive association at or below the median, but no evidence of significant positive association above the median, respectively (1-79 days – OR = 1.88, 95% CI: 1.09-3.24); > 79 days – OR = 1.46, 95% CI: 0.73-2.89)	
Chronic Bronchitis							
Hoppin et al. (2007)	1993-1997 (Enrollment)	Agricultural Health Study (AHS)	Cross-sectional n = 20,908 male applicators	AHS Survey Instrument – Ever/Never Paraquat Use	AHS Survey Instrument: "Has a DOCTOR ever told you that you had (been diagnosed with) chronic bronchitis? If yes, how old were you when a doctor first told you? < 20, 20–39, 40–59, 60+)"	No evidence of a significant positive association between paraquat exposure and chronic bronchitis among male pesticide applicators (OR = 1.17; 95% CI: 0.94, 1.46).	Low
Valcin et al. (2007)	1993-1997 (Enrollment)	Agricultural Health Study (AHS)	Cross-sectional n = 21,541 Female spouses	AHS Survey Instrument (spousal) **Exposures of interest: 1) current farm activities, 2) lifetime non-farm job history, and 3) lifetime pesticide history. Self-reported ever use of paraquat.**	AHS Survey Instrument: **"Has a DOCTOR ever told you that you had (been diagnosed with) chronic bronchitis? If yes, how old were you when a doctor first told you? < 20, 20–39, 40–59, 60+)"**	Evidence of a positive association between chronic bronchitis and paraquat exposure (OR = 1.91: 95% CI: 1.02-3.55, n = 11 paraquat users).	Low

Table A-3: Summary of Epidemiologic Studies on Cancer

First Author (Pub Year)	Study Period	Description of study population	Study design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
Cockburn et al. (2011)	Cases identified August 2005 - July 2006, Exposure 1974 through 1999; Controls recruited 2001, 2004-2006	California Central Valley/Parkinson's Environment and Genes Study (PEG)	Case-Control n = 150 cases, 155 controls	PEG Exposure Measure For each pesticide, cumulative exposure categorized as "Unexposed" (zero exposure) and "Exposed" (further divided into "Low" and "High" exposure based on median exposure/ pesticide among controls)	California Cancer Registry	No evidence of a significant positive association between prostate cancer and residential paraquat exposure (OR = 1.42 95% CI: 0.87 to 2.31, n = 103 exposed cases).	Moderate
Engel et al. (2005)	1993-1997 (Enrollment) to 2000	Agricultural Health Study (AHS)	Prospective Cohort n = 30,145 (309 breast cancer cases)	AHS Survey Instrument – Ever/Never Paraquat Use (Indirect Exposure, based on Husband Self-Report)	Cancer registries in Iowa and North Carolina, coded via ICD-O-2	No evidence of a significant positive association between breast cancer and husband's pesticide use (RR: 1.3, 95% CI: 0.8-2.0, n = 30 exposed breast cancer cases).	Moderate
Ferri et al. (2017)	2009-2014	Bari and Taranto in Southern Italy Hospital Patients	Case-Control n = 158 cases, 76 controls	Qualitative exposure score based on study questionnaire on job activities and Carcinogen Exposure (CAREX) job-exposure matrix. CAREX assigns exposure scores to specific job titles and is based on professional judgement.	Cancer cases (30 HL and 128 NHL) were recruited from the hematology divisions of the University Hospital of Bari "Moscati" Hospital of Taranto.	While evidence of a significant positive association was reported for all lymphomas in the investigators' low exposed group, more specific analysis of HL and HLS, stratified by low and medium-high paraquat exposure, did not provide evidence of a significant positive association in analysis of all lymphomas or stratifying by HL and NHL.	Moderate

First Author (Pub Year)	Study Period	Description of study population	Study design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
Koutros et al et al. (2015)	1993-1997 (Enrollment) to 2011	Agricultural Health Study (AHS)	Prospective Cohort n = 54,344 (321 bladder cancer cases)	AHS Survey Instrument – Ever/Never Paraquat Use and Cumulative Lifetime Use	Cancer registries in Iowa and North Carolina, coded via ICD-O-2	No evidence of an association between ever/never use of paraquat exposure and bladder cancer (RR: 0.86, 95% CI: 0.61-1.20). No evidence of an association between cumulative intensity-weighted days of paraquat and bladder cancer (Exposure Tertile 1 – OR = 0.96, 95% CI: 0.49-1.89, n = 10 exposed cases; Exposure Tertile 2 – OR = 1.64, 95% CI: 0.91-2.96, n = 13 exposed cases; Exposure Tertile 3 – OR = 1.29, 95% CI: 0.69-2.40, n = 12 exposed cases; p-trend = 0.65).	High
Lee et al. (2005)	Cases diagnosed July 1988-June 1993. Glioma cases, controls, proxies interviewed 1992–94	Nebraska Health Study II	Case-Control n = 251 cases, 498 controls	Subjects queried about use of specific pesticides (list developed with assistance of local agricultural experts, included 20 insecticides and 17 herbicides used on Nebraska crops over previous 40 years).	Glioma (Nebraska Cancer Registry, or from 11 participating hospitals in Lincoln and Omaha covering more than 94% of adult glioma cases in the study population)	Evidence of a strong positive association between paraquat use and risks of glioma (OR = 11.1, 95% CI: 1.2- 101); however, this association was based on only 5 exposed cases.	Low
Lee et al. (2007)	1993-1997 (Enrollment) to 2002	Agricultural Health Study (AHS)	Prospective Cohort n = 56,813 pesticide applicators	AHS Survey Instrument – Ever/Never Paraquat Use	Cancer registries in Iowa and North Carolina, coded via ICD-O-2	No evidence of a positive association between colorectal cancer and exposure to paraquat, based on ever-use (OR = 0.9; 95% CI: 0.7-1.3). Similar results were observed when stratifying the analysis by colon and rectal cancer (Colon Cancer – OR = 0.7, 95% CI: 0.5-1.1; Rectal Cancer – OR = 1.5, 95% CI: 0.8-2.6).	High

First Author (Pub Year)	Study Period	Description of study population	Study design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
Monge et al et al. (2015)	1995-2003	Costa Rica childhood leukemia study	Case-Control n = 300 cases, 579 controls	Pesticide-related questions included occupational, environmental, and home exposures of both parents. Those in agriculture reported use of pesticides, agricultural tasks, frequency of exposure (# applications/month and hours/day), determinants of exposure (task technology, PPE, field reentry, storing of pesticides, personal hygiene). Data collected on 25 specific pesticides. Interview data combined with external data on application rates for 14 crops, 21 calendar years, and 14 geographic regions.	All cases of childhood leukemia (age 0 to 14 at diagnosis) in Costa Rica in 1995-2000 identified at the Cancer Registry and confirmed at the Children's Hospital of Costa Rica.	**Maternal Exposure**: There were only 7 exposed cases overall, so the effect estimates are less stable and provide no evidence of a significant positive association for either total leukemia or acute lymphocytic leukemia. **Paternal Exposure:** Evidence of a positive association between paraquat exposure and total leukemia based on stratification by high vs. low exposure and year before conception as the exposure window of interest.	Moderate
Park et al et al. (2009)	1993-1997 (Enrollment) to 1999-2003 (Phase 2 Follow-Up)	Agricultural Health Study (AHS)	Prospective Cohort n = 56,222 (ever use) and 24,655 (LE, IWLE) Licensed applicators	AHS Survey Instrument: Ever personally mixing or applying any pesticide Detailed information on 50 specific pesticides: yrs of use, frequency of use, decade began using. 3 exposure metrics: 1) ever use of specific pesticide (paraquat); 2) Lifetime exposure-days (LE); 3) Intensity weighted lifetime exposure-days (IWLE)	Cancer registries in Iowa and North Carolina, coded via ICD-O-2	No evidence of an association between ever use of paraquat and all cancers (RR: 0.95, 95% CI: 0.86-1.05, n = 667 exposed cases). No evidence of an association between ever use of paraquat and Prostate cancer, Lung cancer, Colon cancer, Kidney cancer, Bladder cancer, Leukemia, Cutaneous melanoma. No evidence of a significant positive association between ever use of paraquat and Rectal cancer, Pancreatic cancer, Kidney cancer, NHL.	High

Table A-4: Summary of Epidemiologic Studies on Other Health Outcomes

First Author (Pub Year)	Study Period	Description of study population	Study design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
Mortality							
Tomenson and Campbell (2011)	1961-2009	U.K. paraquat production plant workers	Retrospective Cohort n = 926 male workers	No quantitative exposure measurements or estimation used in the analysis. Some industrial hygiene sampling was conducted (authors inferred that workers' daily exposures were comparable with those of paraquat sprayers or mixers/loaders)	Mortality; cause-specific mortality (Death Certificates)	No evidence of an association with mortality generally or PD-related mortality. (SMR for all-cause mortality: 88%, 95% CI: 78%-98%) or local mortality (SMR: 66%, 95% CI: 68%-86%). Working in the paraquat production plants was also not associated with PD-related mortality (SMR comparing Parkinson's disease mortality among paraquat plant workers to national mortality rate: 31% (95% CI: 1%-171%); SMR comparing PD-related mortality among paraquat plant workers to local PD-related mortality: (32% (1%-176%).	Moderate
Injury Mortality							
Waggoner et al. (2013)	1993-1997 (Enrollment) to 2008	Agricultural Health Study (AHS)	Prospective Cohort n = 51,035 licensed male applicators	AHS Survey Instrument – Ever/Never Paraquat Use	Annual linkage with death registries in NC and IA and the National Death Index. Injury deaths defined by ICD codes indicating a fatal injury.	Evidence of a positive association between risk of fatal injury and paraquat exposure among male farmers in the AHS, based on ever/never use (HR = 1.35, 95% CI: 1.05-1.74).	Low
End Stage Renal Disease							

First Author (Pub Year)	Study Period	Description of study population	Study design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
Lebov et al. (2015)	1993-2011 (Enrollment) to 2011	Agricultural Health Study (AHS)	Prospective Cohort n = 31,142 Wives of licensed applicators	Husband's Responses to AHS Survey Instrument Ever/Never Paraquat Use and Cumulative Lifetime Use	Linkage with the United States Renal Data System and the National Death Index	Evidence of a positive association between indirect paraquat exposure and ESRD (HR = 1.99; 95% CI: 1.14-3.47). No evidence of a significant positive association based on husbands' cumulative use of paraquat (1.0-15.4 lifetime exposure days – HR: 1.36, 95% CI: 0.43-4.30; > 15.4-102.8 Lifetime Days – HR: 1.78, 95% CI: 0.56-6.62), but was based on only 6 of 21 exposed cases.	Moderate
Lebov et al. (2016)	1993-1997 (Enrollment) to 2011	Agricultural Health Study (AHS)	Prospective Cohort n = 55,580; 24,429 (paraquat) Licensed male applicators	AHS Survey Instrument Ever/Never Paraquat Use and Cumulative Lifetime Use	Linkage with the United States Renal Data System and the National Death Index	Evidence of a positive association using the non-exposed as the referent category: Low Exposure Tertile (< 708.75 days): HR = 1.05, 95% CI: 0.56, 1.97); Middle Exposure Tertile (≥ 708.75 to ≤ 2,334.5 days): HR = 2.3, 95% CI: 1.2-4.41); High Exposure Tertile (≥ 2,334.5 days): 2.15, 95% CI: 1.11-4.15), with p for trend = 0.0164.	High
Renal and liver function and hematology							
Howard et al. (1981)	Not Reported	Malaysia rubber and oil palm estates study	Cross-sectional n = 24 plantation workers, 23 unexposed factory workers	Total amount of paraquat sprayed calculated from Interviews and company records.	Full clinical examination. Renal – blood samples (blood urea nitrogen, serum creatinine); Urine albumen; Hematology – Cyanmethemoglobin, red and white cell counts, PCV, MCHC, MCH, MCV and white cell differential	No evidence of an association for the renal, liver and hematological parameters. The investigators further reported that group means fell within the normal range of laboratory performing the analysis of samples that some lung and liver measurements were higher in the unexposed groups.	Low

First Author (Pub Year)	Study Period	Description of study population	Study design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
Senanayake et al. (1993)	Not Reported	Dickoya, Sri Lanka Study	Cross-sectional n = 85 spraymen (exposed), 76 tea factory workers (unexposed), and 79 general workers (unexposed)	Interview and company record review.	Clinical examination. Hematology - hemoglobin concentration, packed cell volume; Renal - blood urea and creatinine. Liver - alkaline phosphatase, aspartate, alanine transferase, bilirubin, total protein, albumin.	No evidence of an association was found for the hematological and biochemical parameters hemoglobin and packed cell volume. Paraquat sprayers had a mean hemoglobin of 14.50 g/dl and packed cell volume of 45.37%, whereas factory and general workers had a mean hemoglobin of 14.28g/dl and 14.84g/dl, respectively, and mean packed cell volume of 44.87% and 46.35%, respectively	Low
Diabetes							
Montgomery et al. (2008)	1993-1997 (Enrollment) to 2011	Agricultural Health Study (AHS)	Prospective Cohort n = 33,457 (1,176 Diabetes Cases)	AHS Survey Instrument – Ever/Never Paraquat Use	AHS Survey Instrument: Has a doctor ever told you that you had been diagnosed with diabetes (other than while pregnant)?''	Evidence of a positive association between ever use of paraquat and diabetes (OR = 1.45; 95% CI: 1.26, 1.66); however, there was no evidence of an association when also adjusting for BMI and state of residence in addition to age (OR = 1.01; 95% CI: 0.87, 1.18).	High
Starling et al. (2014)	1993-1997 (Enrollment) to 1999-2003 (Phase 2) and 2005-2010 (Phase 3) Follow-up	Agricultural Health Study (AHS)	Prospective Cohort n = 13,637 (688 Diabetes Cases)	AHS Survey Instrument – Ever/Never Paraquat Use (Indirect Exposure Based On husband Self-report)	AHS Survey Instrument: Has a doctor ever told you that you had been diagnosed with diabetes (other than while pregnant)?''	No evidence of a significant positive association between paraquat use and incident diabetes in women based on ever-use (HR = 1.07; 95% CI: 0.67, 1.71).	Moderate
Juntarwijit and Juntarwijit (2018)		Study of the Bang Rakem district of Thailand	Case-Control n = 866 cases, 1021 controls	Interview to ascertain ever/never use of pesticides, including paraquat	Diabetes cases were recruited from 7 randomly selected hospitals from 21 sub-district hospitals in Bang Rakem, based on outpatient service information.	No evidence of a significant positive association between paraquat exposure and diabetes (OR = 1.31, 95% CI: 0.97-1.79, n = 115 paraquat exposed cases).	Moderate
Eye Disorders							

First Author (Pub Year)	Study Period	Description of study population	Study design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
Kirrane et al. (2005)	1993-1997	Agricultural Health Study (AHS)	Cross-sectional n = 31,173 wives of pesticide applicators	AHS Survey Instrument – Ever/Never Paraquat Use	AHS Survey Instrument – Self-reported retinal or macular degeneration	No evidence of a positive association between paraquat exposure and retinal degeneration (OR = 0.7; 95% CI: 0.3, 1.7).	Moderate
Montgomery et al. (2017)	1993-1997	Agricultural Health Study (AHS)	Nested Case-Control n = 161 cases, 39,108 controls	AHS Survey Instrument – Ever/Never Paraquat Use	Cases were ascertained by physicians with supporting pathology or retinal photographs	No evidence of a significant positive association between paraquat and AMD based on ever/never exposure (OR = 1.5; 95% CI: 0.9-2.3). The analysis of cumulative days of use also indicated No evidence of an association between paraquat and AMD (> 0-10 Cumulative Days of Paraquat Use – OR = 1.2, 95% CI: 0.5-2.6, n = 7 exposed cases; > 10 Cumulative days of Paraquat Use – OR = 1.4, 95% CI: 0.6-3.2, n = 6 exposed cases; p-trend = 0.413).	High
Thyroid Disease							
Goldner et al. (2010)	1993-1997 (Enrollment)	Agricultural Health Study (AHS)	Cross-sectional n = 16,529 (169 exposed to paraquat)	AHS Survey Instrument – Ever/Never Paraquat Use	AHS Survey Instrument: Self-reported history of physician diagnosed thyroid disease (hyperthyroid, hypothyroid, other)	Number of exposed cases too small to assess the paraquat association with hyperthyroid. Evidence of a significant positive association was observed for hypothyroid (OR = 1.9; 95% CI: 1.1-2.8) and no evidence of a significant positive association for other thyroid disease (OR = 1.4; 95% CI: 0.73-3.1).	Low
Myocardial Infarction							

First Author (Pub Year)	Study Period	Description of study population	Study design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
Mills et al. (2009)	1993-1997 (enrollment) to 1999-2005	Agricultural Health Study (AHS)	Prospective Cohort n = 54,609 non-fatal MI group, 32,024 non-fatal MI group after 5-year follow-up period.	AHS Survey Instrument – Ever/Never Paraquat Use	Fatal MI ascertained using state and national death databases Non-fatal MI ascertained AHS Survey Instrument	No evidence of a significant positive association was reported for fatal and non-fatal MI and paraquat exposure (fatal MI: HR= 0.90; 95% CI: 0.71-1.15; non-fatal MI: HR = 1.09; 95% CI: 0.97-1.30).	High
Oxidative Stress							
Ranjbar et al. (2002)	Not Reported	Iran	Cross-sectional n = 30 cases, 30 controls	Work in paraquat-formulating factory, unexposed were Tehran University medical sciences employees	Clinical measurement of lipid peroxidation, antioxidant capacity, and total thiol groups	Evidence of an association($p < 0.001$), based on comparison between the paraquat factory workers and unexposed volunteers from Tehran University: Mean lipid peroxidation for cases was 11.46 nmol/ml (95% confidence interval (CI) 10.86 – 12.06) and for controls was 0.11 nmol/ml (95% CI: 9.68 – 10.53) Mean antioxidant capacity for cases was 1.35 µmol/ml (95% CI: 1.32 – 1.38) and for controls was 1.54 µmol/ml (95% CI: 1.51 – 1.57 Mean total (SH) groups for cases was 0.16 mM (95% CI: 0.15 – 0.17) and for controls was 0.21 mM (95% CI: 0.19 – 0.22)	Low
Abnormal Skin Pigmentation							

First Author (Pub Year)	Study Period	Description of study population	Study design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
Jee et al. (1995)	1983-1991	Workers from 28 paraquat production factories in Taiwan	Cross-sectional n = 242	Exposure characterization was based on job classification; workers were classified as "bipyridine exposed" if their job included centrifugation and crystallization processing of bipyridine in open tanks.	Photographs of suspicious lesions corresponding to 156 workers were taken for subsequent objective characterization and evaluation of severity; 86 workers did not have suspicious skin lesions. Of the 156 workers, 133 had skin lesions which were graded for severity on a 1-to-3 scale		
Rheumatoid Arthritis							
Koureas et al. (2017)	June-August, 2010	Thessaly, Greece famers	Cross-sectional n = 80 farm owners, 90 urban males employed by University of Larissa	Lifetime pesticide exposure was ascertained in interview by asking subjects to recall total years of pesticide usage, the area and type of crop treated, the commercial names of the pesticides they have used and the frequency of application (per year) per pesticide.	Medical history, including the outcomes rheumatoid arthritis and allergic rhinitis, was also collected during the interview.	No evidence of an association for rheumatoid arthritis (OR = 0.69, 95% CI: 0.094-5.03), based on 6 subjects reporting diagnosis of rheumatoid arthritis.	Low
Actinic Keratosis							
Cooper et al. (1994)	1990	Texas paraquat production plant	Cross-sectional n = 112 plant workers, 232 unexposed	Employment at a paraquat production facility: cumulative time-intensity index based on employment records and job classification, classified into 3 levels	Full-body dermatologic examination by board-certified dermatologist		Low
Male Reproduction							

First Author (Pub Year)	Study Period	Description of study population	Study design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
Hossain et al. (2010)	Not Reported	Sabah, Malaysia farmers	Cross-sectional n = 62 exposed, 90 unexposed	Self-report via personal interview - history of pesticide exposure, and exposure pattern (type of pesticide, duration of use, spraying and cleaning of pesticide cans)	Semen quality, volume, pH, morphology, motility, WBC count, sperm concentration	Evidence of a positive association between self-reported use of paraquat and/or malathion and several semen quality parameters (paraquat and/or malathion not separated in analyses). Semen Volume – 6.5 (2.7, 15.2); Semen pH – 2.66 (0.1-0.9); Concentration – 8.77 (4-19); Sperm Motility – 5.18 (2.5-10.5); Sperm Morphology – 4.96 (1.6-14.6); and Semen WBC – 4.51 (1.5-13.4).	Low
Cremonese et al. (2017)	2012-2013	rural and urban males aged 18-23 living in Farroupilha, in Rio Grande do Sul.	Cross-Sectional n = 99 rural males, 36 urban males	Questionnaire used to ascertain pesticide exposure and included questions on years of agricultural work, years of mixing/applying pesticides, and frequency of mixing/applying pesticides. Subjects were also asked to recall specific pesticides, based on a list of product trade names that were common to the study area.	Male reproductive function was examined by collecting blood to assess hormone levels (testosterone, LH, FSH, SHBG, prolactin, FAI, and Testosterone:LH), semen samples to assess semen quality, and measuring genitals by a urologist specialist.	Evidence of a significant association for LH (1-5 Years Paraquat Use: Beta: 0.96, 95% CI: 0.75-1.29; ≥ 6 Years Paraquat Use: Beta: 0.83, 95% CI: 0.69-0.99; p-trend = 0.05); and sperm motility (1-5 Years Paraquat Use: Beta: 0.90, 95% CI: 0.66-1.21; ≥ 6 Years Paraquat Use: Beta: 0.66, 95% CI: 0.48-0.92; p-trend = 0.02). No evidence of an association for the hormone/reproductive factors: testosterone, FSH, SHBG, prolactin, FAI, and Testosterone:LH and the semen quality parameters concentration and motility.	Low
Depressive Symptoms							

First Author (Pub Year)	Study Period	Description of study population	Study design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
Beard et al. (2013)	1993-1997 (enrollment) to 2005-2010 (Phase 3 Follow-up)	Agricultural Health Study (AHS)	Prospective Cohort n = 16,893 female spouses completing Phase 2 Follow-up Questionnaire	AHS Survey Instrument – Ever/Never Paraquat Use	Self-reported incident depression between the time of study enrollment (1993-1997) to study follow-up (2005-2010)	No evidence of a positive association between suicide and paraquat exposure (HR = 0.70; 95% CI: 0.42, 1.16 with n = 19 exposed cases, and 43,376 unexposed cases) based on ever/never use.	Moderate
Beard et al. (2014)	1993-1997 (enrollment) to 2005-2010 (Phase 2 Follow-up)	Agricultural Health Study (AHS)	Prospective Cohort n = 21,208 male applicators	AHS Survey Instrument – Ever/Never Paraquat Use	Self-reported incident depression between the time of study enrollment (1993-1997) to study follow-up (2005-2010)	No evidence of a significant positive association was reported for paraquat exposure (RR = 1.22; 95% CI: 0.95-1.56 with n = 101 exposed cases).	Moderate
Kim et al. (2013)	February-March, 2011	Nationwide survey of male farmers in rural South Korea	Cross-sectional n = 1,895	Acute occupational pesticide poisoning during 2010, 21 symptoms and signs selected based on pilot study and reference reviews. Respondents queried as to whether they had experienced any of these symptoms within 48 h of using pesticides. If yes to any, defined as an acute occupational pesticide poisoning.	Depressive symptoms measured by the Korean version of the Geriatric Depression Screening Scale short form (GDS-15).	No evidence of a significant positive association between paraquat exposure and risk of depression for those who reported depression at enrollment only (OR = 1.20; 95% CI: 1.0, 1.5); for those who reported depression at both enrollment and follow-up (OR = 1.1; 95% CI: 0.9, 1.4); and for those who reported depression at follow-up only (OR = 1.1; 95% CI: 0.9, 1.3).	Low
Suicide							
Beard et al. (2011)	1993-1997 (enrollment) to 2009	Agricultural Health Study (AHS)	Prospective Cohort n = 81,998	AHS Survey Instrument – Ever/Never Paraquat Use	Suicide ascertained by linking the AHS cohort to state mortality files and the National Death Index.	No evidence of an association between suicide and paraquat exposure (HR = 0.70; 95% CI: 0.42, 1.16 with n = 19 exposed cases, and 43,376 unexposed cases) based on ever/never use.	Moderate
Infant Birth Weight							

First Author (Pub Year)	Study Period	Description of study population	Study design	Exposure Measurement	Outcome Measurement	Primary Paraquat Results	Study Quality
Sathyanarayana et al. (2010)	1993-1997 (enrollment)	Agricultural Health Study (AHS)	Cross-Sectional n = 2,246 female spouses who had a singleton birth within 5 years of AHS enrollment	AHS Survey Instrument – Ever/Never Paraquat Use	Study subjects reported the weight in pounds and ounces for each most recent birth.	No evidence of a significant association between mother's ever use of paraquat and a change in offspring's birth weight (regression coefficient = -0.2 g; 95% CI: -212, 212 g with 21 women reporting ever use and 2,202 women reporting never use.	Low
Aplastic Anemia							
Prihartono et al. (2011)	1989-2002	Thailand case-control study	Case-Control (clinic-based) n = 2,802 (cases 541, controls 2,261)	Exposure data obtained using 2 approaches: Participant self-report using a questionnaire and expert assessment.	Aplastic anemia diagnosed by meeting at least 2 of 3 criteria: White blood cell count of ≤ 3.5 × 109/L, Platelet count of ≤50 × 109/L; Hemoglobin level of ≤100 g/L or a hematocrit of ≤30%. Diagnosis confirmed by a bone marrow biopsy.	No evidence of a significant positive association between self-reported ever use of paraquat and aplastic anemia (OR = 1.68, 95% CI: 0.92-3.05, n = 17 exposed cases). Based on expert assessment, no evidence of an association in their low/medium paraquat exposed categories (OR = 0.83, 95% CI: 0.63-1.09, n = 76 exposed cases) and evidence of a positive association was observed in the "high/very high" paraquat exposed category (OR = 1.71, 95% CI: 1.32-2.22, n = 141 exposed cases). In their further analysis adjusted for all other pesticide use, no evidence of a significant positive association (OR = 1.62, 95% CI: 0.59-4.45, n = 141 exposed cases).	Moderate