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The Association Between Paraquat Exposure and Parkinson's Disease Mortality: A County-Level Ecological Study in the United States

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THE ASSOCIATION BETWEEN PARAQUAT EXPOSURE AND PARKINSON'S DISEASE MORTALITY: A COUNTY-LEVEL ECOLOGICAL STUDY IN THE UNITED STATES

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ABSTRACT

Objectives: The current study reports the results of an ecological study regarding the association between PQ exposure and Parkinson's disease mortality in the United States.

Methods: The outcome of interest for this study was mortality due to Parkinson's disease, obtained from CDC Wonder. The exposure of interest was PQ exposure at the county level which was obtained from the United States Geological Survey (USGS). Statistical analysis was done using the mortality data, grouped into ten-year age groups, and focused on data from 2015-2019 to account for the lag time between initial Paraquat exposure and Parkinson's Disease mortality. A Negative Binomial model was used to describe the association between PQ exposure and PD mortality, due to the dependent variable, PD mortality, being a count dataset. A sensitivity analysis was run to see if results from the Negative Binomial differed, which would indicate if there were large amounts of missing data in the analysis.

Results: A total of 3,054 counties were assessed for Paraquat use in kilograms, with 5,10, and 15 year low and high averages for each county obtained using the U.S. Geological

Survey (USGS) Pesticide National Synthesis Project data. The results from the Negative Binomial models showed us that when comparing the RR values for the models there was not a significant association between PQ exposure and PD mortality. There was also not a significant association between PQ exposure and PD mortality as exposure levels increased. These results suggest that further studies are needed to better understand individual PQ exposure levels to further investigate an association between PQ and PD mortality.

Conclusions: The current study found that there is not a statistically significant association between PQ exposure and Parkinson's disease mortality. Previous publications have articulated this association between Paraquat exposure and Parkinson's Disease Mortality but failed to describe the duration of the exposure variable properly. Previous publications were also limited, in that case-studies were used which could bring recall bias and small sample sizes. The implications of the findings show how the association of Paraquat, and Parkinson's Disease Mortality might be related, but that there may be additional variables to assess for the association.

TABLE OF CONTENTS

Page

LIST OF TABLES

INTRODUCTION

Paraquat dichloride (PQ) is one of the most widely used herbicides in the United States (EPA,2022). It is classified as a non-selective contact herbicide, or broad spectrum, because it can control for both broadleaf and grass weeds. It is used on a large variety of crops in the United States including soybeans, corn, cotton, peanuts, wheat, citrus, grapes, strawberries, sweet potatoes, artichokes, pears, garlic, and almonds. PQ banned in 32 countries due to its known and suspected health effects (E.m.,2022). Acute PQ exposure is associated with pain and swelling to the mouth and throat followed by gastrointestinal symptoms such as nausea, vomiting, abdominal pain, and diarrhea. Ingestion of large amounts of PQ can lead to acute kidney failure, confusion, coma, increased heart rate, liver failure, pulmonary edema, respiratory failure, seizures, and several other serious health effects within a few hours to days from initial exposure. PQ is one of the most used herbicides causing suicide death among herbicide/pesticide suicide rates. The paraquat poisoning is associated with a very high mortality rate, with 20 per million persons die from paraquat as a suicide method worldwide over the last 30 years (Seok, 2009).

There has been comparatively less research regarding the health effects associated with chronic PQ exposure. A meta-analysis, which included 64 studies, found evidence that pesticide exposure is significantly associated with the risk of Parkinson's disease. The meta-analysis screened 1,800 PubMed publications to arrive at the final 64 studies,

and the criteria for the studies to meet were observational case-control studies and studies investigating the association between exposure to pesticides and the risk of PD or genetic alterations related to PD. The mechanism underlying this association has been attributed to alterations in genes involved in Parkinson's disease pathogenesis. The meta-analysis provided evidence that there is a significant association between chemical pesticide exposure and PD and showed that chemical pesticide exposure induced multiple gene mutations. (Ahmed, 2017).

Based on the published science, our study was designed to better understand the association between Paraquat exposure and Parkinson's Disease mortality. Our study addressed one issue of previous literature, in that we were able to view the herbicide data alone and not in combination with other chemicals. This provided us with a more precise measurement of Paraquat exposure and allowed for a statistical significance between the association to be more accurate. Previous literature also had limitations in their sample sizes, as case-studies were used. Our study was modeled to better quantify this data, by using Parkinson's Disease as a multiple cause of death, which allowed for a much greater sample size for analysis.

METHODS

Study Design

An ecologic study design was used to investigate the association between PQ exposure, at a county-level, and Parkinson's disease mortality. The unit of analysis for this study is the 3,054 counties in the contiguous United States.

Outcome of Interest

The outcome of interest for this study was mortality due to Parkinson's disease. Information regarding the state of residence, county of residence, population based on ten-year age groups, and mortality data for Parkinson's disease as part of a multiple cause of death was obtained using the Centers for Disease Control and Prevention's Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) database (Centers for Disease Control and Prevention,2022).

The mortality data was grouped by county, year, and age group for all contiguous counties in the U.S. States, Hawaii and Alaska were excluded from analysis due to not being in the United States Geological Survey (USGS). The mortality data was from the years 2015-2019. Ten-year age groups were 45-54 years, 55-64 years, and 65-75 years, as mortality for Parkinson's disease is significantly lower for younger age groups. Given the rarity of Parkinson's disease as a cause of death and the suppression of the number of deaths less than 10 per county, the estimated mortality rate for suppressed county level data was calculated using WebDMAP (Tiwari, 2014). County mortality data was suppressed if the count was less than 10 deaths, among these the suppression tool

substituted expected case counts. The suppression tool computed an expected mortality count for suppressed counties by multiplying the population of the county by the regional mortality rate, in this case the statewide mortality rate for the county.

Exposure of Interest

PQ exposure data was obtained from the United States Geological Survey (USGS) under the Estimated Annual Agricultural Pesticide Use survey (USGS NAWQA: The Pesticide National Synthesis Project). The data estimates agricultural pesticide uses at the county level and is based on farm surveys of pesticide use and estimates of harvested crop acres. The data was also adjusted for county land area in square miles. PQ data at a county level for all counties was obtained for the years 2000-2014. According to the USGS, both two estimates are provided, EPest-low and Epest-high annual estimates, methods incorporate proprietary surveyed rates for Crop Reporting Districts (CRDs), but Epest-low and Epest-high estimates differ in how they treat situations when a CRD was surveyed, and pesticide use was not reported for a particular crop present in the CRD. In these situations, Epest-low assumes zero use in the CRD for that pesticide-by-crop combination. Epest-high, however, treats the unreported use for that pesticide-by-crop combination in the CRD as missing data. In this case, pesticide-by-crop use rates from neighboring CRDs or CRDs within the same region are used to estimate the pesticide-by-crop Epest-high rate for the CRD (USGS NAWQA: The Pesticide National Synthesis Project). The current study evaluated two values, high and low estimated averages to include data of counties where pesticide use was not reported. In this case, low estimates assumed a zero value for Paraquat use when use was not reported, and high estimates used neighboring CRDs within the same region to estimate Paraquat use in that county.

Paraquat usage data was then calculated for 5-, 10-, and 15-year High and Low Estimated Averages to illustrate the lag exposure time and to see trends in PQ exposure over time periods.

Statistical Analysis

The exposure variable (Paraquat) was defined by four quartiles that were based on the raw PQ variable. In the analysis, Quartile 1 was used as a reference value, and compared the moderate exposure levels (Quartile 2 and Quartile 3) with the high exposure level (Quartile 4). The exposure variable was then analyzed using a Negative Binomial Regression Analysis to obtain the relative risks (RRs) and associated 95% confidence intervals (Cis). Negative Binomial regression analysis was selected as the statistical test due to the dependent variable being a count of the number of PD deaths and the data being over dispersed. The Negative Binomial regression analysis is appropriate to use for the association between mortality data and the Paraquat exposure because the dependent variable, PD mortality, consists of over dispersed count data.

RESULTS

For the 10-year High and 15-year High Paraquat exposure negative binomial models, there was found an increase in the mortality RR between the moderate exposure quartiles and the high exposure quartiles (10-year High PQ Q2-Q4: 1.03 RR – 1.04 RR, 15-year High PQ Q2-Q4: 1.00 RR – 1.03 RR). The 5-year High Paraquat exposure model showed an increase between the moderate exposure quartiles but showed a decrease between the moderate exposure quartiles and the high exposure quartile (5-year High PQ Q2-Q3: 1.01 RR – 1.04 RR, 5-year High PQ Q3-Q4: 1.04 RR – 1.02 RR). A sensitivity analysis was done to account for missing and incomplete observations in the data, and the results were like the original negative binomial analysis. An additional negative binomial analysis was done looking at counties with a population less than 1,000,000 over the 5-year average, and the results produced were like both the original negative binomial model and the sensitivity analysis. Table 1 below displays the PQ exposure quartiles, the 5-,10-, and 15-year average models, the population associated with each quartile, the range of the exposure in kilograms for each quartile, and the mortality counts.

DISCUSSION

Our study found that there was not a statistically significant association between Paraquat exposure and Parkinson's disease mortality. The results of the statistical analyses suggest that even though there is not a statistically significant association between PQ exposure and PD mortality, further studies are needed to better quantify the exposure levels of Paraquat, and more precise Parkinson's disease mortality definitions to eliminate from analysis those that died from PD without being exposed to PQ.

Our findings were like current publications in that we also showed a potential association between Paraquat exposure and Parkinson's disease mortality, however, our study was able to use more precise exposure data over a longer period. The exposure data was different from current literature in that we were able to review Paraquat data alone, and not within a combination of chemicals. Additionally, our Parkinson's disease data was found using PD as a multiple cause of death, which allowed a much larger sample size for analysis.

A meta-analysis provided evidence that pesticide exposure was significantly associated with the risk of Parkinson's Disease and showed evidence of alterations in genes involved in Parkinson's Disease pathogenesis, however, it was found that the underlying mechanism for the association, the effect of the duration of exposure, and the specific types of pesticides need to be addressed in future research (Ahmed 2017). The association grew closer when it was found that environmental chemistry, among other

factors such as the use of PPE, played a role in the Paraquat to Parkinson's disease association (Zhang, 2016) and this was later validated further when evidence was provided in another study for an association between environmental exposure to specific pesticides and the risk of Parkinson's disease (Brouwer, 2017). Another study found that the simplest mechanism is that pesticides are directly toxic to the mitochondria (Couteur, 1999). To add to this, it was found that exposure to Paraquat with or without Maneb (MB-fungicide) induces neurodegeneration which might occur via an early inflammatory response in young adult animals; this study provided evidence that Paraquat alone and in combination with MB is toxic to rat DA (dopaminergic) neurons both in vitro and in vivo and this combination leads to Parkinson's Disease-like movement deficits (Cicchetti, 2005).

The strength of our study is based on the exposure and outcome variables precision and quantity of data. For the exposure variable, the Paraquat exposure was viewed in three levels, 5-,10- and 15-year intervals, and this provided a better understanding of exposure to Paraquat and how Parkinson's Disease mortality can be affected over time. The exposure variable also contained two sets of data, Low and High averages, and were used to better understand the range of estimates and to get a more accurate estimate of herbicide use. For the outcome variable, the mortality data came from the CDC WONDER database, and obtained mortality data with Parkinson's disease listed as a multiple cause of death. This allowed for a much larger sample size, when compared to previous publications who used observational case-studies and as a result had much smaller numbers of observations. Limitations of our study that future literature could build on, is the need for an even more precise measurement of Paraquat exposure.

Our analysis used survey data and had low and high average estimates per year for each county. A limitation of this, would be not being able to quantify individual levels of exposure, as our analysis provided broader results at the county-level. Another limitation of our study that future publications should build on is more precise mortality data. Our mortality data was obtained from the CDC WONDER database and our data was limited to Parkinson's disease as a multiple cause of death. Future publications should attempt to have more defined case-definitions of Parkinson's Disease to get a better understanding of Parkinson's Disease mortality and how that is associated with differing levels of Paraquat exposure.

These findings indicate that even though we did not find a statistical significance with the association of Paraquat exposure at the county-level and Parkinson's disease mortality, additional studies will need to be conducted to quantify the level of exposure and how differing levels of exposure effect the rate of Parkinson's disease incidence and mortality as a primary factor of disease. Public health implications include a better understanding of Paraquat use around the country, and how this might be affecting health outcomes as well as additional public knowledge that Paraquat exposure could have a significant association with Parkinson's disease mortality and that we as public health officials should strive to find alternatives to using Paraquat as an herbicide.

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APPENDIX: TABLES

Table 1. PQ Exposure and PD Mortality Results by Quartiles				
	1st Quartile	**2nd Quartile**	**3rd Quartile**	**4th Quartile**
5-Year High				
Population	185,864,995	127,147,060	112,795,862	120,674,814
Exposure (kg)	0.0333333 - 118.44	118.44 – 439.31	439.31 – 1159.02	1159.02+
Mortality	8,114	5,716	5,428	5,763
5-Year Low				
Population	103,263,699	143,639,230	139,163,292	160,416,510
Exposure (kg)	0 – 6.60	6.60 – 58.60	58.60 – 335.12	335.12+
Mortality	4,406	6,674	6,250	7,691
10-Year High				
Population	188,868,808	135,893,444	102,512,578	121,487,766
Exposure (kg)	0.0333333 – 136.8	136.8 – 464.32	464.32 – 1166.23	1166.23+
Mortality	8,251	6,128	4,959	5,787
10-Year Low				
Population	114,440,417	137,891,549	135,519,611	160,911,019
Exposure (kg)	0 – 10.9375	10.9375 – 71.0963	71.0963 – 360.810	360.810+
Mortality	4,773	6,587	6,343	7,422
15-Year High				

Population	175,983,682	133,033,558	116,742,117	123,357,000
Exposure (kg)	0.0333333 – 147.617	147.617 – 473.157	473.157 – 1170.93	1170.93+
Mortality	7,711	6,185	5,322	5,923
15-Year Low				
Population	104,298,977	131,059,868	143,515,527	170,241,985
Exposure(kg)	0 – 12.5536	12.5536 – 76.4477	76.4477 – 366.583	366.583+
Mortality	4,273	6,302	6,767	7,799

Table 2: Negative Binomial Model Results				
Variable	RR	Lower Confidence Limit RR	Upper Confidence Limit RR	Pr > ChiSq (p-value)
PQ 15-Year High				
Q2	1	0.89	1.12	0.9785
Q3	1.01	0.91	1.13	0.8159
Q4	1.03	0.92	1.14	0.6439
PQ 15-Year Low				
Q2	1.13	1.01	1.27	0.0346
Q3	1.14	1.01	1.28	0.0294
Q4	1.16	1.03	1.29	0.0135
PQ 10-Year High				
Q2	1.03	0.92	1.14	0.6591
Q3	1.04	0.93	1.16	0.4746
Q4	1.04	0.94	1.16	0.4488
PQ 10-Year Low				
Q2	1.09	0.98	1.22	0.1264
Q3	1.11	0.99	1.24	0.0691
Q4	1.09	0.98	1.23	0.1007
PQ 5-Year High				
Q2	1.01	0.89	1.13	0.9284
Q3	1.04	0.93	1.16	0.5288

Q4	1.02	0.92	1.13	0.7232
PQ 5-Year Low				
Q2	1.09	0.98	1.22	0.1227
Q3	1.11	0.98	1.24	0.0949
Q4	1.1	0.99	1.23	0.0816