BEFORE THE UNITED STATES JUDICIAL PANEL ON MULTIDISTRICT LITIGATION

IN RE PARAQUAT PRODUCTS LIABILITY LITIGATION	)	**MDL Docket No. 3004**

SYNGENTA'S RESPONSE TO THE MOTION TO TRANSFER RELATED ACTIONS FOR COORDINATED PRETRIAL PROCEEDINGS

Syngenta Crop Protection, LLC, Syngenta Seeds, LLC, and Syngenta Corporation (together, "Syngenta") do not oppose centralizing pretrial proceedings in a suitable forum for the pending federal actions related to paraquat and Parkinson's Disease that have been filed against Syngenta and other defendants (the "Related Actions"). To the extent the Panel is inclined to centralize these actions, Syngenta submits that centralization should be before the U.S. District Court for the Eastern District of Missouri.[1] Syngenta further submits that neither the Northern District of California nor the Southern District of Illinois is a suitable or appropriate forum for centralization of this case.

To be clear, Syngenta vigorously disputes the allegations of the complaints at issue here. The Environmental Protection Agency and leading public epidemiologists have specifically considered and exhaustively analyzed the allegations that paraquat causes Parkinson's Disease, and they have found that the evidence does not show a causal link. Moreover, paraquat has been a Restricted Use Pesticide for more than forty years, which means that paraquat is not an over-the-counter product, but rather a pesticide that can be used only by those individuals who satisfy certain training and licensing requirements. However, given that at the time of filing there are sixty-two

[1] For the reasons stated in the response filed by Chevron U.S.A., Inc., ECF No. 68, Syngenta also agrees the District of Minnesota and Northern District of Texas would each be a suitable forum.

cases pending in twelve districts, Syngenta does not oppose centralization. *See In re Farxiga (Dapagliflozin) Prods. Liab. Litig.*, 273 F. Supp. 3d 1380, 1381-82 (J.P.M.L. 2017).

BACKGROUND

Paraquat is a Restricted Use Pesticide that has been approved in the United States for nearly sixty years. Since 1978, paraquat has been available only to licensed applicators who have undergone training and certification in safe handling of Restricted Use Pesticides. Like all pesticides, the Environmental Protection Agency heavily regulates paraquat products under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), 7 U.S.C. § 136 *et seq.*, which requires the EPA to approve and register all pesticides and their accompanying labeling. *See Ruckelshaus v. Monsanto Co.*, 467 U.S. 986, 991-92 (1984). In particular, the EPA will register a pesticide only if the evidence shows that it is safe and that its accompanying labels and materials, when followed, are adequate to protect human health. *See* 7 U.S.C. § 136a(c)(5).

The EPA has specifically reviewed and rejected the central allegation in these lawsuits: that paraquat causes Parkinson's Disease. After an eight-year evaluation, which included a systematic review that screened thousands of studies and included public input, the EPA "conclu[ded] that the weight of evidence was insufficient to link paraquat exposure from pesticidal use of US registered products to [Parkinson's] in humans." Ex. A, EPA, *Paraquat: Response to Comments on the Draft Human Health Risk Assessment* 2 (Sep. 24, 2020).

The EPA's conclusion is supported by a wide variety of literature, including the Agricultural Health Study—a collaborative effort involving investigators from the National Cancer Institute, the National Institute of Environmental Health Sciences, the EPA, and the National Institute for Occupational Safety and Health. The Agricultural Health Study conducted an epidemiological analysis of the alleged link between pesticide use and Parkinson's Disease incidence. After evaluating use of pesticides and Parkinson's incidence in 38,274 pesticide

applicators and 27,836 of their spouses for over 20 years, the Agricultural Health Study reported "null associations among those [study participants exposed to paraquat who] did not report a history of head injury." *See* Ex. B, Srishti Shrestha et al., *Pesticide use and incident Parkinson's disease in a cohort of farmers and their spouses*, 191 Envtl. Research 191 (Sep. 2020).

Yet plaintiffs in the Related Actions nonetheless take the position that the EPA and the Agricultural Health Study are wrong, and allege that their prior use of paraquat products caused them to develop Parkinson's. To date, plaintiffs have filed sixty-two cases in twelve different judicial districts. The first federal complaint was filed July 22, 2020, in the Eastern District of Missouri. *See Holyfield v. Chevron U.S.A.*, No. 3:21-cv-00293 (E.D. Mo. Jul. 22, 20). Beginning in late February 2021—nearly seven months after *Holyfield* was filed—various plaintiffs began filing similar suits in other federal courts, leading to this proceeding.

The defendants in the Related Actions include Syngenta Crop Protection, LLC, an agricultural company principally located in Greensboro, NC; Syngenta Seeds, LLC, which is principally located in Minnesota; Syngenta Corporation, which is principally located in Delaware; those entities' foreign parent Syngenta AG, located in Basel, Switzerland; and Chevron U.S.A., a chemical company headquartered in San Ramon, CA. The Related Actions include sixty-seven plaintiffs from twenty-six states.

On April 7, 2021, Paul Rakoczy, a New Jersey resident who filed suit in the Northern District of California, filed a motion with this Panel to transfer the Related Actions for coordinated pretrial proceedings, requesting centralization before Judge Edward Chen in the Northern District of California.[2] Since then, other plaintiffs' responses have sought consolidation elsewhere. These

[2] Mr. Rakoczy is plaintiff in the Northern District of California's earliest-filed *active* case, but he is not the first plaintiff who filed there. John and Nicole Walker, represented by Mr. Rakoczy's same counsel, filed a case on March 19, 2021, that was assigned to Judge Haywood Gilliam; but

include requests for consolidation in the Eastern District of Missouri before Judge John Ross, Judge Stephen Limbaugh, or Judge Catherine Perry, *see,e.g.*, Holyfield Resp. at 1, ECF No. 57; Adams Resp. at 3-5, ECF No. 22, in the Southern District of Illinois before Chief Judge Nancy Rosenstengel, *see, e.g.*, Burnette Resp. at 1, 10-11, ECF No. 7, and in the District of Minnesota, *see* Elmore et al. Resp. at 5-6, ECF No. 62, and Northern District of Mississippi, *see* Nunnery Resp. at 3, ECF No. 56.[3]

ARGUMENT

I. SYNGENTA DOES NOT OPPOSE CONSOLIDATION IN A SUITABLE FORUM.

Syngenta opposes an MDL in the Northern District of California, but does not otherwise oppose consolidation for pretrial purposes in a forum that makes sense for this case. Syngenta further reserves the right to request transfer to an appropriate court for trial pursuant to *Lexecon, Inc. v. Milberg Weiss Bershad Hynes & Lerach*, 523 U.S. 26 (1998).

Syngenta opposes consolidation in the Northern District of California because the considerable inconvenience of consolidating these particular actions in the San Francisco Bay Area would fall short of "promot[ing] the just and efficient conduct of [the relevant] actions." *See* 28 U.S.C. § 1407(a). Foremost, only ***one*** of the sixty-seven plaintiffs in the sixty-two Related Actions resides in the State of California, much less the Northern District,[4] and that plaintiff filed in the

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they filed a "Notice of Voluntary Dismissal Without Prejudice" on April 6, 2021. *See* Notice of Dismissal, *Walker v. Syngenta AG*, No. 3:21-cv-1947 (N.D. Cal. Apr. 6, 2021), ECF No. 10.

[3] Some of the advocates for these jurisdictions appear to be voting more than once. For example, the motion by Mr. Rakoczy—who resides in New Jersey but seeks consolidation in San Francisco—was filed by "counsel of record for Movant Paul Rakoczy and Plaintiffs Michael and Jean Kearns, Todd Tenneson, and Kenneth Turner." *See* Mot. at 2, ECF No. 1. But Michael and Jean Kearns later lodged a filing of their own supporting the Southern District of Illinois or the Northern District of California, albeit under representation of different named counsel. *See* Kearns Resp. at 10, ECF No. 24.

[4] Plaintiffs reside in Arizona, Arkansas, California, Connecticut, Florida, Georgia, Idaho, Illinois, Indiana, Kansas, Kentucky, Louisiana, Maryland, Minnesota, Mississippi, Missouri, New Jersey,

District of Minnesota.[5] Plaintiffs in the Related Actions are represented by dozens of different law firms, and none of them operates in California either. The named Syngenta entities—Syngenta Crop Protection, Syngenta Seeds, Syngenta Corporation, and Syngenta AG—are each located in North Carolina, Minnesota, Delaware, and Switzerland, respectively.

The only party located in California is Chevron, but that is unlikely to provide much convenience here—because Chevron has not sold paraquat for 35 years and, for what relevant evidence may be there, "the physical location of documents and other evidence has become increasingly irrelevant as electronic discovery becomes more widespread and convenient." *Kriebel v. Life Ins. Co. of N.A.*, No. 1:15-cv-00151, 2015 WL 11347968, at *5 (D.D.C. Oct. 14, 2015). This is especially true in light of the expansion of remote depositions and discovery—in particular amid the COVID-19 pandemic—for which coordinating remote events based on time zone is as important a factor for convenience as coordinating in-person events based on physical proximity. Indeed, Chevron itself does not support consolidation in California. *See* Chevron Resp. at 1, ECF No. 68. Accordingly, Chevron being principally located in California does not provide any meaningful degree of "easy access to documents and witnesses." Mem. at 7, ECF No. 2-1. Any related convenience will be offset by the considerable inconvenience arising from the plaintiffs' locations elsewhere and Syngenta's locations in North Carolina, Minnesota, Delaware, and Switzerland.

As noted, the relevant time zones are more important, and the locations of nearly all the parties and their counsel outside the Pacific Time Zone makes the Northern District of California prohibitively inconvenient. That is, across the sixty-two Related Actions, all but four parties

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New York, Oklahoma, Oregon, Pennsylvania, Tennessee, Texas, Virginia, West Virginia, and Wisconsin.

[5] *See Wilson v. Syngenta Crop Protection, LLC*, No. 21-cv-01113 (D. Minn. Apr. 28, 2021).

(Chevron and three plaintiffs) would be litigating under at least a two-hour time difference. That gap is even more stark for Syngenta witnesses based in the United Kingdom and Switzerland, which have an eight- or nine-hour time difference that would create considerable scheduling difficulties. For example, any depositions of Europe-based witnesses would have to proceed without working access to the court—which does not even open until 5:00 PM in Switzerland.

In addition, initiating new pretrial proceedings in the Northern District of California would risk upsetting the existing pretrial proceedings in the earliest-filed federal action that have been moving forward for nearly ten months before Judge Ross in the Eastern District of Missouri. *See Holyfield v. Chevron U.S.A.*, No. 3:21-cv-00293 (E.D. Mo. Jul. 22, 2020); *see also* Part II.B *infra*. Put together, the prospect of consolidating these cases before the Northern District of California would not "prevent inconsistent pretrial rulings" on motions to dismiss, nor would it "conserve the resources of the parties, their counsel, and the judiciary." *See In re Farxiga (Dapagliflozin) Prods. Liab. Litig.*, 273 F. Supp. 3d at 1382. For these reasons, Syngenta opposes consolidating these actions in the Northern District of California (or in another similarly inconvenient forum), but does not oppose consolidation otherwise.

II. THE EASTERN DISTRICT OF MISSOURI IS THE MOST APPROPRIATE FORUM.

If the Panel opts for consolidation, the Eastern District of Missouri is the most appropriate forum here. ***First***, consolidating the Related Actions in the Eastern District of Missouri is the most efficient use of judicial resources because four of the actions—including the first-filed and most-advanced case in this litigation—are currently pending there. ***Second***, the Eastern District of Missouri's geographically central location (and time zone) make it convenient and accessible by all parties. ***Third***, the Eastern District of Missouri has the appropriate balance of capacity, resources, and experience to ably manage this litigation.

A. The Eastern District Of Missouri Is The Most Efficient Forum.

As the site of the first-filed and most advanced case, the Eastern District of Missouri is the most efficient location for resolving this dispute. *See In re Edward H. Okun I.R.S. § 1031 Tax Deferred Exch. Litig.*, 609 F. Supp. 2d 1380, 1381-82 (J.P.M.L. 2009) (transferring litigation to "the first-filed and most procedurally advanced action"). Indeed, the most advanced case pending before the Eastern District of Missouri—*Holyfield v. Chevron U.S.A.*, No. 3:21-cv-00293 (E.D. Mo. Jul. 22, 20)—was filed nearly ***seven months*** before the next-filed case in this litigation, *Hemker v. Syngenta Crop Protection, LLC*, No. 3:21-cv-00211 (S.D. Ill. Feb. 23, 2021). The Eastern District of Missouri has considered and ruled on a fully briefed motion to dismiss, whereas the majority of the other actions were filed after the *Holyfield* motion to dismiss was resolved. *See In re Prudential Ins. Co. of Am. SGLI/VGLI Contract Litig.*, 763 F. Supp. 2d 1374, 1375 (J.P.M.L. 2011) (ordering centralization to the District of Massachusetts rather than the District of New Jersey because "[t]he first-filed action, in which a fully briefed motion to dismiss [was] currently pending, was filed in the District of Massachusetts … months before the New Jersey action was filed"). This weighs in favor of centralization in the Eastern District of Missouri.

B. The Eastern District Of Missouri Is Convenient And Accessible To Plaintiffs And Defendants.

Moreover, as this Panel has repeatedly observed, the Eastern District of Missouri is "a geographically central and accessible forum" appropriate for "nationwide litigation." *See, e.g.*, *In re Ashley Madison Customer Data Sec. Breach Litig.*, 148 F. Supp. 3d 1378, 1380 (J.P.M.L. 2015) (transferring five actions and thirteen related actions pending in eleven districts to the Eastern District of Missouri); *In re NuvaRing Prods. Liab. Litig.*, 572 F. Supp. 2d 1382, 1383 (J.P.M.L. 2008) (centralizing cases in the Eastern District of Missouri as a "readily accessible district"); *In re Aurora Dairy Corp. Organic Milk Mktg. & Sales Pracs. Litig.*, 536 F. Supp. 2d 1369, 1370-71

(J.P.M.L. 2008) (centralizing cases in the Eastern District of Missouri "[g]iven the geographic dispersal of the constituent actions and the potential tag-along actions").

In contrast to the difficulties of a consolidation in California explained above, *see* Part I *supra*, the Eastern District of Missouri's central geographic location in St. Louis minimizes disparities in time and distance.[6] Consolidating the cases in the Central Time Zone would obviate time-change-related difficulties for domestically located parties and help alleviate difficulties for those in Europe by ensuring at least some access to the court during the business day. St. Louis is also highly accessible, given that Lambert International Airport is a major airport servicing sixty-eight nonstop flights across the country.[7] The Eastern District of Missouri courthouse sits just fourteen miles from the airport—and travelers are much less likely to encounter traffic or other delays there than in San Francisco.[8] Likewise, St. Louis's light rail system travels directly from the airport to the Eastern District of Missouri's courthouse,[9] and numerous hotels surrounding the courthouse are available for reasonable prices well under $200 a night.[10]

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[6] The points made by plaintiffs seeking centralization before Judge Rosenstengel in the Southern District of Illinois, *see, e.g.*, Albanese & O'Connor Resp. at 7, ECF No. 11, apply equally to the Eastern District of Missouri, as the courts are located within several miles of each other, *see* Driving Directions from Eagleton U.S. Courthouse to U.S. Dist. Court House for S.D. Ill., *Google Maps*, https://bit.ly/2QI5HGS. As discussed below, however, the Southern District of Illinois is not as well-equipped to take on a consolidated MDL and the actions filed there lag significantly behind proceedings in the Eastern District of Missouri. *See* Part C *infra*.

[7] *See* St. Louis Lambert Int'l Airport, *Non Stop Service*, https://www.flystl.com/flights-and-airlines/non-stop-service.

[8] *See* Driving Directions from St. Louis Int'l Airport to Thomas F. Eagleton U.S. Courthouse, *Google Maps*, https://bit.ly/3auCg2d.

[9] *See* Transit Directions from St. Louis Int'l Airport to Thomas F. Eagleton U.S. Courthouse, *Google Maps*, https://bit.ly/3tCdJQn.

[10] *See* Hotels near Thomas F. Eagleton U.S. Courthouse, *Google Maps*, https://bit.ly/2RQV9pA.

C. The Eastern District Of Missouri Is Well-Equipped To Manage This MDL.

The Eastern District of Missouri is also best equipped to manage this litigation, particularly in comparison to the Northern District of California and Southern District of Illinois. The Eastern District of Missouri has the capacity and judicial experience to efficiently manage pretrial proceedings in these actions without straining its judicial resources, and it is a far superior option than the other alternatives proposed thus far.

By any measure, the Northern District of California is poorly positioned to take on another MDL. It is already the busiest MDL forum in the federal system, overseeing *twenty* MDL actions that contain a total of 6,546 discrete lawsuits.[11] That high workload comes in the context of the court's three judicial vacancies—all of which the Federal Judicial Center considers "judicial emergencies" that leave the court significantly understaffed.[12] (There are no judicial vacancies, much less *emergencies*, in the Eastern District of Missouri.)

Those concerns are equally true for the Northern District of California's non-MDL docket. According to the most recent data from the Federal Judicial Center, the court has 511 civil cases per judge—the most among all courts with a pending paraquat case.[13] That workload is even more striking considering those cases' complexity. In 2020, the Northern District of California's civil docket received 551 "weighted filings" per authorized judgeship—the ninth most burdensome docket in the country and busiest among MDL possibilities. *See id.* The Panel should not burden

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[11] *See* Jud. Panel on Multidistrict Litig., *MDL Statistics Report - Distribution of Pending MDL Dockets by District*, https://www.jpml.uscourts.gov/sites/jpml/files/Pending_MDL_Dockets_By_District-April-15-2021.pdf.

[12] *See* Fed. Jud. Ctr., *Judicial Emergencies*, https://www.uscourts.gov/judges-judgeships/judicial-vacancies/judicial-emergencies.

[13] *See* U.S. Courts, *US District Courts—Weighted and Unweighted Filings per Authorized Judgeship*, https://www.uscourts.gov/statistics/table/x-1a/judicial-business/2020/09/30.

the Northern District of California with yet another MDL—which would be its sixth new consolidation in the last twelve months—when a more-convenient district has capacity.

Different but equally important concerns make the Southern District of Illinois a poor fit for this case. The Southern District of Illinois has just four authorized judgeships and five judges with active cases,[14] which means assignment of an MDL will have the greatest relative impact on its workload. That is likely one reason why it has overseen so few MDLs: since the 1968 passage of the Multidistrict Litigation Act, the Panel has only consolidated five MDLs there.[15] Although some plaintiffs cite the court's experience with the *Depakote* mass action, *see* Burnette Resp. at 9, ECF No. 7; Denes et al. Resp. at 7, ECF No. 16, those proceedings placed a considerable burden on the court's limited docket. *See In re Depakote*, No. 12-cv-52-NJR, 2017 WL 4518330, at *4 (S.D. Ill. Oct. 10, 2017) ("One need only look at this docket to see the monumental task that the Court undertakes in selecting even one case to proceed to trial out of the hundreds that have been filed."); *In re Depakote*, No. 12-cv-52-NJR, 2017 WL 2645687, at *1 n.2 (S.D. Ill. June 20, 2017) (observing that even if "the Court holds nothing but Depakote litigation trials 365 days a year," having a trial for every case "w[ould] take [Judge Rosenstengel] far past the end of her career to resolve all of the cases currently on the docket").

The state proceedings in *Hoffman v. Syngenta Crop Protection, LLC*, No. 17-L-517 (20th Jud. Cir. St. Clair. Cnty., Ill.), are not a reason to centralize federal proceedings in the Southern District of Illinois. That the district also includes St. Clair County, Ill. has little bearing on its ability to coordinate discovery with state proceedings there or elsewhere. The Federal Rules of

[14] *See* U.S. District Court for S.D. Ill., *Judges*, https://www.ilsd.uscourts.gov/Judges.aspx (listing four District Judges and one Senior District Judge).

[15] *See* Jud. Panel on Multidistrict Litig., *Multidistrict Litig. Terminated Through Sep. 30, 2020*, https://www.jpml.uscourts.gov/sites/jpml/files/Cumulative%20Terminated%202020_0.pdf.

Civil Procedure would govern discovery in a consolidated action no matter its location, and federal courts routinely coordinate with state courts outside their particular judicial district. Indeed, the very example of federal–state discovery coordination in the *Manual for Complex Litigation—In re Diet Drugs Products Liability Litigation*, MDL No. 1203—involved state discovery in California and elsewhere coordinated through the Eastern District of Pennsylvania.[16] In light of how other mass actions have burdened the Southern District of Illinois, it would make little sense to risk overwhelming the court's limited docket again when there is a nearby alternative court with much more capacity and an earlier-filed case underway.

That alternative is the Eastern District of Missouri, which is best equipped to supervise these actions based on its capacity and the experience of its judges—some of whom have presided over other agricultural-related MDLs in the past. To begin, Judge Ross is currently presiding over the first-filed action potentially subject to consolidation. *See Holyfield v. Chevron U.S.A.*, No. 3:21-cv-00293 (E.D. Mo. Jul. 22, 20). Moreover, the Eastern District of Missouri has twelve active judges (compared to five in the Southern District of Illinois), which provides the district enough capacity to handle an MDL like this. It also lacks the Northern District of California's judicial emergencies and overwhelming caseload—specifically, the Eastern District of Missouri counts just 260 "weighted" civil filings per authorized judgeship, which is less than half the 551 in the Northern District of California.[17] This balance of judicial resources and capacity cuts strongly in favor of centralizing the Related Actions in the Eastern District of Missouri—the district with "the

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[16] *See In re Diet Drugs Prods. Liab. Litig.*, MDL No. 1203, 1999 WL 124414, at *1 (E.D. Pa. Feb. 10, 1999) ("the court has conferred with the Honorable Daniel S. Pratt, Judge of the Superior Court of the State of California in the county of Los Angeles, California"), *cited with approval in Manual for Complex Litigation (Fourth)* § 33.2 nn. 710, 714-15 (2004).

[17] *See* U.S. Courts, *US District Courts—Weighted and Unweighted Filings per Authorized Judgeship*, https://www.uscourts.gov/statistics/table/x-1a/judicial-business/2020/09/30.

necessary resources to be able to devote the time and effort to pretrial matters that this docket is likely to require." *In re Wireless Tel. 911 Calls Litig.*, 259 F. Supp. 2d 1372, 1374 (J.P.M.L. 2003).

Finally, the Eastern District of Missouri—and Judges Ross and Limbaugh specifically—is well-equipped to manage the Related Actions and has significant experience with complex MDLs. *See, e.g.*, *In re Ashley Madison Customer Data Sec. Breach Litig.*, MDL No. 2669; *In re Dicamba Herbicides Litig.*, MDL No. 2820 (Limbaugh, J.). The Eastern District of Missouri's suitability has led the Panel to transfer twenty-two prior MDLs there, three of which the court currently oversees. In particular, the Eastern District of Missouri has overseen several MDLs that, like this one, involve the agricultural sector and pesticide products in particular. *See, e.g.*, *In re Dicamba Herbicides Litig.*, MDL No. 2820; *In re Hops Antitrust Litig.*, MDL No. 706; *In re Genetically Modified Rice Litig.*, MDL No. 1811; *In re Aurora Dairy Corp. Organic Milk Mktg. & Sales Pracs. Litig.*, MDL No. 1907. The opportunity to draw on that experience, without overburdening the judiciary, is another factor favoring centralization in the Eastern District of Missouri.

CONCLUSION

If the Panel elects to centralize, Syngenta supports centralization in the Eastern District of Missouri.

April 29, 2021

Respectfully submitted,

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EXHIBIT A

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: September 24, 2020

SUBJECT: **Paraquat**: Response to Comments on the Draft Human Health Risk Assessment

PC Code: 061601
Decision No.: 559059
Petition No.: NA
Risk Assessment Type: Response to Comments
TXR No.: NA
MRID No.: NA

DP Barcode: D456000
Registration No.: NA
Regulatory Action: Registration Review
Case No.: 0262
CAS No.: 1910-42-5
40 CFR: § 180.205

FROM: Wade Britton, MPH, Environmental Health Scientist
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THROUGH: Shalu Shelat, Branch Chief
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AND

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TO: Ana Pinto, Chemical Review Manager
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Paraquat dichloride is a restricted-use quaternary ammonium herbicide employed for weed control and as a harvest aid in the United States. It is currently undergoing Registration Review at the Office of Pesticide Programs (OPP). The draft human health risk assessment (HHRA) and ecological risk assessment authored by the Health Effects Division (HED) and Environmental Fate and Effects Division (EFED), respectively, were published on October 16, 2019 and open for public comment through December 16, 2019. Numerous comments were received from a wide range of stakeholders including environmental non-government organizations (e.g. Beyond Pesticides, Environmental Working Group, Center for Biological Diversity), public interest advocacy groups (e.g. California Rural Legal Assistance Foundation, United Parkinson's Advocacy Council), pesticide registrants (e.g. Syngenta), government agencies (e.g. Washington State Department of Agriculture, United States Department of Agriculture), and individual members of the general public. Comments from the non-government organizations and advocacy groups were also co-signed by affiliated organizations. This memo contains the agency's responses to public comments submitted during the comment period that were directed at the HHRA (Britton W. *et al.,* D430827, 2019). The public comments and agency responses are organized based on the sections of the HHRA to which they pertain and then by content of the comment. Public comments submitted from multiple sources that were similar in substance were binned together and a single response was provided. For topics that had lengthy public comments (e.g. the Parkinson's disease systematic review), the public comments were summarized in the agency's response rather than reprinting each comment in its entirety. The public comments were otherwise reprinted in italics and followed by the agency response below. The agency thanks all commenters for their submissions.

I. Parkinson's Disease Systematic Review

General Comments on the Methods and Conclusions of the Parkinson's Disease Systematic Review (Beyond Pesticides, California Rural Legal Assistance Foundation, Center for Biological Diversity, Pesticide Action Network and the United Parkinson's Disease Advocacy Council, Syngenta)

EPA Response: The agency received numerous comments on its Parkinson's disease (PD) systematic review conducted as part of the paraquat registration review. Those that disagreed with the agency's conclusions, including Beyond Pesticides, California Rural Legal Assistance Foundation, Center for Biological Diversity, Pesticide Action Network and the United Parkinson's Disease Advocacy Council, pointed to positive associations in epidemiology studies and supporting laboratory animal and mechanistic data from the open literature as evidence that there is an association between paraquat exposure and PD. On the other end of the spectrum, Syngenta Crop Protection LLC (hereafter referred to as Syngenta), a registrant of paraquat dichloride, agreed with the overall conclusions of the systematic review, but found some disagreement with HED's characterization of individual study quality and interpretation of the results. Comments from both perspectives cited studies that were considered by the agency in its systematic review, as well as additional publications that were either excluded based on the inclusion criteria, were not captured in the search strategy, or were published after the open literature search. After consideration of the critiques and perspectives from the commenters and review of the newly identified publications, the agency remains confident in its review process and its conclusion that the weight of evidence was insufficient to link paraquat exposure from pesticidal use of US registered products to PD in humans.

The agency arrived at its conclusion after a thorough, systematic review of publications from the open literature and data submitted to the agency voluntarily or as a requirement of registration. The agency collaborated with the National Toxicology Program (NTP) to develop a search strategy for systematically

screening the open literature for human, animal, and *in vitro* publications that investigated the relationship between paraquat exposure and effects associated with PD. In total, 7,166 publications were screened as part of this collaboration. In addition, the agency conducted a separate systematic review of the epidemiology literature that investigated the relationship between paraquat exposure and any adverse human health outcome. A total of 576 publications were screened in this general epidemiology systematic review. Between these two systematic reviews and unpublished studies in the paraquat toxicity database, the agency compiled a PD literature database for the systematic review of 28, 217, and 244 human, animal, and *in vitro* studies, respectively, that were relevant to evaluating the association between paraquat exposure and PD. Most of the studies referenced in the public comments were included in this literature database.

Each study in the PD literature database was individually evaluated for quality, substance, and environmental relevance. Environmental relevance was defined as the likelihood that a given effect would result from an exposure scenario anticipated to occur from typical use of registered paraquat products (e.g. oral including dietary, dermal, and inhalation exposure). The agency integrated environmental relevance considerations into the systematic review in order to contextualize hazard information in terms of risk. This was an important consideration, particularly for the animal literature, given that many of the paraquat studies investigating PD-like hallmarks used a route of administration (e.g. intraperitoneal, intracranial, intravenous, etc.) that did not reflect an anticipated exposure scenario (oral, dermal, and inhalation) for registered pesticidal uses of paraquat. Moreover, the agency determined that, based on available data, toxicokinetic differences between injection and the anticipated routes of administration for paraquat precluded using data from injection studies for evaluating risk from pesticidal uses. These studies are, therefore, not relevant to establishing a causative relationship between exposure from pesticidal uses of paraquat and PD.

The quality assessment for open literature studies was conducted in accordance with the OPP Epidemiology Framework[1] for the human studies and 2012 OPP Literature Review Guidance[2] for the animal and *in vitro* studies. The quality reviews considered study design, reporting, and sources of bias either inherent in the experimental design or introduced by the study authors in their methodology decisions. All of these factors contributed to the agency's level of confidence in the findings reported in each study. Studies that were of sufficient quality and investigated environmentally relevant exposure scenarios were then evaluated in their respective evidence stream (e.g. human, animal, and *in vitro*) and integrated across lines of evidence in the weight of evidence analysis using the modified Bradford Hill criteria which includes considerations for dose response, temporal concordance, strength, consistency, coherence, specificity, and biological plausibility. The agency's systematic review process, study quality evaluation, weight of evidence analysis, and conclusions are summarized in the HHRA and described in extensive detail in the PD systematic review memo (Wray A. and Niman A., D449106, TXR 0057888, 06/26/2019).

The agency's conclusion that the weight of evidence was insufficient to link paraquat exposure from pesticidal use of US registered products to PD in humans was based on a combination of factors including:

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[1] US EPA. December 28, 2016. Office of Pesticide Programs' Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides. https://www3.epa.gov/pesticides/EPA-HQ-OPP-2008-0316-DRAFT-0075.pdf

[2] USEPA OPP. 2012. Guidance for considering and using open literature toxicity studies to support human health risk assessment.

- large variation in study quality across the evidence streams including several studies with critical deficiencies in study design and/or reporting that affected interpretation and diminished confidence in published results;
- limitations in individual studies and the overall dataset that precluded comprehensive evaluation of dose and temporal concordance in each evidence stream;
- mixed findings, particularly in the animal and human evidence streams, that lowered confidence in positive results;
- weak quantitative and qualitative coherence of PD-like effects across the three evidence streams;
- and a lack of biological plausibility that the *in vitro* and *in vivo* laboratory findings would occur in humans following label-directed use of registered paraquat products.

In addition, the agency also compared the PD-like effects noted in the animal literature with other toxic effects attributed to paraquat and determined that contact toxicity and adverse effects in the respiratory and renal system were the most sensitive effects resulting from paraquat exposure. Therefore, the agency concluded that the established points of departure (PODs) based on these effects would be protective of all paraquat toxicity including the neurotoxic effects reported in the open literature.

Several commenters recommended the agency consider mechanistic data in its evaluation of the link between paraquat and PD and referenced publications reporting subcellular effects as well as the use of paraquat in PD research. The agency did consider mechanistic data in the PD systematic review from relevant *in vitro* publications as well as mechanistic findings reported in *in vivo* studies that utilized an environmentally relevant route of administration. The agency notes that the paraquat model described in the review publications cited in the comments (Tieu 2011; McDowell and Chesselet 2012) elicits PD-like hallmarks in mice through weekly injections of paraquat. Moreover, the Tieu (2011) review describes some inconsistencies in the PD-like response between studies when using the standardized exposure regimen for the paraquat PD model as well as limitations of the model to elicit the same PD hallmarks that are observed in humans. The literature database used for the PD systematic review contained a number of publications that utilize paraquat to induce PD-like hallmarks in animals for PD research and the agency found that most of these publications employed either the paraquat model described above or an exposure regimen that also does not reflect the anticipated paraquat exposure scenarios from pesticidal use (e.g. direct injection into the brain). In the PD systematic review, the agency acknowledged that several publications from the open literature have proposed modes of action (MOAs) to explain how paraquat exposure could lead to PD and that an European Food Safety Association (EFSA) working group published a proposed adverse outcome pathway (AOP) for connecting mitochondrial inhibitors such as paraquat to PD (Terron *et al.* 2018). Accordingly, the agency evaluated cellular and subcellular *in vitro* and *in vivo* mechanistic data that related to these proposed MOAs and incorporated it into the weight of evidence discussion.

The agency identified a large body of evidence demonstrating general neurotoxicity (e.g. general cell viability, mitochondrial dysfunction, oxidative stress, and alterations in the ubiquitin-proteasome system) and PD-specific effects (e.g. dopaminergic neuron viability, α-synuclein formation, and neurochemical changes) across multiple *in vitro* nervous system human and rodent models. However, these data are difficult to translate to *in vivo* effects given that they do not account for chemical-specific toxicokinetics that would dictate the extent to which the chemical can reach the active site in laboratory animals or humans. General toxicity (e.g. oxidative stress, inflammation, and mitochondrial dysfunction) was reported in nervous tissues at the same dose that elicited PD-like hallmarks in several mouse studies that used a risk assessment relevant route of exposure; however, variation in study design (i.e. studies examined different nervous tissues), and inconsistencies in the parameters assessed (i.e. only one study evaluated mitochondrial dysfunction) made it difficult to establish dose and temporal concordance for mechanistic effects and PD-like hallmarks, which would be required to establish a paraquat MOA for the

neurobehavioral/neurodegenerative effects. The agency did not evaluate the AOP proposed in the open literature nor develop one from the data gathered in the systematic review. Given the lack of sufficient evidence for a causal association, the agency did not consider an AOP necessary to characterize paraquat toxicity and evaluate risk for registered products.

Comments on the Conclusions of the Epidemiology Review (Center for Biological Diversity, Pesticide Action Network, Beyond Pesticides, California Rural Legal Assistance Foundation, and Unified Parkinson's Advocacy Council)

EPA Response: In addition to comments on the agency's overall systematic literature review of PD, the agency received several comments on its evaluation of the epidemiologic literature on the relationship between paraquat and adverse health outcomes. This includes comments from the Center for Biological Diversity, Pesticide Action Network, Beyond Pesticides, California Rural Legal Assistance Foundation, and Unified Parkinson's Advocacy Council that emphasized findings from epidemiologic studies that reported evidence of a positive association between paraquat and PD, as well as other health outcomes. Conversely, Syngenta commented on potential omissions in the agency's epidemiology review and discussed risk of bias considerations that may be relevant to the agency's overall weight-of-evidence. Syngenta's comments also included supporting comments from Quality Scientific Solutions, which was requested by Syngenta to evaluate the agency's review of the epidemiology literature on paraquat.

With regard to commenters that emphasized findings from epidemiologic studies that reported evidence of an association between paraquat and PD, several commenters suggested that the agency discounted positive epidemiologic findings from the Agricultural Health Study (AHS) and other study populations. These comments included discussion of the epidemiologic literature on PD, but also included other health outcomes evaluated in the agency's evaluation of the epidemiologic literature on paraquat. The Center for Biological Diversity, for example, commented that a number of epidemiologic studies evaluated in the HHRA, including the AHS, reported positive associations between paraquat and PD, respiratory effects, and other chronic diseases and symptoms. Similarly, the Unified Parkinson's Advocacy commented that there are several more recent studies that reported a positive association between paraquat and PD. While these commenters correctly point out that there are epidemiologic studies that report positive associations between paraquat exposure and PD, as well as other health outcomes, the commenters did not take a holistic account of the evaluation of epidemiologic evidence in the agency's Tier II Epidemiology Report (A Niman, D449108, 6/29/2019). The agency's Tier II Epidemiology Report summarized 74 available epidemiologic studies and included a comprehensive evaluation of study quality and overall evaluation of epidemiologic evidence for PD and a range of the health outcomes examined in the scientific literature. The overall conclusion of the agency's Tier II Epidemiology Report on the evidence on the relationship between paraquat and PD was that there is "limited, but insufficient epidemiologic evidence at this time to conclude that there is a clear associative or causal relationship between occupational paraquat exposure and PD." This conclusion was informed by the positive studies highlighted by commenters, but also reflects mixed findings reported in AHS and a number of study quality limitations related to the design of studies, exposure assessment methods, and potential for bias.

Consideration of Additional Epidemiology Publications and Meta-reviews Not Included in the PD Systematic Review

EPA Response: The Unified Parkinson's Advocacy Council identified one additional epidemiologic study (Caballero *et al.* 2018) that was not evaluated in the agency's systematic review of the relationship between paraquat and PD. The study examined the relationship between residential proximity to agricultural land that may use paraquat and PD-related mortality in Washington State and reported no evidence of a significant positive association between paraquat and PD-related mortality (Ever/Never Paraquat Odd Ratio = 1.22 95% CI: 0.99–1.51). The study utilized Washington State's death registry to

identify deaths for the years 2011-2015 in which the underlying cause of death was PD. The study assessed exposure indirectly using an approach that relied as residential proximity, based on residential address at time of death, to agricultural land that may use paraquat. This exposure assessment approach has several substantive deficiencies that limit the quality of the study. In particular, the investigators relied on a crop-pesticide matrix to identify cropland that may use paraquat. The crop-pesticide matrix was based on general information on crops that use paraquat and did not incorporate any information on the actual spatial location, timing and magnitude of paraquat use in Washington State. The investigators then used a 1000m buffer to assign ever/never exposure to paraquat based on only residential address at time of death. Limited information was provided to justify this buffer distance for paraquat, and no information was provided on whether residential address at time of death can be used to assess potential lifetime exposure. Given these exposure assessment limitations, the study would be considered low quality based on OPP's Epidemiology Framework and would contribute limited weight to the overall body of available epidemiologic evidence on the relationship between paraquat and PD.

Two commenters that emphasized epidemiologic studies that reported an association between paraquat exposure and PD also indicated that there are two systematic reviews published in 2019 that provide additional information that should be considered by the agency (Tangamornsuksan *et al,* 2018; Vaccari *et al.* 2019). The California Rural Legal Assistance Foundation, in particular, commented that the agency's conclusion is "inconsistent with two recently released meta-analyses that are not included in this risk assessment that each strengthen the evidence linking paraquat exposure and Parkinson's disease." HED is aware of these meta-analyses as well as other literature reviews and meta-analyses of epidemiologic studies that were published prior to the public release of the HHRA and Tier II Epidemiology Report (e.g., Breckenridge *et al.* 2016; Friere and Koifmann 2012; Allen and Levy 2013). However, the agency independently evaluated the underlying original ("primary") research findings included in these meta-analyses in its own weight-of-evidence evaluation of the relationship between paraquat exposure and PD. This approach ensures that the agency critically evaluated the available literature and did not rely on the conclusions of external authors that are not subject to the agency's public review process.

While the agency's review focused on its own independent review, the primary difference between the agency's evaluation and the two meta-analyses are methodological with respect to study quality and synthesis of findings. In particular, both articles used different methodologies to assess study quality (i.e., Newcastle-Ottawa quality assessment scale and the modified Newcastle Ottawa Scale, respectively) and reported a statistically significant association between paraquat and PD based on their quantitative synthesis of study findings using meta-analysis. Although there were methodological differences, it is incorrect to conclude that the agency's conclusion on the association between paraquat and PD is inconsistent with the authors of the two meta-analyses. Rather, the conclusions of each meta-analysis are excerpted below and emphasize that while they both reported evidence of an association between paraquat and PD, the available studies that themselves were incorporated into the meta-analysis have substantive limitations and require replication in higher quality studies. These conclusions are similar to the agency's determination that the overall epidemiologic evidence is limited, but insufficient based on somewhat conflicting findings in the AHS cohort, mixed findings in other study populations, and substantive limitations across studies that related to their exposure assessment approach and potential bias that introduces additional uncertainty.

> *Our analysis with new data re-affirms the association of paraquat use with PD. However, objective measurement of paraquat exposure was inadequate and future studies are needed to focus on exposure assessment, disease progression and clinical manifestations thereby providing clues about the mechanism for this insidious disease. Accordingly, further studies to elucidate the effect of paraquat on PD are still warranted especially studies conducted with high quality of exposure assessments in more refined case-control studies.*
> **Tangamornsuksan et al., (2019)**

> *In summary, positive OR estimates indicate a weak association between exposure to paraquat and occurrence of PD. This association appears to be more evident in individuals exposed to paraquat for extended periods or co-exposed to paraquat and any other dithiocarbamates, although more studies with this information need to be analyzed. The relatively low estimates of risk and low quantity of evidence gathered by this SR and meta-analysis does not enable one to propose a definitive conclusion regarding a causal relationship between paraquat and PD.*
> **Vaccari et al., (2019)**

In addition to the commenters that suggested the agency inappropriately discounted epidemiological literature relating to PD and exposure to paraquat, Syngenta commented on potential omissions in the agency's review of the epidemiologic literature and discussion of risk of bias considerations in weighing studies in the overall weight-of-evidence. With respect to omissions, Syngenta indicated that publications from Elbaz *et al.* (2009), Kuopio *et al.* (1999), Rugbjerg *et al.* (2011), Seidler *et al.* (1996), and Semchuk *et al.* (1992) provide information on the association between paraquat exposure and PD but were not included in HED's Tier II Epidemiology Report.

Syngenta is correct that these studies attempted to assess the association between paraquat and PD. As also noted by Syngenta, however, four of these five studies did not report effect estimates because of the small number of PD cases exposed to paraquat (Kuopio *et al.* 1999; Rugberg *et al.* 2011; Seidler *et al.* 1996; and Semchauk *et al.* 1992). These studies, therefore, would contribute limited, if any, weight to the overall body of epidemiologic evidence on the relationship between paraquat and PD. The agency also notes that the exclusion criteria described in its literature search methodology indicate that articles were excluded from review if no risk/effect estimates were reported.

The remaining study by Elbaz *et al.* (2009) considered paraquat exposure in its discussion, but only reported on the association between the quaternary ammonium class of herbicides and PD. The quaternary ammonium class of herbicides includes paraquat as well as other compounds and may not be a reliable surrogate of paraquat exposure alone. No additional information is provided by Elbaz *et al.* (2009) to determine if their study population used paraquat rather than other quaternary ammonium herbicides, including cyperquat, chlormequat diethamquat, difenzoquat, diquat, and mepiquat. As such, Elbaz *et al.* (2009) provides insufficient information to specifically assess the relationship between paraquat and PD and was not included in the agency's evaluation.

Syngenta also commented that the agency's evaluation of the epidemiologic evidence did include the study by Tomenson and Campbell (2011), which examined mortality in an occupational cohort from a UK paraquat manufacturing facility. This study was reviewed in the agency's Tier II Epidemiology Review and was the only study identified that assessed the relationship between paraquat exposure and mortality, including mortality caused by PD. While this study provides information on mortality from PD, there was only a single PD case identified in the study. While Syngenta is correct that the results of the study provide no evidence of an association between paraquat and mortality caused by PD, the study focused on a subset of the 307 deceased workers from a larger cohort of 968 workers. As such, while the study may have some ability to identify deceased workers that had PD, a larger number of workers were excluded from the study (68%) because they were still alive when the study was conducted. For this reason, the agency believes the Tomenson and Campbell (2011) provides only supplemental information on the relationship between paraquat and PD and was not considered in the agency's systematic review. Syngenta also made note that the agency included the AHS study Shrestha *et al.* (2018) in its systematic review even though it focused on the health outcome self-reported dream enacting behavior, rather than PD. While this study was summarized in the agency's systematic review, it was considered supplemental to the AHS studies that directly examined the relationship between paraquat and PD. For example, the agency's review made note that the "relationship between dream enacting behavior and other non-motor symptoms is an area of active research in clinical and epidemiologic research." This focus on the

prodromal PD symptom dream enacting behavior enabled Shrestha *et al.* (2018) to leverage the prospective design of AHS – by focusing on a potential precursor to PD – and provides additional characterization of other AHS studies on PD that focused directly on PD.

Syngenta's comments also suggested that the agency did not fully assess risk of bias in its evaluation of epidemiologic studies and overall weight-of-evidence assessment of the association between paraquat and PD. These comments included more general considerations on potential selection bias in case-control studies that recruit controls from hospitals and family/friends of cases, relative importance of statistical power and risk of bias, and terminology used to describe case-control studies (hospital vs. population-based studies). Syngenta also provided more specific comments on the agency's study quality assessment. This included additional evaluation considerations on the AHS-FAME Study that was rated as being high quality by the agency, five case-control studies rated as being moderate quality by the agency (Liou *et al*. 1997; Tanner *et al.* 2009; Costello *et al.* 2009; Brouwer *et al.* 2017; van der Mark *et al.* 2014), and one case-control study being rated as low quality by the agency (Firestone *et al.* 2005; 2010).

With regard to the agency's quality assessment of the AHS-FAME Study, Syngenta commented that the AHS-FAME Study did not warrant a high-quality rating because of recall bias and potential selection bias. The agency considered risk of bias in its assessment of the AHS-FAME Study but designated it as high quality because the nested case-control design, nested with the AHS, enabled the investigators to examine the association between paraquat use and PD in well characterized agricultural populations in Iowa and North Carolina. This study design also allowed the investigators to consider demographic and lifestyle factors that could act as confounders and examine potential effect modification of genetic factors and occupational hygiene practices. While the agency rated the AHS-FAME as high quality, its findings on the association between paraquat and PD are not definitive and are subject to substantive limitations that were summarized in the agency's evaluation. In particular, the agency noted that there were conflicting findings with respect to incident and prevalent PD cases within the AHS. The AHS-FAME study also may have introduced additional recall bias by conducting a separate exposure assessment after cases and controls were enrolled in the study. As such, the agency considered the strengths and limitations of the AHS-FAME Study in its overall conclusion that 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.

Syngenta's comments on five case-control studies rated as being moderate quality by the agency (Liou *et al*. 1997; Tanner *et al.* 2009; Costello *et al.* 2009; Brouwer *et al.* 2017; van der Mark *et al.* 2014) and one case-control study being rated as low quality by the agency (Firestone *et al.* 2005; 2010) will not substantively change the agency's overall conclusions on the available epidemiologic evidence. In characterizing its overall conclusion, the agency made note that these studies yield mixed results with respect to potential occupational and non-occupational exposure and may also be subject to recall bias, limitations in their exposure assessment approach, and potential selection bias. Similarly, Syngenta's comments on the study quality assessment of Firestone *et al.* (2005; 2010) will not change the agency's overall conclusions because the study only had two paraquat exposed PD cases and contributed limited weight in the agency's overall evaluation.

Consideration of Additional Animal and *In Vitro* Publications Not Included in the PD Systematic Review

EPA Response: Additional animal and *in vitro* publications were identified in the public comments that were not included in the literature database compiled for the PD systematic review. The registrant, Syngenta, also submitted four additional industry funded non-guideline studies (identified with MRID numbers below) after publication of the HHRA. The agency reviewed all newly identified and submitted studies and concluded that they would not impact the PD systematic review conclusions. Most of the

additional laboratory animal publications and non-guideline studies administered paraquat via injection into the peritoneal cavity [Chinta *et al.* 2018; Marks 2007a (MRID 50958001, unpublished); Marks 2007b (MRID 50958002, unpublished); Marks 2007c (MRID 50958003, unpublished)] and one study perfused paraquat directly to the substantia nigra (Tamano *et al.* 2019). As stated above, injection is not a relevant route of exposure for pesticidal uses of paraquat and cannot be used to evaluate toxicity and risk for anticipated exposure scenarios. Direct perfusion to the substantia nigra is, likewise, not a relevant exposure pathway. Studies that administered paraquat via injection or perfusion are also of limited utility as mechanistic information given the lack of conclusive evidence that oral, dermal, or inhalation exposure elicits the same PD-like effects in animals reported in these studies. The toxicity data reported in these studies are, therefore, not pertinent to evaluating the connection between exposure from paraquat pesticidal use and PD. One study submitted by Syngenta [Ray 2011 (MRID 50958004, unpublished)] quantified paraquat in cortical brain tissue collected from spider monkeys. The brain tissue samples were provided to Syngenta by SRI International and were collected as part of a separate study conducted at SRI International to investigate the effects of paraquat on nigrostriatal function/integrity. The original study was conducted 3-4 years prior to the brain tissue analysis during which time the tissues were kept in frozen storage. Although the study demonstrated quantifiable concentrations of paraquat in brain tissue, the study report did not indicate the route of administration nor dosing regimen in the original study. The agency thus could not utilize these data to further characterize paraquat toxicokinetics in monkeys.
One additional *in vitro* study was referenced in the comments (Colle *et al.* 2018) that was not included in the PD systematic review literature database because it was published after the final open literature search conducted for the PD systematic review. The agency reviewed this study and determined that while it does report relevant *in vitro* mechanistic information, the findings were consistent with *in vitro* paraquat effects already discussed in the PD systematic review and, as a result, do not alter the agency's overall conclusion from the PD systematic review.

II. Endpoint and uncertainty factor selection

The EPA Did Not Adequately Explain Why the Acute and Chronic Points of Departure Were Updated and They Are Not Health Protective (Pesticide Action Network)

EPA Response: The Pesticide Action Network expressed concerns that the updated acute and chronic dietary points of departure (PODs) were not adequately explained and not health protective. The rationale for updating the dietary PODs is described in Section 4.5 in the paraquat HHRA (Britton W. *et al.,* D430827, 06/26/2019) and is summarized here for reference.

The acute dietary POD (5 mg paraquat ion/kg) was updated for the most recent risk assessment because the POD (1.25 mg paraquat ion/kg) used in the previous risk assessment (T. Morton, D415809, 08/25/2014) was not based on an acute effect (e.g. the lung response in the rat multigeneration study was observed during the histopathology analysis at the end of the study and could not be unequivocally attributed to a single dose). The agency considered the acute mortalities and associated clinical signs in the developmental study in rats to be the most appropriate effect for the acute dietary POD because it was consistent with evidence in other acute oral studies and human incident reports of delayed symptoms and lethality from acute exposure and was protective of other acute effects noted in the database and in the open literature. As discussed in the HHRA, the agency identified a study from the open literature (Lou *et al.* 2016) that was both acceptable for use in risk assessment and reported findings relevant to the risk assessment (e.g. delayed acute mortality, age-related sensitivity, and behavioral changes). The agency initially considered the literature study for the acute dietary POD, but ultimately selected the guideline developmental study because the agency had more information on the methods for the guideline study including analytical results for the dosing solution (concentration and stability), the agency could review all individual animal data for the parameters assessed, and the paraquat product used in the guideline study was thought to be more representative of the available technical and end-use products. It was not

the agency's position that the findings in the literature study were unrelated to paraquat. Rather, the agency considered that the lack of similar findings in the guideline studies might be related to the lower purity compounds used in those studies and thus the findings from the guideline studies would be more reflective of toxicity from the commercially available pesticide products that were ≤48% paraquat. However, further review of the original guideline studies revealed several transcription errors in the data evaluation records and it was determined that several guideline studies did, in fact, use the high purity paraquat dichloride including the developmental rat study used for the acute POD.

Based on this discovery the agency re-evaluated the Lou *et al.* (2016) study. Originally the study was classified acceptable for quantitative use; however, in a recent follow-up communication with the authors they mentioned that they were not able to analytically confirm the concentration of the dosing solutions during the study. The agency is still of the opinion that the study was well conducted; however, the lack of analytical confirmation has introduced uncertainty to the dose response assessment and lowered confidence in the quantitative findings of the study as the agency could not confirm whether the actual concentrations were similar to the reported nominal concentrations. The findings from this study are still considered to be related to paraquat treatment; however, the uncertainty in the exposure concentrations precludes the agency from considering the findings quantitatively in the POD selection and uncertainty factor determination. Given this uncertainty, the agency reclassified this study as acceptable for qualitative use only. This re-evaluation reinforced the original conclusion that the acute effects in the developmental study were the most robust acute endpoint of the acute toxicity data available and, therefore, the most appropriate study to establish the acute POD.

The agency revised the chronic dietary POD from 0.45 mg paraquat ion/kg/day (NOAEL from the subchronic dog study) to 0.5 mg paraquat ion/kg/day (NOAEL from the chronic dog study) because the two dogs studies reported similar respiratory effects, the NOAELs were similar, and selecting the slightly higher NOAEL from the chronic dog study was still health protective of the toxicity noted in both dog studies as well as other effects reported in the paraquat toxicity database and the open literature.

The EPA Should Reconsider the Selection of a Respirable POD for the Inhalation Assessment (Syngenta)

EPA Response: One of the paraquat registrants, Syngenta, disagreed with the agency's decision to conduct an inhalation assessment using a POD based on upper respiratory effects reported in the guideline inhalation study. Their comments expressed that a non-respirable particle POD was more appropriate, but also that they concurred with a previous agency conclusion that an inhalation risk assessment is not warranted . Their rationale for not using the POD from the rat inhalation study and for not conducting an inhalation assessment was that application equipment commonly used for applying aqueous non-selective herbicides do not produce droplets in sizes that fall within the respirable range tested in the subchronic rat inhalation study used to establish the inhalation POD for the HHRA. Syngenta referred to an analysis of open literature data that indicated spray equipment used for aqueous non-selective herbicides produce larger particles ranging from 200-400 µm in order to improve coverage of target species and minimize spray drift. In addition, Syngenta submitted summary and raw data from a 2009 study conducted in Brazil that demonstrated simulated terrestrial application of water and several paraquat formulations using common nozzle sizes and pressure settings produce spray droplets with volume median diameter >200 µm, size range from 220-340 µm. The study also reviewed water droplet size distribution data compiled in the AgDRIFT® library for aerial applications which demonstrated a volume median diameter >200 µm, size range from 218-457 µm for a range of common nozzles. Based on these data, the study authors concluded that terrestrial and/or aerial application of paraquat using these nozzles would result in a very small proportion of respirable or inhalable droplets and thus negligible inhalation exposure.

The agency notes that, contrary to Syngenta's comment, inhalation risks were assessed in previous paraquat risk assessments using a "non-respirable" POD that was based on effects reported in an oral study. Moreover, the agency recognizes that it mischaracterized the "respirable" POD selected for assessing inhalation risk in previous assessments as well as the draft risk assessment for registration review. The most sensitive effects reported in the guideline inhalation study that were used to establish the inhalation POD were noted in the extra-thoracic region of the respiratory system. These effects in the upper respiratory tract were the result of exposure to a polydisperse distribution of aerosols that includes droplets in the inhalable range for the rat. Consequently, the "respirable" descriptor used for the inhalation POD in the risk assessment is not accurate and the inhalation POD actually accounts for and is protective of exposure to aerosols in the inhalable range, which includes respirable droplets.

Although the data from the 2009 study support Syngenta's assertation that a majority of the spray droplets produced from these nozzles will be larger than the 1-3 µm droplets produced in the guideline inhalation study, the agency cannot assume in its assessment that every paraquat applicator will use the nozzles tested in these studies. The agency also notes that 3-17% of the droplets produced were in the inhalable range indicating inhalation exposure is not negligible when using the two nozzles tested in the 2009 study. Evaluation of spray nozzle data used for spray drift analyses indicates that aerosols in the inhalable range are produced regardless of spray quality, but that the fraction of droplets in the inhalable range decreases for spray nozzles designed to produce coarser particles. As part of registration review, Syngenta is proposing to add language to the existing and new product labels that will require use of large nozzles with their products to minimize the production of inhalable or respirable droplets; however, there is no indication that other registrants intend to apply similar requirements to their product labels. The agency further notes apparent inconsistencies between the air monitoring and droplet size data referenced by Syngenta and human incidents involving inhalation exposure. In a memo from 2000 (J. Blondell; D260797; 08/10/2000), the agency evaluated the frequency of incidents associated with inhalation exposure reported in the Poison Control Center data from 1993-1998 and the open literature and remarked on the apparent disconnect between these incidents and findings from the National Institute for Occupational Safety and Health (NIOSH) and others that suggested respirable levels of paraquat produced under normal circumstances would not be sufficient to cause poisoning. While no reason for the discrepancies between incident and exposure data could be determined, the agency expressed concern in its conclusions that even nasal exposure to non-respirable droplets could result in serious or fatal poisoning given that larger paraquat droplets could be retained in the nasal mucosa and that nosebleeds – an effect associated with exposure to paraquat spray droplets and dust – could enhance absorption across nasal membranes. In addition, the Tier II incident report (E. Evans and S. Recore, D446902, 07/25/2018) composed for registration review describes incidents occuring between 1998 and 2018 reported in several incident databases that were attributed to inhalation exposure as well as symptoms of respiratory irritation and upper respiratory pain following exposure which are distinct from the systemic lung effects noted in the animal studies following oral exposure. These incidents suggest that paraquat use produces droplets that are at least in the inhalable range – a conclusion that is supported by the droplet size data from the 2009 Syngenta study – and results in appreciable inhalation exposure and adverse portal-of-entry effects. . The agency acknowledges that the discrepancies are difficult to reconcile given that route of exposure is not always confirmed for incidents; however, it does reduce the agency's confidence that the open literature droplet size data accurately reflect exposure for all paraquat uses.

The agency cannot rule out the potential for inhalation exposure from paraquat use based on the findings reported above; therefore, an inhalation assessment is warranted for the paraquat registration review. Conducting an inhalation assessment for paraquat using only an oral POD, consistent with previous risk assessments, would not account for the potential of portal of entry toxicity in the upper respiratory tract tissues resulting from inhalable particles for a chemical that is known to be corrosive to skin and mucus membranes and that animal studies and human incidents suggest is a possible consequence of paraquat use. Given the uncertainties outlined above, the agency considers the POD selected in the paraquat

HHRA based on upper respiratory effects in the rat inhalation study to be more appropriate for assessing inhalation risk, particularly for route-specific portal of entry toxicity, and thus will retain it for the inhalation risk assessment.

The EPA Should Reconsider the Uncertainty Factors Applied to the Dermal POD (Syngenta)

EPA Response: Syngenta recommended that the agency consider reducing the interspecies factor (UF_A) for the dermal POD from 10X to 3X because using the rabbit as a model for paraquat dermal toxicity is overly conservative for evaluating dermal irritation, skin damage, and predicating systemic toxicity. The agency does not agree with this proposal. The agency does have policies and practices in place that allow for reduction of the interspecies uncertainty factor for different exposure scenarios when there are well established pharmacokinetic (e.g. human equivalent calculations for inhalation studies) and/or pharmacodynamic (e.g. thyroid effects in rats) differences between model species and humans. These policies or practices are developed through comprehensive review of a robust body of evidence and are data driven. The agency routinely uses animal dermal studies, usually performed with either rats or rabbits, to evaluate risks for dermal exposure; however, it does not have a policy or practice in place to reduce the uncertainty factors based on interspecies differences in skin penetration. The agency does not consider the current evidence on interspecies differences in paraquat dermal absorption to be robust given that there is limited dermal toxicity information available and the dermal penetration literature does not adequately address the influence of paraquat's corrosive properties.

The rabbit dermal toxicity study is the only guideline study available to evaluate paraquat toxicity from dermal exposure. The agency acknowledged in the risk assessment that there were no systemic effects noted at the highest dose tested in the rabbit dermal study and established it as the systemic NOAEL for the study. The lack of systemic effects suggests that dermally applied paraquat was unable to reach systemic circulation even at the highest dose tested where progressive skin lesions were noted, which is consistent with human dermal penetration data for this chemical. Yet, a LOAEL for systemic toxicity could not be established because the study authors elected not to test at a higher dermal dose due to welfare concerns for the animals. Given the dose response observed for the skin lesions in rabbits, it is likely that higher doses would further erode the skin layer, resulting in increased dermal absorption and associated systemic toxicity. Though aspects of the study design may have influenced the extent of dermal irritation and damage, there are no other studies available to evaluate dermal or systemic toxicity from repeat dose dermal exposure at doses above those tested in the rabbit dermal study. This introduces considerable uncertainty in estimating human risk for dermal exposure.

The agency agrees with Syngenta that the available evidence indicates paraquat is poorly absorbed across intact human skin; however, evidence of severe dermal toxicity in human incidents also suggests that paraquat can affect the integrity of human skin after prolonged dermal exposure. The dermal dose that resulted in skin damage reported in these human incidents is not clear, but it is evident that paraquat can elicit mild to severe dermal toxicity in humans. Given the uncertainties from the laboratory animal toxicity study, the agency recommended in the risk assessment that the registrants conduct a skin irritation assay to better understand how paraquat interacts with human skin at dermal doses above those tested in the human dermal absorption study. With the currently available data, the agency elected not to use the previous oral POD to estimate an equivalent dermal dose because it does not account for potential changes in skin permeability with increasing dermal dose.

Syngenta referenced several studies from the open literature (Bartek *et al.*, 1972; Scott *et al.*, 1986; Phillips *et al.*, 1972) to support their conclusion that the rabbit model is overly conservative. The agency did not have access to the raw data for these studies to confirm the findings reported and in one case (Scott *et al.*, 1986) could not access the full text of the study. Regardless, the findings reported in these studies, whether in the abstract or in the text, did not demonstrate unequivocally that the rabbit is a

conservative model for paraquat dermal toxicity. The studies suggest that systemic absorption would be greater in rabbits compared to humans across intact skin; however, they do not address species differences in skin corrosion and the irritation study (Phillips *et al.*, 1972) focused on species differences for acute exposure rather than repeat dose exposure. The findings in these studies do not address the agency's concern that repeat dermal exposure in humans would cause the same progressive damage to the epidermal layer that was observed in rabbits and would lead to enhanced absorption at dermal doses above those investigated in the human dermal absorption study and the current dermal POD. The agency will, thus, retain the current dermal POD and the 10X uncertainty factors for interspecies extrapolation and intraspecies variation to be protective of the potential for systemic toxicity from skin corrosion at higher dermal doses.

EPA Should Retain the Food Quality Protection Act (FQPA) Safety Factor (SF) for the Paraquat HHRA (Center for Biological Diversity, Environmental Working Group, and Pesticide Action Network)

EPA Response: The Center for Biological Diversity, Environmental Working Group, and Pesticide Action Network expressed concern with the Agency's decision to reduce the FQPA SF to 1X and singled out the age sensitivity findings in the Lou *et al.* (2016) study and that the agency did not account for neurotoxicity effects in the POD selection as evidence for retaining the FQPA SF. The PODs selected in the paraquat HHRA to evaluate dietary, occupational and non-occupational risks were all below the lowest dose tested in the Lou *et al.* 2016 study (5 mg paraquat dichloride/kg/day), with the exception of the acute POD. As stated above, the uncertainty in the exposure levels reported in the Lou *et al.* (2016) study precluded using it quantitatively for risk assessment and, therefore, could not be considered in selection of the acute POD. Moreover, the agency's confidence in the evidence of age-related sensitivity is affected by the uncertainty in the actual concentration administered to the different age groups, as it was not analytically confirmed by the study authors. No other evidence of lifestage sensitivity was observed in the guideline studies nor in studies from the open literature that investigated toxicity at or below the current PODs. In addition, as detailed in several other responses, the agency conducted a thorough systematic review of the paraquat open literature to identify toxicity information that were not captured in the guideline and non-guideline studies submitted to the agency including evidence of PD effects in humans and PD-like hallmarks in animals. After reviewing all relevant data, the agency determined that the respiratory and contact toxicity effects used to establish the current PODs were the most sensitive effects reported following exposure to paraquat. Given lower confidence in the finding of age-related sensitivity reported in the open literature, the lack of evidence of pre- or postnatal sensitivity in the guideline studies, and that the PODs were based on the most sensitive effects observed following paraquat exposure, the agency is confident the current PODs are protective of all lifestages and supports a reduction in the FQPA SF to 1X.

One commenter also mentioned that the agency had retained a 3X FQPA SF in previous risk assessments. The agency had retained the 3X for acute dietary risk assessments conducted prior to 2012 based on the lack of a non-rodent developmental study; however, the agency determined in 2012 (Rury K., TXR 0056294, 04/12/2012) that a non-rodent developmental study was not likely to add information that would impact the paraquat risk assessment and thus the lack of this study was no longer considered a database gap. This decision was one of several considerations, including those outlined above, in the agency's decision to reduce the FQPA SF to 1X.

The EPA Did Not Account for Combined Inhalation, Dermal, and Oral Exposure in its Assessment (California Legal Assistance Foundation and Pesticide Action Network)

EPA Response: The California Legal Assistance Foundation and Pesticide Action Network questioned why the agency did not combine inhalation exposure with the dermal and oral exposures for the

occupational risk assessment. In accordance with HED policy, oral, dermal, and inhalation exposure can only be combined if the PODs are based on the adverse effects in the same target organs/systems. For paraquat, inhalation exposure estimates cannot be combined with dermal and oral exposures because the inhalation POD is based on portal of entry toxicity that is unique to the inhalation route of exposure. Commenters also expressed concerns that the inhalation POD did not account for systemic effects that could result from paraquat inhalation. Portal of entry effects were the most sensitive response to repeated paraquat inhalation exposure in the inhalation guideline study. The study did not include hematology or clinical chemistry evaluations nor conduct gross or histopathological evaluations on non-respiratory tissues. Nevertheless, the lungs were evaluated in this study and lung effects were commonly the most sensitive systemic effect observed in rats in the paraquat toxicity database. No lung effects or mortalities were observed at the lowest concentration level that elicited portal of entry effects suggesting that paraquat absorption in the respiratory tract and/or clearance to the gastrointestinal tract was not contributing to toxicity at the lowest-observed-adverse-effect-level (LOAEL) established for this study. Mortality and lung effects were only noted at higher inhalation concentrations. In selecting a no-observed-adverse-effect-level (NOAEL) based on portal of entry effects as the POD, the risk assessment accounts for and is protective of the subsequent systemic effects reported at higher concentrations.

The EPA Did Not Consider Open Literature Data in POD Selection (Center for Biological Diversity and Environmental Working Group)

EPA Response: The Center for Biological Diversity and Environmental Working Group expressed concern that the agency was using outdated guideline studies, ignored peer-reviewed studies from the open literature, and did not consider effects reported in the literature, including neurotoxicity, in the paraquat HHRA. As part of the paraquat registration review, the agency conducted a general review of the open literature for all reported effects. The goal of this review is to capture a broad selection of the paraquat open literature by searching based on chemical name and common animal models and not date limiting the search. The publications returned from our search strategy include studies conducted up to 2018 and thus provide more recent toxicity data for paraquat to complement the data available from the guideline studies. In addition, the agency conducted a general epidemiology systematic review as well as a systemic review of human, animal, and *in vitro* publications that reported neurotoxic effects from exposure to paraquat with a focus on PD and PD-like responses. Between the three reviews, the agency screened 11,713 studies (**Note: this is not the number of unique publications as the search strategies overlapped resulting in a number of duplicates**).

Studies identified as relevant to evaluating human health risk from paraquat pesticidal use were individually evaluated for quality and substance. The quality assessment for open literature studies was conducted in accordance with the OPP Epidemiology Framework for the human studies and 2012 OPP Literature Review Guidance for the animal and *in vitro* studies. The agency's evaluation considered study design, reporting, and sources of bias when interpreting the findings reported in each study. The agency uses the recommendations in the toxicity study guidelines as a starting point in the review; however, an open literature study does not have to include every aspect of the guideline study to be considered for risk assessment. The agency also took into account the relative impact of each deficiency to determine if it would only affect a subset of the data presented (e.g. bias in analysis of a particular parameter) or diminish confidence in the entire study (e.g. inadequate sample size or the identity and purity of the product was not reported or could not be deduced from the information provided in the publication). Publications were considered unacceptable for use in risk assessment only when its deficiencies diminished all confidence in the reported conclusions. In studies deemed acceptable for risk assessment, the agency then evaluated the substance of the findings relative to the information already reported in the agency's paraquat toxicity database. As part of the substance evaluation, the agency compared the effect level to the POD selected for risk assessment and determined whether the effects reported were biologically significant and adverse. Studies that reported unique effects not covered in the HHRA, but

only at doses above the current PODs, contributed qualitative information to the paraquat hazard characterization but did not have a quantitative impact on the risk assessment. The findings from these literature reviews were summarized in the HHRA and are discussed in more detail in their respective documents (Wray A. and Niman A., D449106, TXR 0057888, 06/26/2019; Wray A., D449107, TXR 0057887, 06/26/2019; Niman A., D449108, 06/26/2019).

All relevant, acceptable laboratory animal publications identified in the open literature reviews as well as the conclusions of the epidemiology and PD systematic reviews were considered with the guideline studies in selecting PODs and UFs for the paraquat HHRA. After reviewing all of the available data including the risk assessment relevant neurotoxicity studies in mice, the agency determined the respiratory effects and contact toxicity noted in the guideline studies were the most sensitive effects reported in animal studies from repeated exposure to paraquat for all routes of exposure and for all lifestages. Accordingly, the agency established the repeat dose PODs based on respiratory and contact toxicity effects. The HHRA, therefore, accounts for and is protective of all reported paraquat toxicity in the guideline studies and the open literature including the PD-like hallmarks observed in laboratory animals at higher dose levels. Moreover, the agency determined that additional UFs were not warranted to be adequately protective of neurotoxicity and other health effects associated with paraquat exposure given that the PODs were based on the most sensitive effects reported for paraquat and the lack of sufficient evidence to suggest a causal or associative relationship between exposure and health outcomes investigated in the epidemiology literature.

III. Co-exposures and mixtures

The EPA Should Consider Co-Exposures to Paraquat, Its Metabolites/Degradates, and Other Pesticides in the HHRA (Center for Biological Diversity, the City of Sacramento, and the California Legal Assistance Foundation)

EPA Response: The Center for Biological Diversity, the City of Sacramento, and the California Legal Assistance Foundation recommended that the agency consider co-exposures of paraquat with other pesticides in evaluating the link between paraquat exposure and PD as well as in the overall evaluation of human health risks from paraquat pesticidal uses. The agency does not assess human health risks from mixtures or co-exposures with the exception of chemicals that exhibit a common mechanism of toxicity and/or chemicals that produce a toxic metabolite or degradate that is shared by other chemicals. At the time the HHRA was completed, the agency had not made a common mechanism of toxicity finding for paraquat nor did the agency identify a toxic metabolite/degradate produced by other substances. The agency, therefore, did not assume paraquat had a common mechanism with other substances and a cumulative assessment was not conducted. The City of Sacramento also recommended the agency consider co-exposures to the parent compound and its metabolites, degradates, and transformation products formed in the environment and/or during wastewater treatment. As part of registration review, the agency determined that no major metabolites or degradates were formed from registered uses of paraquat products that would be considered residues of concern in food and/or drinking water. Therefore, the HHRA evaluated risk for exposure to paraquat only.

IV. Endocrine Disruption

The EPA Did Not Adequately Assess the Potential for Paraquat to Cause Endocrine Disruption (Beyond Pesticides and the Center for Biological Diversity)

EPA Response: Beyond Pesticides and the Center for Biological Diversity expressed concerns that the paraquat HHRA did not fully assess the potential for endocrine disruption from paraquat exposure. As part of registration review, the agency reviews numerous studies that investigate general systemic toxicity

following acute, subchronic, and chronic exposure, as well as several studies that focus on particular systems including the reproductive system. Most of these studies evaluate endpoints that may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. In its review, the agency did not find any evidence of endocrine disruption in either the general toxicity guideline studies or those more focused on the endocrine system (e.g. multi-generation reproduction study).

Paraquat was not included on either list of chemicals selected for EDSP screening; however, the agency does conduct a general literature review for all reported effects, including endocrine disruption in laboratory animals and human studies as part of registration review. This review captures a broad selection of the paraquat open literature by searching based on chemical name and common animal models and not date limiting the search. The publications returned from our search strategy include studies conducted after the guideline studies and thus provide more recent toxicity data for paraquat. The agency screened 3,971 studies for the general paraquat open literature review and more thoroughly reviewed 26 (17 of these studies were separately identified in the PD systematic review that screened 7,166 publications) that reported unique information with a potential to impact the risk assessment. None of the peer-reviewed published studies screened and reviewed reported evidence of endocrine disruption at dose levels below the current points of departure (PODs) used to assess dietary, occupational, and non-occupational risks. In addition, a general epidemiology review of the open literature was conducted that screens 576 publications. Several epidemiology studies were identified in this screen that examined health outcomes related to endocrine disruption (e.g. thyroid disruption and male reproduction). The agency identified several limitations in these studies including their cross-sectional design and classified them as low quality in accordance with the OPP Epidemiology Framework. Consequently, the agency determined that there was insufficient evidence to conclude that there is a clear associative or causal relationship between paraquat and the endocrine disruption health outcomes. Given the lack of endocrine disruption findings at or below the current PODs and insufficient evidence in the epidemiology literature, the agency is confident the HHRA adequately accounts for and is protective of potential endocrine disrupting effects that could result from exposure to paraquat.

V. Residential and Occupational Risk Assessments

EPA Overestimates the Efficacy of Protective Clothing and Engineering Controls (California Rural Legal Assistance Foundation, Farmworker Association of Florida and Farmworker Justice and the environmental organizations Earthjustice, Toxic Free NC and Pesticide Action Network):
The data utilized in the occupational handler assessments are based on exposure monitoring studies where workers/handlers wore typical clothing and recommended personal protective equipment (PPE) as they normally would. Therefore, the risk estimates for the different exposure scenarios are representative of current practices and potential exposures under real world conditions. During the risk management process, consideration is given towards not only the risk estimates provided in the human health risk assessment, but also on the impact of PPE (e.g., heat stress, etc). It is acknowledged that engineering controls provide a higher level of protection compared with PPE, and this is also considered when making risk management decisions.

The Worker Protection Standard (WPS) is very clear in section 170.507(b) on the requirement that the employer provide PPE to employees: "Employer responsibilities for providing personal protective equipment. The handler employer must provide to the handler the personal protective equipment required by the pesticide product labeling in accordance with this section. The handler employer must ensure that the personal protective equipment is clean and in proper operating condition..."""... if an employer fails to provide the handler with the label information, which includes the

information about the PPE they must wear, they are in violation of the WPS, which constitutes an unlawful use of the pesticide."

EPA Response: EPA agrees with the comment. The WPS requirements for employers to provide the necessary protective equipment as assessed in the occupational handler assessment and as required by product labeling is necessary for protection of human health. Failure of an employer to supply the necessary label-required PPE is inconsistent with WPS Section *170.507(b)*and could result in an increased risk potential for the occupational handlers exposed.

Failure to Account for Exposure from Inhalation of Paraquat-Contaminated Dust (California Rural Legal Assistance Foundation, Farmworker Association of Florida and Farmworker Justice and the environmental organizations Earthjustice, Toxic Free NC and Pesticide Action Network):
USEPA's failure to analyze the risk of exposure to paraquat from dust undermines the validity of the risk assessment. Paraquat has a low vapor pressure and adheres strongly to soil clays, does not photodegrade and is resistant to microbial degradation. In the assessment, USEPA acknowledges that "There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and particles that contain pesticides." The assessment includes the explanation that during Registration Review, the Agency will use the Volatilization Screening Analysis to determine if data or further analysis is needed for paraquat. Notably, assessment of exposure through dust is not mentioned. Failure to include an assessment of the risks associated with inhalation exposure from paraquat contaminated dust for post-application workers and farmworkers in paraquat treated fields and for bystanders and those living in farmworker housing near treated fields is a serious omission in this assessment that underestimates exposure and thus underestimates risk.

EPA Response: The agency acknowledges the potential for paraquat adherence to soils and subsequent inhalation of dusts as these are generated during post-application activities in previously treated fields. Occupational exposures to paraquat from handling activities (i.e., mixing/loading, application, and mixing/loading/application) are expected to be greater than any potential exposures to dusts. Therefore, the assessment of the inhalation exposures from the occupational handling of paraquat products is protective of any potential inhalation exposure from dusts which are not believed to be a significant exposure source.

EPA Must Take into Account Real-World Scenarios (Center for Biological Diversity)
The EPA often claims that it is acting conservatively by using the maximum labeled use rates when estimating exposure to plants and animals. These upper-level exposure scenarios, however, do not take into account accidental spills and illegal uses of the pesticide. An assumption of 100 percent label compliance underestimates risk and is unsupported by state-collected data. EPA even discounts incident data if there was the possibility that the pesticide was not used in accordance with the law, even though it was demonstrated to happen.

The data that are available on label compliance indicate that it is unreasonable to assume that pesticides are always applied in accordance with the label or with proper PPEs. We feel that when communicating findings to a risk manager, the EPA should no longer refer to its use of maximum labeled rates as "conservative" or accurately estimating peak exposures that may occur. And modeling of maximum use rates should absolutely never be used to discount level of concern ("LOC") or population adjusted dose ("PAD") exceedances.

EPA Response: EPA assesses potential exposures and risks to pesticide products assuming that the product user, whether occupational or residential, reads the product label and follows any label directions and heeds all safety precautions with use of the product. A critical function of the product label is to manage the potential risks as identified by EPA's assessment. It is a violation of Federal law to use a pesticide product in a manner inconsistent with its labeling. Therefore, the potential illegal usage of pesticide products is not quantitatively assessed by EPA.

EPA acknowledges that there is the potential for accidental spills and accounts for this risk assessment consideration through the evaluation of reported incident information from multiple sources including: the National Pesticide Information Center (NPIC); NIOSH's Sentinel Event Notification System for Occupational Risk (SENSOR); American Association of Poison Control Centers; information submitted directly to EPA, and voluntary reporting through by the public. In addition, pesticide registrants (i.e., the manufacturers of pesticide products) are required by law to submit to the EPA reports of adverse effects from usage of their products. EPA's incident report evaluation helps the Agency to determine whether the pesticide's application directions require clarification, some uses of a pesticide should be limited, or whether additional personal protective equipment (PPE) should be required.

Based on the high number and severity of human health incidents reported for the ingestion of paraquat, both accidental and intentional, the EPA determined that risk mitigation measures were necessary for paraquat pesticide products to meet the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) standard for registration. This mitigation decision[1] was published in January 2017. The following mitigation measures were implemented in three phases. Submission deadlines and implementation timeframes for these measures are discussed below.

1. Label amendments to emphasize paraquat toxicity and restrict use of all paraquat products to certified applicators only (i.e., prohibiting use by uncertified persons working under the supervision of a certified applicator), and supplemental warning materials
    a. Implementation timing:
        i. Revised labels and supplemental materials were submitted to EPA in March 2017
        ii. Revised labels and supplemental materials were stamped approved by EPA in late Summer/Fall 2018
        iii. New products released into commerce must bear this new labeling by late Summer/Fall 2019

2. Targeted training materials for paraquat users
    a. Implementation timing:
        i. Released online in March 8, 2019
        ii. New products released into commerce must bear new labeling specifying the requirement to take the targeted paraquat training by late Summer/Fall 2019

3. Closed-system packaging for all non-bulk (less than 120 gallon) end use product containers of paraquat
    a. Implementation timing:
        i. Revised labels specifying the closed system requirement were due to EPA on March 29, 2019
        ii. The revised labels are currently under review in EPA and should be stamped in Summer/Fall 2019

[1] M. Mannix. Amended: Paraquat Dichloride Human Health Mitigation Decision. January 12, 2017. *This document supersedes the December 14, 2016 Paraquat Dichloride Human Health Mitigation Decision.*

iii. All non-bulk products must be in closed systems one year from the date that the labels are stamped by EPA
iv. EPA's existing stock provision applies

Lack of Clarity Relating to the Level of Personal Protective Equipment Assumed for Occupational Handler Risks Assessed (National Cotton Council)
It is unclear if EPA is stating that both the existing (occupational handler) PPE and the amended label additions, such as the closed-system packaging, were included together in the risk assessment or viewed separately. The NCC believes the assessment should be reflective of all requirements based on the current label and urges EPA to verify this is the case.

EPA Response: The occupational handler exposure scenarios assessed for paraquat were quantified for various levels of PPE or engineering controls. Results for the paraquat risk assessment were presented starting at the lowest levels of PPE (mixers, loaders, and applicators and other handlers to wear baseline clothing, chemical resistant gloves, and a NIOSH approved half-mask, PF10 respirator) required by the product labels for each exposure scenario. Engineering controls, consistent with the closed system requirements, were assessed separate from the assessment of label-required PPE.

Lack of Clarity Relating to the Inhalation Exposure Assessment (National Cotton Council)
The NCC asks for greater clarity related to the inhalation exposure component of the risk assessment. Technology has dramatically improved worker environments with closed cab equipment and filtered air conditioning. The NCC requests clarity if the assessment accounts for these technologies.

EPA Response: EPA's assessment of occupational post-application exposures and risks from cotton harvesting are based on transfer coefficient (TC) data derived from a study which measured exposures resulting from conventional harvest practice and associated activities. The paraquat occupational post-application assessment also considered the submission of summary information from a 2016 survey by the National Cotton Council[3] and an October 18, 2018 meeting with OPP and the National Cotton Council. While this information suggests that technology is moving increasingly toward the newer mini-module harvesters, the conventional harvest practice remains in use by approximately half of the survey participants. EPA acknowledges that the newer mini-module harvester, as well as new technologies such as closed cab filtered air conditioners, may reduce potential worker exposures from cotton harvest. However, 1) EPA is limited to the conventional harvest TC exposure data and 2) the EPA assessment is protective for cotton harvest workers using the conventional harvest equipment (i.e., EPA cannot assume that all cotton harvest is conducted with either conventional harvest practice equipment employing new technologies, or conducted with the newer mini-module harvester).

Additional Information on Mechanical Cotton Harvest Transfer Coefficients (National Cotton Council)
NCC appreciated HED's recognition of their 2016 Survey of Harvest Transport Practices and committed to work with the EPA to develop appropriate pathways related to harvest and post-harvest practices associated with current production. The NCC included additional information relating to cotton trailer packing, conventional module builders, the harvesters with round bale module, and the harvester with mini-module.

EPA Response: EPA appreciates the additional information relating to cotton harvest practice and encourages further engagement with the NCC to better understand and evaluate cotton harvest exposures and risk.

[3] Steve Hensley. Response: Docket ID Number EPA-HQ-OPP-2012-0167. 04/30/2018.

Dislodgeable Foliar Residue Data Requirement (National Cotton Council)
The NCC is not in agreement with entry and exposure assumptions regarding Dislodgeable Foliar Residue (DFR) and Dislodgeable Boll Residue (DBR). Crop production equipment today has greatly advanced beyond practices utilized at the period of time these exposure pathways were developed (eg. DBR in the early 1990's). The NCC desires further engagement with EPA to appropriately revise these exposure pathways to reflect today's technology."..." Additionally, the NCC does not believe DFR and DBR assumptions of contact are appropriate. When paraquat is used as a defoliant, the crop is ready for harvest. Pest scouting by individuals has ended.

EPA Response: The paraquat HHRA recommends for dislodgeable foliar residue (DFR) and dislodgeable boll residue (DBR) data for paraquat. While data needs are identified for both, EPA encourages prioritization of the DBR data. As described in a prior response, EPA is limited to use of the best available data, a conventional harvest TC study which is not reflective of newer technologies such as closed cab filtered air conditioners; therefore, the occupational post-application risks presented are not reflective of newer technologies but assume that the older conventional practice harvest technologies remain in practice and are protective for harvest workers using this equipment. Further, the agency evaluated available field trial data for paraquat residues on desiccated commodities. Residues were detectable in undelinted cotton seed up to 14 day PHI and cotton gin byproducts at 3 day PHI. Field trial data are not typically used for quantitative assessment of occupational post-application exposures and risks since these data represent residues available in/on the plant and, therefore, potentially overestimate the foliar residues to which a worker would be exposed. However, these data confirm the presence of paraquat residues in cotton bolls and were considered relevant for qualitative characterization of potential occupational post-application exposures. In the absence of DBR data for cotton, EPA uses default inputs to estimate this value for risk assessment. The submission of paraquat DBR data would allow for a refined assessment of potential occupational post-application exposures from cotton harvest activities.

Occupational Post-application Exposure Estimates Are Not Reflective of Current Technology in Cotton Production (USDA)

EPA Response: The HHRA extensively discusses the occupational post-application assessment including the cotton harvest equipment types assumed and the exposure data (TCs) used. Further, the risk assessment details the use of 2016 survey data submitted by the National Cotton Council and uses these data to develop characterization for the mechanical harvest equipment type and harvest activities assessed. As described in a previous comment, the agency acknowledges that the survey information, "suggests that technology is moving increasingly toward the newer mini-module harvesters, the conventional harvest practice remains in use by approximately half of the study participants," and that these new technologies, "may reduce potential worker exposures from cotton harvest." However, the occupational post-application assessment was conducted with the intent to be protective for all potential equipment types and associated harvest activities.

EPA Occupational Handler Inputs and Assumptions (USDA)
For occupational handler exposure scenarios of concern, USDA urges EPA to consider the most up-to-date and realistic estimates for typical application rates, modern application equipment technology, and typical agricultural practices when addressing these risks within the context of paraquat's high importance to agriculture. For example, USDA notes that flagging is no longer a common practice for aerial application.

EPA Response: Per HED policy, the occupational handler risk assessment relies on maximum registered application rates. This approach ensures a health protective assessment for the potential handling of paraquat at allowable application rates. The agency may consider the assessment of typical use rates as a risk mitigation option; i.e., reducing the maximum application rates allowed by product labeling.

At the time of EPA's HHRA, the most up-to-date exposure data were used to conduct the occupational handler exposure scenarios assessed. In March 2020, EPA made public and updated the reference table which captures changes to the unit exposures recommended for occupational handler assessment. The occupational handler assessment will be updated, where changes are applicable. The update encompasses the best exposure data available to EPA and are intended to be representative of modern application equipment and typical agricultural practice.

EPA Fails to Account for the Actual Use Pattern of Alfalfa (USDA)
In general, paraquat is most commonly applied to alfalfa as a burn-down tool post-planting and pre-emergence. In some cases, paraquat can be applied between cuttings to provide a burn-down benefit, similar to what is done by flaming. Paraquat would never be applied to fully grown alfalfa fields, from which EPA's exposure estimates are derived.

EPA Response: As described in the HHRA, the agency consulted with OPP's Biological and Economic Analysis Division (BEAD) relating to the occupational post-application activities associated with the registered uses of paraquat. Broadcast applications of paraquat are applied directly to the crop for foliage desiccation (to the crop and any weeds in the field) to expedite harvest and reduce seed loss upon harvest. Per BEAD, at this late stage of the crops, scouting to make sure the application was effective, would be the only activity conducted. Further, per BEAD, the EPA Special Local Need (SLN) product registration, Paraquat SL Herbicide (EPA Reg. No. 82557-1), allows for applications immediately prior to alfalfa harvest. The agency assessed scouting for alfalfa in accordance with this recommendation. The agency will consult further with BEAD and consider the additional information provided by USDA as characterization relating to scouting activities in alfalfa.

USDA Suggests the Default 48-Hour Re-Entry Interval (REI) Negatively Impacts Growers and Is Highly Unlikely to Exist Under Real World Conditions (USDA)

EPA Response: Under 40 CFR 156.208, Subpart K. Worker Protection Statements, (c) (2), active ingredients classified as Acute I for acute dermal, eye irritation and primary skin irritation are assigned a 48-hour REI. Therefore, for paraquat, a Toxicity Category I eye irritant, a minimum 48-hour REI is required.

EPA Only Assesses Broadcast Applications (Pesticide Action Network)
There is no acknowledgement of occupational exposure except for the broadcast application route. For directed applications the assumption is that occupational post application exposures are not likely; which seems an overly risky assumption considering the high toxicity of paraquat.

EPA Response: For occupational handler risk assessment, the agency assessed all application types including both broadcast and directed. For occupational post-application risk assessment, the application type (broadcast or directed) was taken into account when determining the likelihood of foliar contact by workers performing activities following paraquat applications. The agency assumed that directed spray applications of paraquat are targeted for control of individual weeds and grasses. Such applications are made with the intent of minimizing the risk of injuring the crop and/or non-target vegetation which are not tolerant of directed applications. Since these applications are not expected to result in foliar residues on the crop and/or non-target vegetation, occupational post-application exposures are not likely for directed applications and were not assessed. Occupational post-application risks from broadcasted applications were assessed due to the likelihood of residues on foliar surfaces and worker contact while conducting activities.

Proposed Label Amendments to Address Estimated Spray Drift Risks (Syngenta Crop Protection)
Syngenta is submitting a label amendment for Gramoxone 3LB (EPA Reg. No. 100-1652) and will be modifying the pending registration label for Gramoxone Magnum (EPA Reg. No. 100-RAUR) to add the following use restrictions for applications:
• Applicators are required to use a coarse or larger spray quality (droplet size) according to the American Society of Agricultural and Biological Engineers (ASABE) Standard S572.2 for spray applications.
• Requiring that ground applications NOT exceed a boom height of 24 inches above target pest or crop canopy.
When these changes are factored into the AgDrift exposure estimates for the nonoccupational spray drift scenarios, the resulting MOEs (combined dermal and incidental oral risk estimates from indirect exposure to paraquat upon modelled deposition at 0 feet from the field's edge) were determined to be ≥ 115 which is above the minimum required LOC (MOE ≥ 100) for all populations.

EPA Response: The agency will consider Syngenta's label amendment proposal for mitigation of spray drift risks during Registration Review.

Occupational Mixer Loader Risk Assessment: Paraquat Closed System Transfer (Syngenta Crop Protection)
Syngenta has developed a closed transfer system that complies with the paraquat human health mitigation decision (HHMD) requirements being implemented for paraquat products distributed in containers < 120 gallons. In addition to minimizing the potential for exposure to the mixer/loader during the dispensing by ensuring integrity of the closed system throughout the process, this system also functions to rinse the container with pressurized water to remove any residual product in the container.

EPA Response: HED acknowledges Syngenta's development of the closed system technology being implemented for products distributed in containers < 120 gallons. The agency's occupational handler assessment for mixing/loading paraquat with a closed system is based on the best exposure data currently available for closed system technologies; the estimated risks are assumed to be the best representation of the potential exposures from this handling activity. New exposure data for closed loading of liquid formulations conducted by the Agricultural Handler Exposure Task Force is under review by the agency. These data will be used to update the paraquat handler assessment for this exposure scenario when the agency's review is finalized and these data are approved and incorporated for use.

Paraquat Mandated Label PPE (Syngenta Crop Protection)
For some products, instead of using increased PPE, an engineering-controlled (closed system) solution is used which may allow for a reduction in PPE due to the protective nature of the enclosed system. For paraquat products, the mandated transition to closed Public Comments Syngenta Crop Protection, LLC Docket: EPA–HQ–OPP–2011–0855 December 16, 2019 Page 16 systems does not include a reduction in the extensive PPE mandated by the current labels.

EPA Response: The agency occupational handler assessment intentionally presented risks to all levels of personal protection, as well as the closed system, to account for occupational handler exposure scenarios and associated risks which do not fall under the mandated transition to closed system; i.e., bulk containers greater than 120 gallons or mixing/loading/applying exposure scenarios for which a closed system is not a feasible option.

The Dislodging of Paraquat Residues from Plants (Syngenta Crop Protection)
The physico-chemical properties of paraquat result in rapid foliar adsorption and any remaining surface residues would strongly adhere to plant surfaces. The dislodging of these residues would be minimal under the mild conditions utilized in DFR studies. In the absence of DFR/DBR data for paraquat, the

Agency has utilized field crop trial residue data for qualitative characterization of paraquat post application exposure risks.

EPA Response: In the absence of DFR or DBR exposure data, HED policy is to rely on a default transfer value of 25% from foliar surfaces. While this value may overestimate residues transferring from foliar surfaces following paraquat application, the agency has no other data from which to rely to refine this estimate. Therefore, DFR/DBR data were recommended to refine the occupational post-application risk estimates.

Alfalfa Maximum Application Rate (Syngenta Crop Protection)
The agency's risk calculations were based upon a single maximum application rate for alfalfa of 1.5 lb paraquat cation/Acre. This application rate is higher than the maximum allowed single application rate for alfalfa on Syngenta paraquat products which is 1.0 lb paraquat cation/Acre.

EPA Response: For the purpose of occupational risk assessment, HED uses the maximum application rate for all crops in consideration of all products and pesticide registrants. While the Syngenta product is registered for alfalfa use at a maximum application rate of 1.0 lb cation/A, the special local need (SLN) registrations CO170001 and WY140004 associated with product EPA Reg. No. 66222-130 allow for a maximum application rate of 1.5 lb cation/A.

Changes in Cotton Harvest Technologies (Syngenta Crop Protection)
While the Agency has acknowledged cotton harvest practice is moving to these new mechanized approaches, the risk assessments for post-application harvest activities in the draft risk assessments were driven by the older higher exposure manual practices that despite becoming obsolete, were still assessed.

EPA Response: As described in the responses to the National Cotton Council public comments, "EPA's assessment of occupational post-application exposures and risks from cotton harvesting are based on transfer coefficient (TC) data derived from a study which measured exposures resulting from conventional harvest practice and associated activities. The paraquat occupational post-application assessment also considered the submission of summary information from a 2016 survey by the National Cotton Council[4] and an October 18, 2018 meeting with OPP and the National Cotton Council. While this information suggests that technology is moving increasingly toward the newer mini-module harvesters, the conventional harvest practice remains in use by approximately half of the study participants. EPA acknowledges that the newer mini-module harvester, as well as new technologies such as closed cab filtered air conditioners, may reduce potential worker exposures from cotton harvest. However, 1) EPA is limited to the conventional harvest TC exposure data and 2) the EPA assessment is protective for cotton harvest workers using the conventional harvest equipment (i.e., EPA cannot assume that all cotton harvest is conducted with either conventional harvest practice equipment employing new technologies, or conducted with the newer mini-module harvester)."

Human Flagger Assessment Is Not Practical (Syngenta Crop Protection)
From a practical standpoint, the use of human flaggers for aerial applications is exceptionally low and as referenced in Agency's assessment was determined by National Agricultural Aviation Association (NAAA) to have fallen to 1% in 2012. In the pending label amendment for Gramoxone 3Lb, the use of human flaggers for aerial applications of paraquat will be prohibited.

EPA Response: Per the paraquat HHRA, "The Agency matches quantitative occupational exposure assessment with appropriate characterization of exposure potential. While the agency presents

[4] Steve Hensley. Response: Docket ID Number EPA-HQ-OPP-2012-0167. 04/30/2018.

quantitative risk estimates for human flaggers where appropriate, agricultural aviation has changed dramatically over the past two decades. According to the 2012 National Agricultural Aviation Association (NAAA) survey of their membership, the use of GPS for swath guidance in agricultural aviation has grown steadily from the mid 1990's. Over the same time period, the use of human flaggers for aerial pesticide applications has decreased steadily from ~15% in the late 1990's to only 1% in the most recent (2012) NAAA survey. The Agency will continue to monitor all available information sources to best assess and characterize the exposure potential for human flaggers in agricultural aerial applications."

Enclosed Airplane Cockpit Exposures (Syngenta Crop Protection)
The use of enclosed cockpits and cabs for applicators reduces the potential for exposure to application sprays and for a low volatility product like paraquat, there would be no potential for exposure to vapours. Furthermore, requiring a pilot operating in an enclosed cockpit to wear a respirator may interfere with the safe operation of the aircraft.

EPA Response: Per the paraquat HHRA, "HED has no data to assess exposures to pilots using open cockpits. The only data available is for exposure to pilots in enclosed cockpits. Therefore, risks to pilots are assessed using the engineering control (enclosed cockpits) and baseline attire (long-sleeve shirt, long pants, shoes, and socks); per the Agency's Worker Protection Standard stipulations for engineering controls, pilots are not required to wear protective gloves for the duration of the application." The HHRA did not quantify exposures to pilots wearing a respirator as a risk mitigation option.

VI. Tolerances and Residue Chemistry

Table 2.2.2 Contains Several Discrepancies that Require Clarification (Washington State Department of Agriculture)

The Washington State Department of Agriculture (WSDA) identified several discrepancies and misprints in Table 2.2.2 of the HHRA. The agency provides the following corrections and clarifications in response to their comments pertaining to the tolerances (in italics):

1) *In Table 2.2.2. Summary of Paraquat Established and Recommended Tolerances for Registration Review, the following seem inconsistent: Cotton, gin byproducts—the established tolerance was 110.0, the revised tolerance is 100, and the reason is "Corrected value to be consistent with OECD Rounding Class." Shouldn't the revised value be 110 (instead of 100) to be consistent with the OECD Rounding Class? The assumption is made that the tolerances are listed in parts per million (ppm) but this is not clearly stated. Are the tolerances listed supposed to be ppm? Endive—the established tolerance was 0.05, the revised tolerance is 0.07, but there is no explanation of this change in the comments field.*

   EPA Response: The correct cotton gin byproducts tolerance is 150 parts-per-million (ppm) following Organisation for Economic Co-operation and Development (OECD) Maximum Residue Level (MRL) Calculator input. There will be a listing for ppm added to columns for tolerance value. The endive tolerance will remain at 0.05 ppm.

2) *In Table 2.2.2. Summary of Paraquat Established and Recommended Tolerances for Registration Review, the following seem inconsistent: Spanish lime-- the established tolerance was 0.05, but there is no revised tolerance, and no comment. Has the tolerance for this commodity been revoked or has it been combined into another commodity group? Sugar apple-- the established tolerance was 0.05, but there is no revised tolerance, and no comment. Has the tolerance for this commodity been revoked or has it been combined into another commodity group?*

EPA Response: There are no changes to the established tolerances for Spanish lime and sugar apple. A comment will be added to the table explaining the revised tolerances are identical to the established tolerances.

3) *In Table 2.2.2. Summary of Paraquat Established and Recommended Tolerances for Registration Review, the following seems inconsistent: Wheat, forage-- the established tolerance was 0.5, the revised tolerance is 0.5. There does not appear to be a change, however "Corrected value to be consistent with OECD Rounding Class" is stated in the comments field. Is there supposed to be a different value?*

EPA Response: The comment "Corrected value to be consistent with OECD Rounding Class" was provided erroneously for the wheat, forage tolerance and will be removed.

The EPA Should Require Analytical Standards for Enforcement (Beyond Pesticides)
Analytical standards for paraquat need to be submitted because an enforcement analytical method is required.

EPA Response: The agency identified this as a deficiency in the HHRA and Syngenta has committed to submitting the standards in their comment.

VII. General Editorial Comments (Washington State Department of Agriculture)

Paraquat dichloride is incorrectly identified as an insecticide. It is an herbicide.

EPA Response: The agency thanks the WSDA for their comment and will correct this error.

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EXHIBIT B

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Pesticide use and incident Parkinson's disease in a cohort of farmers and their spouses

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ABSTRACT

Background: Extensive literature suggests an association between general pesticide use and Parkinson's disease (PD). However, with few exceptions, little is known about associations between specific pesticides and PD.
Objective: We evaluated use of pesticides and incident PD in 38,274 pesticide applicators and 27,836 of their spouses in the Agricultural Health Study cohort followed over 20 years.
Methods: We used self-reported information on ever-use of 50 specific pesticides as of enrollment for both applicators and spouses, and considered intensity-weighted lifetime days (IWLD) reported at enrollment and through the first 5-year follow-up among applicators. We estimated covariate-adjusted hazard ratios (HR) and 95% confidence intervals (CI) using Cox regression. We also examined heterogeneity in associations by history of head injury and chemical resistant glove use.
Results: A total of 373 applicators and 118 spouses self-reported incident doctor-diagnosed PD. Ever-use of the insecticide terbufos (HR:1.31, 95%CI:1.02–1.68) and the herbicides trifluralin (HR:1.29, 95%CI: 0.99–1.70) and 2,4,5-T (HR:1.57, 95%CI:1.21–2.04) was associated with elevated PD risk. On the other hand, diazinon (HR:0.73, 95%CI: 0.58–0.94) and 2,4,5-TP (HR:0.39, 95%CI:0.25–0.62) were associated with reduced risk. We observed heterogeneity in ever-use associations by head injury and chemical-resistant glove use for some pesticides, with higher risk among those who reported a history of head injury, or who did not use gloves. PD risk was also elevated for applicators in the highest category of IWLD for dichlorvos, permethrin (animal use), and benomyl.
Conclusions: We found evidence of increased PD risk for some pesticides. Our results also suggest higher susceptibility for pesticide-associated PD among individuals with head injury as well as protection with use of chemical resistant gloves, although further research is needed to understand the impact of head injury. Research on current and newer pesticides, including mechanisms relevant to PD, is important given widespread pesticide use.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting around 1–2% of adults over the age of 65 years (Hirtz et al., 2007). PD is associated with substantial economic burden (Kowal et al., 2013) which is likely to increase with the aging of the population (US Administration on Aging, 2012). Many pesticides are neurotoxic, and some epidemiologic studies have linked general pesticide use with PD (Goldman et al., 2017; Pezzoli and Cereda, 2013; van der Mark et al., 2012). Although most of these studies evaluated functional (i.e., fungicides, insecticides, and herbicides) or chemical (i.e., organochlorine or organophosphate insecticides) classes, rather than

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individual pesticides, some evidence from human and toxicological studies points to associations of PD with the insecticides dieldrin and rotenone and with the herbicides 2,4-dichlorophenoxyacetic acid (2, 4-D) and paraquat (Goldman et al., 2017; Kanthasamy et al., 2005; Tanner et al. 2009, 2011; Weisskopf et al., 2010). Given that some of these and other pesticides continue to be widely used, with annual usage of all pesticides totaling over one billion pounds in the United States (US) alone (Atwood and Paisley-Jones, 2017), identifying links between specific pesticides and PD can have important implications.

The Agricultural Health Study (AHS) is a prospective cohort study of farming populations from North Carolina and Iowa (Alavanja et al., 1996), with follow-up ongoing for over 20 years. Two previous investigations on pesticides and PD were conducted in the AHS. The first included data from the full cohort and examined pesticide exposure data collected at enrollment in relation to self-reported PD through the first study follow-up, approximately 5 years later (Kamel et al., 2007). The second effort, the Farming and Movement Evaluation (FAME) study, was a case-control study nested within the cohort, which assessed PD cases through the first follow-up, but with self-reported PD confirmed by in-person assessment by movement disorder specialists and with collection of additional exposure data for specific pesticides (identified *a priori*) including some not well covered in the original AHS surveys (Tanner et al., 2011). Since then, self-reported incident PD was ascertained in two additional follow-up surveys. A recent update of mortality in the AHS found that pesticide applicators experience higher than expected mortality from PD than the general populations of Iowa and North Carolina, indirectly implicating farming exposures including pesticides (Shrestha et al., 2019a). Therefore, with additional PD cases identified from extended follow-up as well as updated exposure data, we examined associations between individual pesticides and incident PD that occurred over 20 years of follow-up among private pesticide applicators and their spouses.

2. Material and methods

2.1. Study population

The AHS is described in detail elsewhere (Alavanja et al., 1996). In 1993–1997 (Phase 1), 52,394 private pesticide applicators (97.4% male, mainly farmers) completed an enrollment questionnaire at pesticide licensing locations (see Supplemental Fig. 1 for study timeline). A take-home questionnaire requesting additional pesticide use information, was completed by 22,916 (44% of those who enrolled). Applicators were also given a questionnaire to be filled out by their spouses; 32,345 spouses (75% of married spouses, 99.3% female) enrolled in the study. Enrollment questionnaires were self-administered. Computer-assisted follow-up telephone interviews were conducted in 1999–2003 (Phase 2) and 2005–2010 (Phase 3). Participants completed either self-administered mailed questionnaires or computer-assisted telephone interviews in 2013–2016 (Phase 4). Questionnaires can be found at https://aghealth.nih.gov/collaboration/questionnaires.html. The Phase 2 survey was completed by 33,456 applicators and 23,796 spouses, Phase 3 by 24,170 applicators and 19,959 spouses, and Phase 4 by 24, 145 applicators and 18,186 spouses. The institutional review boards of the National Institute of Environmental Health Sciences and the National Cancer Institute approved the study.

2.2. Pesticide use

The applicator enrollment questionnaire asked about ever-use of 50 pesticides, and duration and frequency of use for 22 specific pesticides. The applicator take-home questionnaire asked participants to provide duration and frequency of use for the remaining 28 pesticides, and to complete a checklist of ever-use of additional specific pesticides ("other pesticides used") that were not covered in the enrollment questionnaire. Our current analysis focuses on the 50 pesticides for which detailed information on duration and frequency of use were collected either in the enrollment or the take-home questionnaire (although other pesticides were considered in some analyses as noted). These questionnaires also sought detailed information on pesticide use practices including application methods, mixing processes, personal protective equipment use, and other workplace hygiene factors. The enrollment questionnaire asked applicators what type of personal protective equipment they generally wore when they personally handled pesticides, including respirator/gas mask, fabric/leather gloves, and chemical-resistant gloves. The enrollment spouse questionnaire only asked about ever-use of the 50 specific pesticides. All participants were asked about their overall use of any pesticides, including years and days personally mixed or applied pesticides.

We also used pesticide information collected at Phase 2 (conducted 2–10 years after enrollment, 5 years on average). At this interview, applicators and spouses were asked to provide the names and number of days of use of specific pesticides in the year prior to the interview (or most recent year used) and information on pesticide use practices. Although the Phase 2 interview asked only about pesticide use in the most recent year, when estimating cumulative exposure, we assumed that year represented pesticide use during the period since the Phase 1 exposure assessment.

We used several approaches to characterize pesticide exposures. First, we examined ever-use of the 50 specific pesticides. Exposure intensity weights were previously derived using an algorithm that incorporates information on mixing practices, application methods, repair status, and personal protective equipment use (Coble et al., 2011). We then used intensity-weighted lifetime days (IWLD) of pesticide use (i.e., the product of years of use and days used per year weighted by exposure intensity) as a measure of cumulative exposure for applicators. IWLD days were categorized using cut-points based on the exposure distribution of the full sample and number of PD cases (i.e., at least five cases) in each exposure category. Specifically, we created a four-category exposure variable (never use and three categories among users with cut-points at tertiles of IWLD). When sample size was limited, we created a three-category variable by cutting at the median of IWLD. As only applicators were asked about duration and frequency of use of specific pesticides in Phase 1, the IWLD analyses were limited to the applicators. We further restricted these analyses to male applicators due to the small number of female applicators.

In addition to examining individual pesticides, we created two ever-use pesticide groups based on potential mechanisms implicated in PD pathogenesis. The first group included use of any pesticides linked to mitochondrial complex I inhibition (namely, benomyl, permethrin, rotenone, dichlorvos, and thiabendazole) (Binukumar et al., 2010; Tanner et al., 2011); the second group included pesticides linked to aldehyde dehydrogenase inhibition (namely, benomyl, captan, folpet, aldrin, dieldrin, mancozeb/maneb, ferbam, thiram and ziram) (Fitzmaurice et al. 2013, 2014). Some pesticides of interest, including rotenone, thiabendazole, folpet, ferbam, and thiram, were not among the 50 main pesticides queried at enrollment and were only asked of applicators (not spouses) on the checklist of "other pesticides used" in the Phase 1 take home questionnaire. Although both applicators and spouses could have reported their use in the Phase 2 open-ended survey, we considered only Phase 1 exposures for these analyses to maximize the analytical sample with complete information on these pesticides and for analytical simplicity. To accommodate the fact that not all participants provided data and only a portion completed the take-home questionnaire, we conducted analyses (that focused on Phase 1 exposures only) in two different analytical subsets. We first considered only those participants with complete data on all individual pesticides in a group (so, the analysis was limited to the male applicators who returned the take-home questionnaire). In a secondary analysis in the overall sample, we considered participants as exposed if they indicated they used *at least one* of the pesticides in the group, regardless of missing information on other pesticides in that group.

2.3. Parkinson's disease

Potential PD cases were identified by self-report in all AHS surveys (i.e., positive response to "has a doctor ever told you that you had been diagnosed with Parkinson's disease?), as well as via linkage to the National Death Index and state death registries (with PD recorded as an underlying or contributing cause of death). Self-reported PD cases identified through Phase 2 were previously confirmed by movement disorder specialists as a part of the FAME study, via structured clinical examinations and medical records; self-reported PD was confirmed in 84% (Tanner et al., 2011). Between 2012 and 2017 (around and following the Phase 4 survey), we attempted to validate all potential PD cases (prevalent as well as incident), including those considered PD cases in FAME (n = 810). Briefly, each participant with potential PD, or their proxy (if deceased or too ill), was asked to complete a detailed screening questionnaire on PD diagnosis, symptoms, characteristics, and treatment. We also requested consent to obtain medical records from their treating or diagnosing physician. Screeners were obtained for 510 prevalent and incident cases. The PD screeners were evaluated by a movement disorder specialist to adjudicate PD status using criteria analogous to clinical diagnostic criteria proposed by Gelb et al. (1999). This evaluation classified 75% as probable or possible PD, 11% as questionable or other neurological disorders, and 14% as not having PD. Among those for whom medical records were obtained (n = 65), 91% were confirmed as PD by medical records and 9% were considered questionable (because of conflicting information from multiple physicians and/or physician's reporting of inadequate evidence to distinguish from other neurological disorders).

After excluding self-reported prevalent cases (age at diagnosis ≤ age at enrollment) and those with no information on age at diagnosis, we had 598 eligible incident potential cases (440 with and 158 without screener data; Supplemental Fig. 2). We excluded cases without supporting PD symptoms or medications (99 of 440 participants screened) and those who did not provide consistent responses across surveys (8 of the 158 without screener information), leaving 491 cases for analysis. Overall, 80.6% of the 491 cases had some confirmatory information from a validation screener, medical record, FAME evaluation, or death certificate. We used the age at diagnosis provided at the earliest survey in which age at diagnosis was reported.

2.4. Study sample

Participants eligible for our analysis included a total of 38,798 applicators and 28,238 spouses who completed at least one follow-up survey or the PD validation screening questionnaire (Fig. 1). After excluding prevalent cases, those with inconsistent PD information across surveys, or those lacking other supporting information, we had 38,274 applicators and 27,836 spouses for ever-use of pesticides analyses (n = 66,110; 491 with PD). For IWLD analyses of the 22 pesticides for which frequency and duration of use were asked in the enrollment questionnaire, the final sample size included 37,284 male applicators (372 PD cases) and for the 28 pesticides for which frequency and duration of use were asked in the take-home questionnaire, the final sample size included 19,068 male applicators (237 PD cases).

2.5. Statistical analysis

2.5.1. Pesticide use at enrollment

We first examined bivariate relations of incident PD with baseline covariates that included applicator status, sex, state of residence, cigarette smoking, alcohol consumption, and education. We used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (95% CI) for associations between pesticide use reported at enrollment and incident PD. We used attained age as the time scale with left truncation at enrollment and always adjusted for sex, state of residence, smoking status, and education. Models for individual pesticides were additionally adjusted for the top four pesticides among those whose Spearman correlation with the pesticide of interest was 0.40 or greater. Whenever the proportional hazards assumption failed for a pesticide (p-value for interaction between age and pesticide ≤ 0.10), we allowed hazards to vary by the median age (63 years). Ever-use analyses were conducted in a combined sample of applicators and spouses, and separately for male applicators (n = 37,284) and female spouses (n = 27,673) (female applicators and male spouses, respectively, were excluded from these analyses due to small numbers). In the IWLD analyses among male applicators, we conducted a test for trend using the median value for each exposure category as an ordinal variable in regression models.

Information on smoking (n = 691) and education (n = 2474) was missing for some participants, and further, some participants reported 'something else' for education (n = 2625). We treated 'something else'

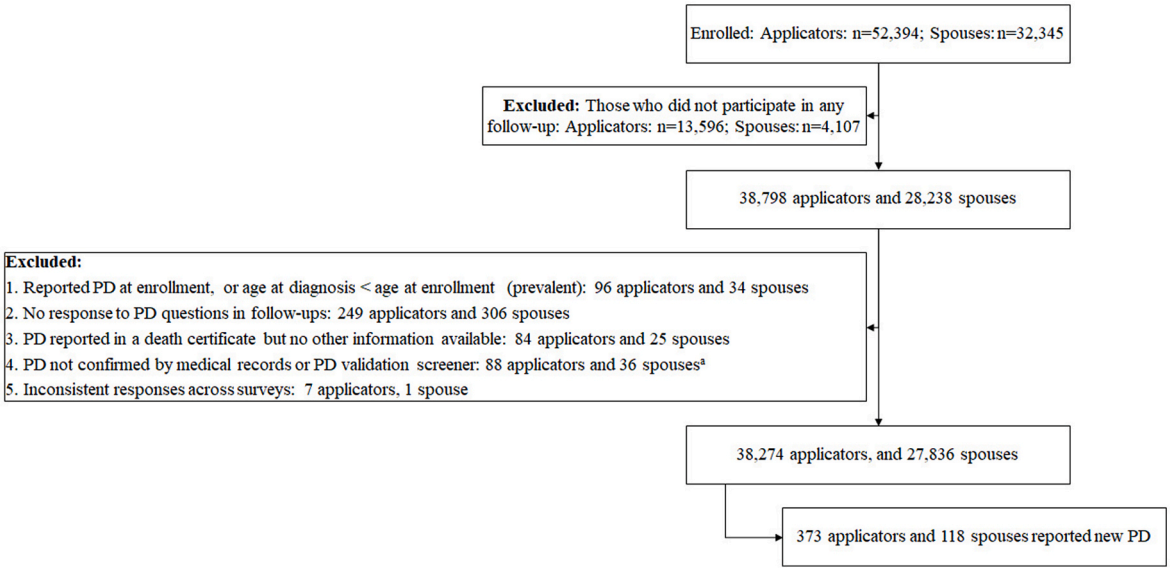

Fig. 1. Sample selection for pesticide and Parkinson's disease (PD) analysis in the Agricultural Health Study. [a]includes n = 2 spouses selected for validation based on FAME screening who did not report PD.

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as a missing covariate and used multiple imputation to impute missing covariates (i.e., education and smoking). We created five imputed datasets, performed regression analysis in each dataset, and combined those results to estimate parameters and their standard errors using SAS PROC MIANALYZE (SAS Institute Inc, 2015).

Wearing chemical-resistant gloves was previously shown to modify PD associations with some pesticides (Furlong et al., 2015). Further, individuals with head injury may be more susceptible to pesticide-associated PD risk – the underlying hypothesis being combinations of risk factors acting in concert increase disease vulnerability (the "multiple-hit hypothesis") (Lee et al., 2012). We examined potential heterogeneity in the associations of PD with ever-use of pesticides by these characteristics (by testing for the interaction between pesticides and these characteristics), when each cross-classified category of exposure and factor contained at least five cases. Applicators were asked about a history of head injury requiring medical attention only in the take-home questionnaire, whereas all spouses were asked about head injury, and thus heterogeneity by head injury was evaluated in a smaller subset (19,222 applicators and 26,666 spouses resulting in a total of 45,888 participants). Only applicators (in the enrollment questionnaire) but not spouses were asked about chemical resistant glove use and thus heterogeneity by chemical resistant glove use was evaluated in male applicators only (n = 32,816). We also stratified the analysis by follow-up time (≤10 years and >10 years) for ever-use analysis. Potential heterogeneity was not examined for IWLD due to limited sample size.

To examine the potential impact of loss-to-follow up, we performed a sensitivity analysis using inverse probability of censoring weights (Howe et al., 2016). Briefly, we used weighted Cox models to estimate HRs and 95% CIs, adjusting for covariates and using stabilized inverse probability weights. For stabilized weight estimation, first we transformed our data from a single record per person into person-year data (i.e., with multiple records per person). Then, we used logistic regression analyses to calculate the denominator of the weights, or probability of overall participation in Phase 4 conditional on exposure, year and baseline covariates (age, sex, education, smoking, alcohol use, state of residence; missing values imputed for covariates whenever applicable), as well as to calculate the numerator of the weights, or probability of overall participation in Phase 4 conditional only on year. We estimated stabilized weights as the ratio of cumulative conditional probabilities.

Lastly, we used logistic regression to analyze two other groups of cases (i) all "confirmed" prevalent and incident PD cases (n = 66,216 with 597 PD cases), and (ii) all "potential" prevalent and incident PD cases (any self-reported cases or reported on death certificates) (n = 84,739, with 860 PD cases). Statistical significance was determined using two-sided tests with α of 0.05. We performed statistical analyses using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

2.5.2. Pesticide use through Phase 2

We also examined associations between cumulative pesticide use through Phase 2 and incident PD. However, given the lower exposure and outcome prevalence in spouses, we performed this analysis only in male applicators. About 14% of the applicators included in our analysis were missing Phase 2 exposure data due to Phase 2 non-response. To account for the missing exposure data due to non-response, we used a multiple imputation approach developed specifically for AHS applicators (Heltshe et al., 2012). This approach used information on several factors including demographics, farm characteristics, prior pesticide use, and medical conditions that predicted missingness to impute use of specific pesticides for the Phase 2 non-responders. We created five imputed datasets which were then converted to person-year datasets allowing pesticide exposure information (ever-use and IWLDs) through Phase 2 to vary until their time at risk. We applied a Cox model applied to each imputed dataset and combined those results to obtain an HR and 95% CI using SAS PROC MIANALYZE (SAS Institute Inc, 2015). This analysis was limited to the previously described 50 specific pesticides. Information on smoking and education was missing for only 1% and 4% of the sample, and we used a missing indicator category for this analysis.

3. Results

Characteristics of participants at enrollment differed by PD status (Table 1). Older participants, applicators, males, and those from North Carolina were more likely to develop PD, while current smokers and alcohol drinkers were less likely to develop PD. Chemical resistant glove use and a history of head injury requiring medical attention were similar between the two groups, although when adjusted for age, sex, state, education, and smoking status, we found an inverse association between having a head injury and incident PD (HR: 0.71, 95% CI: 0.46, 1.09).

3.1. Phase 1 pesticides

In the analysis examining lifetime days of *any* pesticide use in relation to incident PD in the overall sample, we generally observed positive HRs for higher lifetime days compared to never use, although we did not see a monotonic increasing trend (for example, HRs for the third and the fourth quartiles compared to never use were 1.27 (95% CI: 0.82, 1.98) and 1.07 (95% CI: 0.69, 1.67), respectively, Supplemental Table 1). In the female spouses only analysis, we observed increased risk (HR: 1.58,

Table 1
Characteristics of Agricultural Health Study participants at enrollment (n = 66,110).

Characteristics	No PD (n (%))[a] (n = 65,619)	Incident PD (n (%))[a] (n = 491)
Age (years)		
≤45	31,843 (48)	53 (11)
46–55	16,479 (25)	109 (22)
56–65	12,382 (19)	206 (42)
>65	4915 (7)	123 (25)
Participant		
Spouse	27,718 (42)	118 (24)
Applicator	37,901 (58)	373 (76)
Sex		
Female	28,546 (44)	117 (24)
Male	37,073 (56)	374 (76)
State of residence		
Iowa	43,319 (66)	299 (61)
North Carolina	22,300 (34)	192 (39)
Education[b]		
≤ High school graduate	31,301 (50)	300 (64)
1–3 years beyond high school	16,507 (26)	94 (20)
College graduate or more	12,732 (20)	77 (16)
Something else	2624 (4)	1 (0)
Smoking status[c]		
Never smoker	40,305 (62)	296 (61)
Former smoker	16,573 (26)	159 (33)
Current smoker	8056 (12)	30 (6)
Alcohol consumption (past 12 months)[d]		
No	23,979 (38)	221 (49)
Yes	38,420 (62)	230 (51)
Chemical resistant glove use[e]		
No	6193 (19)	65 (20)
Yes	26,299 (81)	259 (80)
Head injury requiring medical attention[f]		
No	41,911 (92)	316 (93)
Yes	3638 (8)	23 (7)

[a] % may not add to 100% due to rounding.
[b] Education missing for n = 2474.
[c] Smoking status missing for n = 691.
[d] Alcohol consumption missing for n = 3260.
[e] Chemical resistant glove use information was not sought from spouses and missing for n = 5458 applicators.
[f] Applicators provided information on head injury only in the take-home questionnaire.

95% CI: 1.00, 2.50) in those exposed to more than the median days as compared to never use. In the male applicators only analysis, associations for higher quartiles of lifetime days compared to the lowest quartile were slightly inverse. In a combined analysis of applicators and spouses (Table 2), we found positive associations for the organophosphate insecticide terbufos (HR:1.30, 95% CI: 1.02, 1.68) and the herbicides trifluralin (HR:1.29, 95% CI: 0.99, 1.70) and 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) (HR:1.57, 95% CI: 1.21, 2.04), and inverse associations for ever-use of the organophosphate insecticide diazinon (HR: 0.73, 95% CI: 0.58, 0.94), the fumigant ethylene dibromide (HR: 0.35, 95% CI: 0.14, 0.84), and the herbicide 2,4,5-TP [2,4,5-T,P, 2-(2,4,5-trichlorophenoxy) propionic acid] (HR: 0.39, 95% CI: 0.25, 0.62). These associations remained when analyses were performed separately for male applicators (Supplemental Table 2). Separate analyses for female spouses (Supplemental Table 2) were limited to only a few pesticides due to fewer PD cases; elevated (HR > 1.40), yet imprecise, risk was observed for the herbicides glyphosate, trifluralin, and cyanazine.

We found heterogeneity in associations for ever-use of some pesticides and PD risk by head injury (Table 3). We found higher PD risk for the three organochlorine insecticides chlordane, dichlorodiphenyltrichloroethane (DDT), and toxaphene, the two organophosphate insecticides diazinon and phorate, the insecticide permethrin (animal and crop use combined), the fumigant methyl bromide, and the herbicides paraquat and pendimethalin among those who reported a history of head injury as compared to reduced or null associations among those did not report a history of head injury (p for heterogeneity ≤0.10). For example, the HR for paraquat among those with a history of head injury was 3.20 (95%CI: 1.38, 7.45) versus 1.00 (95%CI: 0.71, 1.41) for those without a history (p for heterogeneity = 0.01).

Similarly, we found that five herbicides (dicamba, imazethapyr, metolachlor, trifluralin, and metribuzin) were associated with elevated PD risk among those who did not use chemical-resistant gloves as compared to reduced or null associations among glove users, although directions were reverse for metalaxyl (Table 3). In the analyses stratified by follow-up time (≤10 years and >10 years), we found that HRs for some herbicides including alachlor, butylate, chlorimuron ethyl, trifluralin, 2,4-D, and atrazine were elevated for the first 10 years of follow-up, but not for later years (Supplemental Table 3).

In the analyses examining IWLD through Phase 1 in male applicators (Table 4), we saw no clear monotonic exposure-response for pesticides associated with elevated PD risk. There were a few suggestive patterns. Specifically, we saw elevated HRs for individuals in the highest category of IWLD of the insecticides dichlorvos [HR:1.46 (95% CI: 0.98, 2.19), p-trend:0.06] and permethrin (animal use)[HR:1.44 (95% CI: 0.85, 2.44), p-trend: 0.21], and the fungicides benomyl (HR: 1.34 (95% CI: 0.64, 2.80), p-trend:0.31], captan [(HR: 1.27 (95% CI: 0.74, 2.20), p-trend:0.36], and chlorothalonil [HR: 1.29 (95% CI: 0.66, 2.56), p-trend:0.41] as compared to those who never used those pesticides, although risk estimates were very imprecise as reflected by the wide confidence intervals. For the herbicides terbufos and trifluralin (for which we observed significant positive association in the ever-use analysis), HRs were generally elevated for all tertiles as compared to never use. For heptachlor, HRs were higher for the two lower tertiles than for the upper. HRs in the higher tertiles of the insecticides aldrin, toxaphene, carbaryl, diazinon, and malathion were lower than in the never use category. The results (odds ratio estimates) were similar when we included "confirmed" prevalent cases (Supplemental Tables 4 and 5), or any "potential" PD cases (data not shown). The HR estimates using inverse probability weights were also similar (Supplemental Table 6).

In the male applicators returning take-home questionnaires, none of the pesticide groups – mitochondrial complex I inhibitors [HR: 0.96 (95%CI: 0.71, 1.29)] or aldehyde dehydrogenase inhibitors [(HR: 0.84 (95%CI: 0.65, 1.11)] – were associated with increased PD risk, although we observed heterogeneity by head injury for ever-use of mitochondrial complex I inhibitors with higher HR among those who experienced head injury [HR: 2.42 (95%CI: 0.91, 6.47)] vs reduced HR among those

Table 2
Ever-use of pesticide reported at enrollment and Parkinson's disease (PD) risk in all participants (n = 66,110).

Pesticide	No PD, n (%)[a]	PD, n (%)[b]	HR (95% CI)[c]
Organochlorine insecticide			
Aldrin	6507 (11.1)	98 (23.7)	0.91 (0.68, 1.23)
Chlordane	9758 (16.5)	125 (29.8)	1.05 (0.82, 1.34)
Dieldrin	2440 (4.1)	38 (9.2)	0.88 (0.60, 1.30)
DDT	8954 (15.4)	143 (34.8)	0.86 (0.67, 1.12)
Heptachlor	5442 (9.4)	87 (21.3)	1.01 (0.74, 1.38)
Toxaphene	5160 (8.7)	59 (14.1)	0.80 (0.60, 1.08)
Lindane	7250 (12.1)	74 (17.7)	0.92 (0.71, 1.19)
Carbamate insecticide			
Aldicarb	3809 (6.5)	28 (6.9)	1.05 (0.68, 1.62)
Carbaryl	27,180 (45.5)	231 (55.4)	1.09 (0.87, 1.37)
Carbofuran	10,017 (16.7)	110 (26.6)	0.95 (0.74, 1.21)
Organophosphate insecticide			
Chlorpyrifos	16,700 (26.8)	143 (30.7)	0.92 (0.74, 1.13)
Coumaphos	3423 (5.7)	35 (8.4)	1.04 (0.73, 1.47)
Diazinon	13,979 (23.3)	105 (25.1)	0.73 (0.58, 0.94)
Dichlorvos	4425 (7.3)	48 (11.5)	1.12 (0.83, 1.53)
Fonofos	8219 (13.6)	75 (17.7)	0.91 (0.70, 1.19)
Malathion	28,496 (48.7)	253 (62.6)	1.01 (0.78, 1.30)
Parathion	5661 (9.5)	62 (14.8)	0.98 (0.74, 1.30)
Phorate (≤63 y)[d]	5618 (18)	39 (36.1)	1.33 (0.85, 2.08)
>63 y	5786 (22.1)	73 (26.1)	0.71 (0.52, 0.97)
Terbufos	13,718 (23.8)	138 (35.4)	1.30 (1.02, 1.68)
Permethrin insecticide			
Permethrin (Crops)	5263 (8.8)	36 (8.8)	0.99 (0.70, 1.40)
Permethrin (Animals)	5696 (9.4)	41 (9.8)	1.07 (0.77, 1.48)
Fumigant			
Carbon disulfide/Carbon tetrachloride	2099 (3.5)	31 (7.3)	1.03 (0.71, 1.50)
Aluminum phosphide	1707 (2.8)	16 (3.8)	1.08 (0.65, 1.78)
Ethylene dibromide	1294 (2.2)	5 (1.2)	0.35 (0.14, 0.84)
Methyl bromide	5707 (9.5)	46 (10.8)	0.86 (0.59, 1.25)
Fungicide			
Benomyl[e]	*3492 (6)*	*26 (6.4)*	*0.80 (0.48, 1.31)*
Benomyl (≤ 63y)[d, e]	*1664 (5.3)*	*4 (3.6)*	*0.35(0.11, 1.10)*
> 63y	*1828 (6.8)*	*22 (7.5)*	*0.99 (0.58, 1.68)*
Captan	4617 (7.7)	33 (8)	0.84 (0.59, 1.20)
Chlorothalonil	2899 (4.8)	21 (5)	0.97 (0.59, 1.60)
Maneb (≤63 y)[d]	1685 (5.2)	8 (7)	1.43 (0.63, 3.22)
>63 y	2030 (7.3)	21 (7)	0.75 (0.44, 1.25)
Metalaxyl	7968 (13.6)	58 (14.3)	0.85 (0.61, 1.18)
Herbicide			
Alachlor	19,057 (32.1)	187 (45.6)	1.13 (0.88, 1.45)
Butylate (≤63 y)[d]	5750 (18.3)	38 (34.9)	1.31 (0.86, 2.01)
>63 y	5245 (19.7)	65 (23.4)	0.87 (0.64, 1.20)
Chlorimuron ethyl	12,693 (21.8)	101 (25.6)	1.04 (0.80, 1.36)
Dicamba	17,945 (31)	161 (41.2)	0.94 (0.72, 1.22)
EPTC	7049 (12.2)	54 (14.1)	0.84 (0.61, 1.15)
Glyphosate	35,406 (58.6)	291 (67.4)	1.10 (0.87, 1.39)
Imazethapyr	15,124 (26.3)	126 (32.6)	1.04 (0.79, 1.37)
Metolachlor	16,114 (27.9)	127 (32.6)	0.80 (0.62, 1.03)
Paraquat	8526 (14.2)	87 (20.4)	1.09 (0.84, 1.41)
Pendimethalin	15,250 (26.1)	127 (31.9)	1.07 (0.83, 1.37)
Petroleum distillate	16,756 (28.9)	146 (37)	0.93 (0.73, 1.18)
Trifluralin	18,665 (32.2)	182 (46.8)	1.29 (0.99, 1.70)
2,4-D	28,871 (49.8)	262 (66.7)	1.06 (0.79, 1.43)
2,4,5-T	7264 (12.5)	116 (28.3)	1.57 (1.21, 2.04)
2,4,5-TP	3287 (5.5)	23 (5.5)	0.39 (0.25, 0.62)
Atrazine	25,297 (42.8)	237 (58.2)	1.03 (0.77, 1.38)
Cyanazine	14,641 (25.2)	133 (33.6)	0.90 (0.69, 1.18)
Metribuzin	15,500 (26.8)	137 (35.7)	0.86 (0.65, 1.14)

Abbreviation: 2,4-D, 2,4-Dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-Trichlorophenoxyacetic acid; 2,4,5-T,P, 2-(2,4,5-trichlorophenoxy) propionic acid; CI, Confidence Intervals; DDT, Dichlorodiphenyltrichloroethane; EPTC, S-Ethyl dipropylthiocarbamate; HR, Hazard Ratio; PD, Parkinson's disease.

[a] Exposed individuals who did not develop PD.

[b] Exposed individuals who developed PD.

[c] HR adjusted for sex, state of residence, smoking status, education, and ever-use of correlated pesticides (other pesticides whose ever-use variable had Spearman correlation ≥ 0.40 with the ever-use variable of the target pesticide).

[d] Hazard ratio allowed to vary by the median age (i.e., 63 years) for pesticides that did not meet proportional hazards assumption (p ≤ 0.10).

[e] Proportional hazards assumption did not meet for those in italics, but there was not adequate sample size meeting the criteria of at least five exposed cases in cross-classified categories.

without head injury [HR: 0.83 (95%CI: 0.61, 1.12), p for heterogeneity: 0.04]. The results were similar (i.e., no independent associations for the pesticide groups but heterogeneity by head injury for the mitochondrial complex I inhibitors), when we also considered participants as exposed if they indicated they used *at least one* individual pesticide in the group in the overall sample.

3.2. Pesticide exposure through Phase 2

Among male applicators, associations between ever-use of individual pesticides through Phase 2 were similar to the results using information reported at enrollment; specifically, PD risk was reduced among those who ever-used diazinon, ethylene dibromide, and 2,4,5-TP, and elevated among those who ever-used terbufos, 2,4,5-T, and trifluralin (Supplemental Table 7). Results that used IWLD through Phase 2 were also similar (Table 4).

4. Discussion

In this study, we found that ever-use of the insecticide terbufos and the herbicides trifluralin and 2,4,5-T was associated with elevated PD risk. Positive associations of PD with ever-use of the herbicides trifluralin and 2,4,5-T are consistent with the prior AHS-wide analysis based on 78 self-reported incident PD cases identified through Phase 2 (Kamel et al., 2007). We also found lower PD risk for ever-use of some pesticides including diazinon and 2,4,5-TP. In IWLD analyses, however, we did not see evident monotonic exposure response gradients for these pesticides, although HRs for higher exposure categories reflected findings of ever-use analyses. We observed heterogeneity in the pesticide-PD associations by head injury and chemical-resistant gloves use, indicating higher PD risk for use of certain organochlorine insecticides (chlordane, DDT, and toxaphene), organophosphate insecticides (diazinon and phorate), insecticide permethrin, and herbicides (paraquat and pendimethalin) among those who reported head injury and for use of certain herbicides (dicamba, imazethapyr, and trifluralin) among those who did not use chemical-resistant gloves.

To the best of our knowledge, no studies have linked the insecticide terbufos with PD, although a few prior studies have linked other individual organophosphate insecticides that also act by inhibiting the enzyme acetylcholinesterase with PD (Gatto et al., 2009; Wang et al., 2014). We also found elevated PD risk in AHS applicators who were exposed to higher IWLD of the organophosphate insecticide dichlorvos. Chronic dichlorvos exposure in rats has been shown to induce degeneration of nigrostriatal dopaminergic neurons and alpha-synuclein aggregation, the hallmarks of PD pathogenesis, as well as to inhibit mitochondrial complexes and alter mitochondrial structures (Binukumar et al., 2010). We are aware of only one study on dichlorvos and PD, and in that study, individuals in the lower, although not the highest, exposure-day category of dichlorvos had elevated PD risk as compared to the individuals who were never exposed (van der Mark et al., 2014). On the other hand, we saw an inverse association between the organophosphate insecticide diazinon and PD risk in the overall sample and among those without head injury but saw elevated yet not statistically significant risk among those with head injury. A few prior studies, although not all, have linked diazinon with increased PD risk (Firestone et al., 2010; Gatto et al., 2009; Narayan et al., 2013). We observed

Table 3
Ever-use of pesticides reported at enrollment and Parkinson's disease (PD) risk by head injury status and chemical resistant glove use.

Pesticide	Head injury	Exposed/Unexposed PD cases	HR (95% CI)[a]	P[b]
Chlordane	No	77/206	1.10 (0.81, 1.51)	0.01
	Yes	16/6	4.08 (1.58, 10.55)	
Diazinon	No	57/223	0.64 (0.47, 0.88)	0.07
	Yes	10/11	1.48 (0.62, 3.51)	
DDT	No	87/189	0.86 (0.62, 1.19)	0.06
	Yes	15/7	2.12 (0.85, 5.31)	
Methyl bromide	No	22/265	0.67 (0.40, 1.11)	0.01
	Yes	6/15	2.85 (1.06, 7.65)	
Paraquat	No	45/239	1.00 (0.71, 1.41)	0.01
	Yes	10/12	3.20 (1.38, 7.45)	
Pendimethalin	No	65/207	0.90 (0.65, 1.25)	0.03
	Yes	10/6	2.85 (1.02, 7.91)	
Permethrin (animal and crop use combined)	No	33/260	0.79 (0.54, 1.14)	0.08
	Yes	6/12	2.04 (0.76, 5.44)	
Phorate	No	60/205	0.74 (0.53, 1.04)	0.03
	Yes	10/6	2.47 (0.89, 6.89)	
Toxaphene	No	31/248	0.69 (0.46, 1.03)	0.08
	Yes	7/15	1.64 (0.66, 4.04)	
	Chemical resistant glove[c]			
Dicamba	No	21/20	2.10 (1.11, 3.98)	0.008
	Yes	127/100	0.85 (0.63, 1.15)	
Imazethapyr	No	18/23	3.34 (1.75, 6.39)	0.0002
	Yes	100/127	0.92 (0.69, 1.24)	
Metalaxyl	No	8/39	0.44 (0.20, 0.96)	0.05
	Yes	48/191	1.00 (0.70, 1.43)	
Metolachlor	No	18/26	1.60 (0.88, 2.94)	0.01
	Yes	98/132	0.70 (0.54, 0.91)	
Metribuzin	No	17/25	1.48 (0.78, 2.81)	0.06
	Yes	110/109	0.78 (0.58, 1.06)	
Trifluralin	No	25/18	2.64 (1.42, 4.92)	0.03
	Yes	144/80	1.24 (0.91, 1.68)	

Abbreviation: CI, Confidence Intervals; DDT, Dichlorodiphenyltrichloroethane; HR, Hazard Ratio; PD, Parkinson's disease.

[a] HR adjusted for state of residence, smoking status, education, and ever-use of correlated pesticides (other pesticides whose ever-use variable had Spearman correlation ≥ 0.40 with the ever-use variable of the target pesticide); HR for head injury also adjusted for sex.

[b] P-value for test for heterogeneity.

[c] Male applicators only.

similar heterogeneity by head injury for the organophosphate phorate. One prior study has reported an association between phorate exposure and elevated PD risk (Wang et al., 2014). Apart from a common pathway for pesticidal action, i.e., inhibition of acetylcholinesterase, individual organophosphate insecticides may exert neurotoxicity through a wide range of mechanisms including oxidative stress and neuroinflammation (Terry, 2012) resulting in varying degrees of toxicity. We are uncertain, however, about the reasons underlying the observed inverse association for some pesticides in the overall sample or among those without head injury.

Besides the prior AHS reports (Furlong et al., 2015; Kamel et al., 2007), we are not aware of other epidemiologic evidence linking the herbicides trifluralin and 2,4,5-T and PD, although an *in vitro* study has shown that trifluralin accelerates the formation of alpha-synuclein fibrils, a finding relevant to PD pathogenesis (Uversky et al., 2002). In another analysis, AHS applicators who experienced high pesticide exposure events involving trifluralin were also more likely to report olfactory impairment, one of the important prodromal symptoms of PD (Shrestha et al., 2019b). To our knowledge, the only other study (based on only four and seven exposed cases and controls respectively) that examined 2,4,5-T in relation to PD did not find any association (Dhillon et al., 2008). We found that the herbicide dicamba was associated with increased PD risk among those who did not use chemical-resistant gloves during handling of pesticides. Dicamba, structurally similar to the phenoxy herbicide 2,4,5-T (Bradberry et al., 2004), was associated with increased, although statistically non-significant, PD risk in the prior AHS investigation in the overall sample (Kamel et al., 2007). We observed an unexpected inverse association with the herbicide 2,4,5-TP, another phenoxy pesticide structurally similar to 2,4,5-T. Use of both 2,4,5-T and 2,4,5-TP was suspended in the US in 1979 due to potential contamination by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and associated health concerns (Gintautas et al., 1992; Lilienfeld and Gallo, 1989; Ware, 1988).

We found that ever-use of certain individual pesticides and the pesticide group mitochondrial complex I inhibitors was associated with increased PD risk among those who reported a history of head injury requiring medical attention, although head injury itself was not independently associated with elevated PD risk. While sequelae of traumatic brain injury, including microglial activation, alpha-synuclein aggregation, mitochondrial dysfunction, and other chronic inflammatory responses have been suggested as potential mechanisms for PD predisposition (Acosta et al., 2015; Hutson et al., 2011; Lifshitz et al., 2004; Loane et al., 2014), findings of prior epidemiologic studies on head injury and PD risk have been conflicting (Gardner et al., 2015; Kenborg et al., 2015; Taylor et al., 2016). With the notion that traumatic brain injury potentially requires synergistic factors to lead to PD, a case-control study examined PD risk in relation to joint exposure to head injury and paraquat (assessed using geographical information system-based land use and historic pesticide use reporting data); it found that paraquat-associated PD risk was greater among individuals with head injury and that the joint exposure was associated with higher PD risk as compared to exposure to paraquat or head injury alone (Lee et al., 2012). An experimental study in rats also demonstrated that acute traumatic brain injury induced progressive degeneration of nigrostriatal dopaminergic neurons, microglial activation, and alpha-synuclein accumulation were exacerbated when the animals were exposed to concentrations of paraquat that alone would not induce nigrostriatal death (Hutson et al., 2011). We are not aware of reports that examined interaction between other pesticides and head injury, but potential interaction is plausible as some of these pesticides have been implicated in PD pathogenesis (Furlong et al., 2015; Wang et al., 2014). We note several limitations in this particular analysis – our questionnaire did not capture head injury not requiring medical attention, and limited information was available on age at injury which precluded analysis on the timing of injury occurrence.

Although our subgroup analysis did hint at higher PD risk for paraquat as well as for the pesticide group mitochondrial complex I inhibitors among individuals with head injury, we found limited evidence for independent associations of incident PD with these pesticides, whereas both were independently associated with PD in FAME (Tanner et al., 2011). Among other specific pesticides previously examined in FAME, we saw some suggestions of elevated PD risk for those with higher IWLD of the fungicide benomyl and the insecticide permethrin (animal use), though HR estimates were imprecise.

Limited reproducibility of FAME findings in the current study could be due to differences in study design, exposure data, and criteria for inclusion in analyses. FAME, although conducted within the AHS framework, collected more granular exposure data on some pesticides suspected to be etiologically relevant to PD, some of which were infrequently-used and therefore covered superficially at AHS enrollment (ever-use of "other pesticides"). The AHS questionnaires at enrollment focused, in part, on frequently-used pesticides. Further, AHS questionnaires differed for applicators and spouses, leading to lack of information in the AHS on certain pesticides of interest in FAME. For example, information on rotenone (included in the group mitochondrial complex I inhibitor) was not asked of spouses and was collected only from applicators who completed the take-home questionnaire. Likewise, although all participants were asked about ever-use of paraquat, information on duration and frequency of paraquat use was not asked of spouses and was collected only from the applicators returning the take-home questionnaire. Differences in study design and outcome ascertainment also could have contributed to differences in findings. Our analysis included all cohort members with at least some follow-up information and involved a longer follow-up period, whereas FAME involved a small subset of the cohort with fewer PD cases and shorter follow-up. Our current analysis utilized pesticide data obtained before PD diagnosis; whereas the exposure data in FAME were collected retrospectively after PD diagnosis (from participants or their proxies if participants were deceased), thereby opening the possibility of bias associated with differential recall of pesticide use (for example, if cases were more likely to recall such exposures). On the other hand, FAME benefitted from more detailed exposure information on relevant pesticides. Further, in FAME, both cases and controls underwent in-person assessment, while in the current study, we mainly relied on self-reports and those who self-reported to be PD-free did not undergo additional evaluation. Since we also included the FAME cases, however, a portion of our cases had an earlier in-person exam. Disease misclassification is possible and could have led to diminish estimates of relative risk in our analyses. In fact, while pesticide-use agreement was good overall, we did see some evidence of differential reporting by cases and controls in FAME when comparing data reported in both FAME and in the main AHS enrollment questionnaire (Supplemental Table 8 presents some comparisons, although we note that exposure timeframes are different as FAME asked exposures before PD diagnosis for cases or a reference date for controls). Lastly, FAME and our current cohort-wide effort are capturing different time windows of exposure relative to disease onset. The insidious onset of PD that is difficult to capture in non-clinical settings together with limited knowledge of induction and latent periods makes determination of exposure-relevant time windows difficult.

Specifically, for the herbicide paraquat, animal and earlier human studies offer persuasive evidence for a potential link with PD, despite continuing debate (Goldman et al., 2017; Jones et al., 2014). Some subgroups, including those with specific genetic makeup, head injury, and certain dietary intake have been found particularly vulnerable to PD following paraquat exposure (Goldman et al., 2012; Kamel et al., 2014; Lee et al., 2012; Ritz et al., 2009). We cannot rule out the possibility that limited evidence of independent associations between PD and ever-use of some pesticides (including paraquat) in the current study resulted from non-differential bias attenuating HR estimates; for example, the HR for ever-use of paraquat was elevated [HR: 1.09 (95% CI: 0.84, 1.41)], but not statistically significant. Nevertheless, we were still able to observe associations among those potentially more susceptible due to head injury.

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Table 4
Intensity-weighted lifetime days of pesticide use at enrollment and incident PD in male applicators.

		Pesticide exposure through enrollment				Pesticide exposure through Phase 2				
Pesticide	Lifetime days[a]	No PD, n (%)	PD, n (%)	HR (95% CI)[b]	p[c]	Lifetime days[a]	No PD, n (%)	PD, n (%)	HR (95% CI)[b]	p[c]
Organochlorine insecticide										
Aldrin [d]	Never use	13,427 (82.7)	145 (75.5)	Ref	0.08	–	–	–	–	
	>0–≤315	994 (6.1)	18 (9.4)	0.84 (0.50, 1.42)						
	>315–≤980	911 (5.6)	17 (8.9)	0.82 (0.47, 1.41)						
	>980	905 (5.6)	12 (6.3)	0.56 (0.30, 1.06)						
Chlordane [d]	Never use	13,516 (80.7)	144 (72.7)	Ref	0.69	–	–	–	–	
	>0–≤236	1090 (6.5)	18 (9.1)	1.04 (0.63, 1.71)						
	>236–≤735	1111 (6.6)	17 (8.6)	0.92 (0.55, 1.53)						
	>735	1039 (6.2)	19 (9.6)	1.02 (0.62, 1.68)						
Dieldrin [d]	Never use	15,739 (96.2)	178 (93.2)	Ref	0.61	–	–	–	–	
	>0–≤338	307 (1.9)	8 (4.2)	1.24 (0.60, 2.59)						
	>338	308 (1.9)	5 (2.6)	0.77 (0.31, 1.93)						
DDT [d]	Never use	12,823 (78.3)	117 (60.6)	Ref	0.61	–	–	–	–	
	>0–≤341	1221 (7.5)	21 (10.9)	0.84 (0.52, 1.37)						
	>341–≤1675	1175 (7.2)	35 (18.1)	1.39 (0.92, 2.08)						
	>1675	1150 (7)	20 (10.4)	0.87 (0.53, 1.43)						
Heptachlor [d]	Never use	14,332 (87.4)	155 (78.7)	Ref	0.93	–	–	–	–	
	>0–≤280	673 (4.1)	14 (7.1)	1.41 (0.79, 2.51)						
	>280–≤882	729 (4.4)	17 (8.6)	1.44 (0.85, 2.46)						
	>882	660 (4)	11 (5.6)	1.02 (0.54, 1.94)						
Toxaphene [d]	Never use	16,128 (88.6)	200 (89.7)	Ref	0.12	–	–	–	–	
	>0–≤315	714 (3.9)	7 (3.1)	0.54 (0.26, 1.16)						
	>315–≤1181	670 (3.7)	8 (3.6)	0.66 (0.32, 1.33)						
	>1181	681 (3.7)	8 (3.6)	0.59 (0.29, 1.21)						
Lindane	Never use	15,591 (86.3)	186 (85.3)	Ref	0.56	Never use	15,424 (84.4)	183 (83.6)	Ref	0.62
	>0–≤315	823 (4.6)	7 (3.2)	0.56 (0.26, 1.2)		>0–≤341	944 (5.2)	8 (3.7)	0.59 (0.29, 1.21)	
	>315–≤1232	839 (4.6)	16 (7.3)	1.23 (0.73, 2.06)		>341–≤1232	961 (5.3)	18 (8.2)	1.26 (0.76, 2.07)	
	>1232	815 (4.5)	9 (4.1)	0.77 (0.40, 1.51)		>1232	940 (5.1)	10 (4.6)	0.80 (0.42, 1.51)	
Carbamate insecticide										
Carbaryl	Never use	9547 (57.8)	111 (56.3)	Ref	0.12	Never use	9194 (52)	106 (53)	Ref	0.11
	>0–≤387	2432 (14.7)	32 (16.2)	0.96 (0.65, 1.44)		>0–≤441	2904 (16.4)	37 (18.5)	0.90 (0.60, 1.36)	
	>387–≤2460	2403 (14.6)	30 (15.2)	0.81 (0.53, 1.26)		>441–≤2320	2918 (16.5)	30 (15)	0.78 (0.50, 1.22)	
	>2460	2123 (12.9)	24 (12.2)	0.64 (0.38, 1.08)		>2320	2675 (15.1)	27 (13.5)	0.63 (0.37, 1.05)	
Carbofuran [e]	-	–	–	–		Never use	23,500 (71.3)	198 (64.5)	Ref	0.41
						>0–≤368	3133 (9.5)	41 (13.4)	0.90 (0.60, 1.36)	
						>368–≤1370	3200 (9.7)	41 (13.4)	0.78 (0.50, 1.22)	
						>1370	3127 (9.5)	27 (8.8)	0.63 (0.37, 1.05)	
≤ 63y	Never use	13,827 (76.4)	52 (61.9)	Ref	0.28	–	–	–	–	
	>0–≤784	2156 (11.9)	24 (28.6)	1.88 (1.15, 3.05)						
	>784	2117 (11.7)	8 (9.5)	0.66 (0.31, 1.4)						
>63y	Never use	10,581 (67.5)	148 (66.4)	Ref	0.93					
	>0–≤784	2534 (16.2)	38 (17)	0.99 (0.69, 1.42)						
	>784	2551 (16.3)	37 (16.6)	1.02 (0.71, 1.46)						
Organophosphate insecticide										
Chlorpyrifos	Never use	18,564 (55)	191 (58.2)	Ref	0.60	Never use	19,755 (55.4)	220 (61.1)	Ref	0.78
	>0–≤455	5003 (14.8)	54 (16.5)	1.14 (0.84, 1.55)		>0–≤490	5251 (14.7)	55 (15.3)	1.04 (0.77, 1.41)	
	>455–≤1848	5165 (15.3)	33 (10.1)	0.68 (0.47, 0.99)		>490–≤1903	5406 (15.2)	38 (10.6)	0.71 (0.5, 1.01)	
	>1848	4994 (14.8)	50 (15.2)	1.12 (0.82, 1.54)		>1903	5243 (14.7)	47 (13.1)	0.99 (0.72, 1.35)	
Coumaphos	Never use	29,725 (91.2)	271 (90)	Ref	0.99	Never use	29,678 (91)	271 (90)	Ref	0.93
	>0–≤380	955 (2.9)	9 (3)	0.87 (0.45, 1.7)		>0–≤385	975 (3)	9 (3)	0.85 (0.44, 1.65)	
	>380–≤1418	979 (3)	12 (4)	1.07 (0.6, 1.91)		>385–≤1428	986 (3)	12 (4)	1.07 (0.6, 1.91)	
	>1418	938 (2.9)	9 (3)	0.99 (0.51, 1.92)		>1428	966 (3)	9 (3)	0.96 (0.49, 1.87)	
Diazinon[f]	*Never use*	*13,412 (79.2)*	*162 (81)*	Ref	0.23	Never use	13,202 (75.4)	162 (79.8)	Ref	0.11
	>0–≤328	*1194 (7.1)*	*13 (6.5)*	*0.79 (0.45, 1.40)*		>0–≤350	1443 (8.2)	13 (6.4)	0.68 (0.38, 1.21)	

(*continued on next page*)

Table 4 (*continued*)

Pesticide	Lifetime days[a]	Pesticide exposure through enrollment: No PD, n (%)	PD, n (%)	HR (95% CI)[b]	p[c]	Pesticide exposure through Phase 2: Lifetime days[a]	No PD, n (%)	PD, n (%)	HR (95% CI)[b]	p[c]
	>328–≤1274	*1213 (7.2)*	*14 (7)*	*0.78 (0.45, 1.35)*		>350–≤1270	1476 (8.4)	16 (7.9)	0.81 (0.48, 1.36)	
	>1274	*1116 (6.6)*	*11 (5.5)*	*0.69 (0.37, 1.29)*		>1270	1391 (7.9)	12 (5.9)	0.6 (0.32, 1.12)	
Dichlorvos	Never use	29,516 (89.2)	264 (86.3)	Ref	0.06	Never use	29,409 (88.9)	264 (86.3)	Ref	0.06
	>0–≤1344	1783 (5.4)	15 (4.9)	0.79 (0.46, 1.33)		>0–≤1360	1844 (5.6)	15 (4.9)	0.79 (0.46, 1.33)	
	>1344	1773 (5.4)	27 (8.8)	1.46 (0.98, 2.19)		>1360	1832 (5.5)	27 (8.8)	1.46 (0.98, 2.19)	
Fonofos	Never use	25,838 (77.6)	240 (77.4)	Ref	0.32	Never use	25,820 (77.5)	240 (77.4)	Ref	0.32
	>0–≤455	2467 (7.4)	26 (8.4)	1.06 (0.7, 1.61)		>0–≤455	2468 (7.4)	26 (8.4)	1.06 (0.7, 1.61)	
	>455–≤1680	2526 (7.6)	24 (7.7)	0.92 (0.60, 1.42)		>455–≤1696	2538 (7.6)	24 (7.7)	0.92 (0.6, 1.41)	
	>1680	2463 (7.4)	20 (6.5)	0.80 (0.50, 1.27)		>1696	2470 (7.4)	20 (6.5)	0.8 (0.5, 1.27)	
Malathion	Never use	6436 (35.7)	76 (35)	Ref	0.08	Never use	6107 (30.4)	69 (29.2)	Ref	0.12
	>0–≤368	3832 (21.3)	53 (24.4)	1.13 (0.79, 1.61)		>0–≤384	4797 (23.9)	68 (28.8)	1.26 (0.89, 1.79)	
	>368 ≤ 1440	3948 (21.9)	46 (21.2)	0.89 (0.62, 1.29)		>384–≤1344	4603 (22.9)	47 (19.9)	0.93 (0.64, 1.35)	
	>1440	3795 (21.1)	42 (19.4)	0.75 (0.51, 1.10)		>1344	4584 (22.8)	52 (22)	0.83 (0.57, 1.2)	
Parathion	Never use	16,605 (92.1)	201 (91)	Ref	0.97	Never use	16,580 (91.9)	201 (90.5)	Ref	0.76
	>0–≤882	718 (4)	10 (4.5)	0.94 (0.49, 1.78)		>0–≤880	728 (4)	10 (4.5)	0.86 (0.44, 1.69)	
	>882	697 (3.9)	10 (4.5)	0.99 (0.52, 1.89)		>880	726 (4)	11 (5)	1.05 (0.56, 1.94)	
Phorate	Never use	11,467 (68.4)	121 (61.4)	Ref	0.55	Never use	11,523 (67.8)	122 (61.3)	Ref	0.47
	>0–≤315	1771 (10.6)	25 (12.7)	1.18 (0.75, 1.86)		>0–≤320	1818 (10.7)	25 (12.6)	1.14 (0.72, 1.79)	
	>315–≤1176	1809 (10.8)	34 (17.3)	1.61 (1.07, 2.41)		>320–≤1176	1874 (11)	35 (17.6)	1.62 (1.09, 2.41)	
	>1176	1715 (10.2)	17 (8.6)	0.84 (0.50, 1.40)		>1176	1781 (10.5)	17 (8.5)	0.8 (0.48, 1.34)	
Terbufos	Never use	19,869 (59.8)	168 (54.4)	Ref	0.50	Never use	19,649 (59.1)	168 (54)	Ref	0.53
	>0–≤646	4397 (13.2)	46 (14.9)	1.34 (0.96, 1.88)		>0–≤660	4497 (13.5)	48 (15.4)	1.35 (0.97, 1.89)	
	>646–≤2400	4536 (13.7)	54 (17.5)	1.46 (1.06, 2.00)		>660–≤2436	4623 (13.9)	53 (17)	1.39 (1.01, 1.91)	
	>2400	4411 (13.3)	41 (13.3)	1.16 (0.82, 1.65)		>2436	4480 (13.5)	42 (13.5)	1.16 (0.82, 1.64)	
Permethrin insecticide										
Permethrin (crops)	Never use	28,383 (86.5)	269 (89.4)	Ref	0.21	Never use	27,839 (84.8)	265 (88.3)	Ref	0.27
	>0–≤273	1470 (4.5)	15 (5)	1.30 (0.77, 2.2)		>0–≤288	1639 (5)	17 (5.7)	1.19 (0.7, 2.01)	
	>273–≤1080	1492 (4.5)	11 (3.7)	1.01 (0.55, 1.84)		>288–≤1117	1695 (5.2)	11 (3.7)	0.94 (0.51, 1.72)	
	>1080	1466 (4.5)	6 (2)	0.59 (0.26, 1.33)		>1117	1643 (5)	7 (2.3)	0.66 (0.31, 1.4)	
Permethrin (animals)	Never use	28,783 (86.3)	272 (88.6)	Ref	0.21	Never use	28,163 (84.3)	270 (87.9)	Ref	0.16
	>0–≤368	1574 (4.7)	11 (3.6)	0.93 (0.50, 1.70)		>0–≤392	1737 (5.2)	11 (3.6)	0.84 (0.46, 1.53)	
	>368–≤1418	1505 (4.5)	9 (2.9)	0.77 (0.40, 1.51)		>392–≤1512	1781 (5.3)	9 (2.9)	0.68 (0.34, 1.35)	
	>1418	1493 (4.5)	15 (4.9)	1.44 (0.85, 2.44)		>1512	1721 (5.2)	17 (5.5)	1.49 (0.9, 2.46)	
Fumigant										
Carbon disulfide/carbon tetrachloride[d]	Never use	17,467 (95.8)	209 (94.6)	Ref	0.74	–	–	–	–	
	>0–≤172	398 (2.2)	6 (2.7)	0.82 (0.36, 1.86)						
	>172	364 (2)	6 (2.7)	0.88 (0.39, 1.98)						
Methyl Bromide	Never use	28,072 (84.9)	274 (85.9)	Ref	0.58	Never use	28,084 (84.8)	276 (85.7)	Ref	0.52
	>0–≤320	1613 (4.9)	13 (4.1)	0.82 (0.46, 1.47)		>0–≤326	1669 (5)	14 (4.3)	0.78 (0.44, 1.41)	
	>320–≤1372	1670 (5.1)	17 (5.3)	1.03 (0.60, 1.78)		>326–≤1395	1673 (5.1)	17 (5.3)	0.98 (0.57, 1.7)	
	>1372	1706 (5.2)	15 (4.7)	0.82 (0.46, 1.48)		>1395	1696 (5.1)	15 (4.7)	0.8 (0.45, 1.42)	
Fungicide										
Benomyl	Never use	14,990 (92.8)	174 (91.6)	Ref	0.31	Never use	14,977 (92.4)	174 (90.6)	Ref	0.35
	>0–≤868	591 (3.7)	5 (2.6)	0.62 (0.24, 1.61)		>0–≤868	623 (3.8)	6 (3.1)	0.73 (0.31, 1.75)	
	>868	574 (3.6)	11 (5.8)	1.34 (0.64, 2.80)		>868	613 (3.8)	12 (6.3)	1.34 (0.64, 2.79)	
Captan	Never use	29,167 (89.8)	274 (90.7)	Ref	0.36	Never use	28,708 (88.2)	270 (88.8)	Ref	0.26
	>0–≤9	1224 (3.8)	8 (2.6)	0.83 (0.41, 1.68)		>0–≤10	1278 (3.9)	8 (2.6)	0.78 (0.39, 1.59)	
	>9–≤212	1046 (3.2)	6 (2)	0.65 (0.29, 1.46)		>10–≤540	1311 (4)	10 (3.3)	0.83 (0.44, 1.57)	
	>212	1060 (3.3)	14 (4.6)	1.27 (0.74, 2.20)		>540	1264 (3.9)	16 (5.3)	1.33 (0.80, 2.21)	
Chlorothalonil	Never use	30,547 (92.8)	293 (94.2)	Ref	0.41	Never use	30,371 (92.2)	291 (93.6)	Ref	0.47
	>0–≤1535	1132 (3.4)	7 (2.3)	0.74 (0.34, 1.61)		>0–≤1613	1245 (3.8)	7 (2.3)	0.71 (0.32, 1.55)	
	>1535	1221 (3.7)	11 (3.5)	1.29 (0.66, 2.56)		>1613	1312 (4)	13 (4.2)	1.41 (0.75, 2.66)	
Maneb[g]	-	–	–	–		Never use	15,464 (92.3)	186 (93)	Ref	0.34
						>0–≤1268	660 (3.9)	8 (4)	0.69 (0.31, 1.53)	
						>1268	636 (3.8)	6 (3)	0.59 (0.25, 1.4)	

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Table 4 (*continued*)

Pesticide	Lifetime days[a]	Pesticide exposure through enrollment				Pesticide exposure through Phase 2				
		No PD, n (%)	PD, n (%)	HR (95% CI)[b]	p[c]	Lifetime days[a]	No PD, n (%)	PD, n (%)	HR (95% CI)[b]	p[c]
Metalaxyl	Never use	14,301 (81.6)	177 (82.3)	Ref	0.14	Never use	14,239 (79.1)	175 (80.6)	Ref	0.47
	>0–≤312	1060 (6.1)	17 (7.9)	1.27 (0.77, 2.11)		>0–≤312	1241 (6.9)	18 (8.3)	1.26 (0.76, 2.08)	
	>312–≤1568	1094 (6.2)	15 (7)	1.18 (0.66, 2.11)		>312–≤1488	1286 (7.1)	15 (6.9)	1.17 (0.64, 2.13)	
	>1568	1061 (6.1)	6 (2.8)	0.53 (0.22, 1.27)		>1488	1240 (6.9)	9 (4.1)	0.79 (0.38, 1.65)	
Herbicide										
Alachlor	Never use	15,100 (45.7)	127 (41.9)	Ref	0.80	Never use	14,974 (45.3)	124 (40.9)	Ref	0.73
	>0–≤809	5925 (18)	63 (20.8)	1.11 (0.82, 1.52)		>0–≤809	6011 (18.2)	65 (21.5)	1.15 (0.85, 1.57)	
	>809–≤3132	6056 (18.3)	55 (18.2)	0.95 (0.69, 1.30)		>809–≤3145	6121 (18.5)	56 (18.5)	0.97 (0.7, 1.33)	
	>3132	5927 (18)	58 (19.1)	1.07 (0.78, 1.46)		>3145	5977 (18.1)	58 (19.1)	1.09 (0.8, 1.5)	
Butylate	Never use	11,964 (71.9)	144 (72.7)	Ref	0.22	Never use	13,263 (73)	164 (73.9)	Ref	0.24
	>0–≤473	1564 (9.4)	25 (12.6)	1.26 (0.81, 1.95)		>0–≤473	1626 (9)	26 (11.7)	1.26 (0.81, 1.95)	
	>473–≤1519	1583 (9.5)	16 (8.1)	0.85 (0.50, 1.45)		>473–≤1512	1659 (9.1)	18 (8.1)	0.91 (0.54, 1.53)	
	>1519	1531 (9.2)	13 (6.6)	0.73 (0.41, 1.30)		>1512	1619 (8.9)	14 (6.3)	0.73 (0.41, 1.3)	
Chlorimuron Ethyl	Never use	12,384 (68)	163 (73.4)	Ref	0.44	Never use	12,187 (65.4)	162 (72.6)	Ref	0.22
	>0–≤245	1930 (10.6)	25 (11.3)	1.22 (0.80, 1.87)		>0–≤263	2140 (11.5)	30 (13.5)	1.28 (0.85, 1.9)	
	>245–≤784	1977 (10.9)	17 (7.7)	0.80 (0.49, 1.33)		>263–≤817	2169 (11.6)	15 (6.7)	0.69 (0.4, 1.18)	
	>784	1910 (10.5)	17 (7.7)	0.85 (0.52, 1.41)		>817	2127 (11.4)	16 (7.2)	0.77 (0.46, 1.28)	
Dicamba	Never use	15,344 (47.7)	141 (48)	Ref	0.33	Never use	14,269 (44.3)	131 (44.4)	Ref	0.13
	>0–≤564	5548 (17.2)	50 (17)	0.90 (0.63, 1.28)		>0–≤694	5897 (18.3)	58 (19.7)	0.99 (0.7, 1.41)	
	>564–≤2184	5761 (17.9)	46 (15.6)	0.81 (0.56, 1.17)		>694–≤2380	6126 (19)	43 (14.6)	0.83 (0.56, 1.22)	
	>2184	5524 (17.2)	57 (19.4)	1.11 (0.79, 1.56)		>2380	5950 (18.5)	63 (21.4)	1.25 (0.88, 1.77)	
EPTC	Never use	26,190 (79.7)	249 (83)	Ref	0.74	Never use	26,155 (79.6)	249 (83)	Ref	0.73
	>0–≤315	2215 (6.7)	19 (6.3)	0.93 (0.58, 1.49)		>0–≤315	2222 (6.8)	19 (6.3)	0.93 (0.58, 1.49)	
	>315–≤1181	2245 (6.8)	14 (4.7)	0.67 (0.39, 1.15)		>315–≤1190	2261 (6.9)	14 (4.7)	0.66 (0.39, 1.14)	
	>1181	2192 (6.7)	18 (6)	0.97 (0.60, 1.57)		>1190	2205 (6.7)	18 (6)	0.97 (0.6, 1.57)	
Glyphosate	Never use	8307 (23.3)	86 (24.2)	Ref	0.09	Never use	5247 (14.8)	62 (17.5)	Ref	0.10
	>0–≤677	8996 (25.2)	106 (29.8)	1.17 (0.88, 1.55)		>0–≤970	9965 (28)	132 (37.2)	1.21 (0.88, 1.65)	
	>677–≤2604	9313 (26.1)	91 (25.6)	0.99 (0.73, 1.33)		>970–≤3352	10,318 (29)	84 (23.7)	0.92 (0.64, 1.34)	
	>2604	9015 (25.3)	73 (20.5)	0.85 (0.62, 1.17)		>3352	10,018 (28.2)	77 (21.7)	0.88 (0.62, 1.25)	
Imazethapyr	Never use	17,941 (55.5)	173 (58.6)	Ref	0.38	Never use	17,152 (53.1)	169 (56.9)	Ref	0.64
	>0–≤341	4874 (15.1)	42 (14.2)	1.00 (0.70, 1.45)		>0–≤403	5007 (15.5)	47 (15.8)	1.03 (0.72, 1.47)	
	>341–≤1008	4752 (14.7)	41 (13.9)	1.05 (0.73, 1.52)		>403–≤1176	5205 (16.1)	42 (14.1)	0.92 (0.63, 1.35)	
	>1008	4733 (14.7)	39 (13.2)	1.18 (0.81, 1.72)		>1176	4964 (15.4)	39 (13.1)	1.11 (0.76, 1.62)	
Metolachlor	Never use	17,519 (52.8)	182 (60.1)	Ref	0.79	Never use	16,273 (49)	174 (57.4)	Ref	0.71
	>0–≤720	5255 (15.8)	35 (11.6)	0.67 (0.46, 0.96)		>0–≤760	5600 (16.9)	41 (13.5)	0.72 (0.51, 1.03)	
	>720–≤2688	5322 (16)	44 (14.5)	0.84 (0.6, 1.17)		>760–≤2700	5776 (17.4)	44 (14.5)	0.78 (0.55, 1.1)	
	>2688	5079 (15.3)	42 (13.9)	0.90 (0.64, 1.26)		>2700	5585 (16.8)	44 (14.5)	0.89 (0.63, 1.25)	
Paraquat	Never use	15,305 (84.1)	188 (82.5)	Ref	0.45	Never use	15,216 (81.9)	188 (81.7)	Ref	0.36
	>0–≤289	961 (5.3)	13 (5.7)	1.03 (0.58, 1.81)		>0–≤308	1111 (6)	13 (5.7)	0.92 (0.51, 1.63)	
	>289–≤1232	975 (5.4)	18 (7.9)	1.42 (0.86, 2.33)		>308–≤1308	1135 (6.1)	20 (8.7)	1.49 (0.92, 2.41)	
	>1232	960 (5.3)	9 (3.9)	0.74 (0.37, 1.49)		>1308	1113 (6)	9 (3.9)	0.69 (0.34, 1.38)	
Pendimethalin	Never use	11,440 (62.9)	154 (68.1)	Ref	0.25	Never use	10,685 (53.9)	145 (60.9)	Ref	0.57
	>0–≤341	2262 (12.4)	32 (14.2)	1.13 (0.77, 1.66)		>0–≤378	3003 (15.2)	38 (16)	1.1 (0.77, 1.57)	
	>341–≤1320	2263 (12.4)	23 (10.2)	0.90 (0.58, 1.40)		>378 ≤ 1232	3114 (15.7)	32 (13.4)	0.97 (0.65, 1.44)	
	>1320	2227 (12.2)	17 (7.5)	0.76 (0.46, 1.26)		>1232	3005 (15.2)	23 (9.7)	0.89 (0.57, 1.39)	
Petroleum	Never use	14,257 (78.9)	184 (83.6)	Ref	0.72	Never use	14,169 (78.1)	183 (82.8)	Ref	0.59
	>0–≤515	1266 (7)	9 (4.1)	0.57 (0.29, 1.11)		>0–≤495	1317 (7.3)	11 (5)	0.67 (0.36, 1.23)	
	>515–≤2500	1286 (7.1)	13 (5.9)	0.91 (0.52, 1.61)		>495–≤2408	1355 (7.5)	13 (5.9)	0.88 (0.5, 1.55)	
	>2500	1261 (7)	14 (6.4)	0.89 (0.52, 1.53)		>2408	1312 (7.2)	14 (6.3)	0.85 (0.49, 1.47)	
Trifluralin	Never use	14,464 (45.7)	116 (40.4)	Ref	0.07	Never use	14,106 (44.5)	113 (39.4)	Ref	0.10
	>0–≤1008	5653 (17.9)	61 (21.3)	1.40 (1.01, 1.95)		>0–≤1046	5779 (18.2)	64 (22.3)	1.42 (1.02, 1.97)	
	>1008–≤3828	5877 (18.6)	47 (16.4)	1.05 (0.73, 1.52)		>1046–≤3906	6144 (19.4)	49 (17.1)	1.05 (0.73, 1.52)	
	>3828	5669 (17.9)	63 (22)	1.50 (1.06, 2.11)		>3906	5672 (17.9)	61 (21.3)	1.48 (1.04, 2.1)	
2,4-D	Never use	8108 (22.9)	72 (20.5)	Ref	0.52	Never use	6928 (19.5)	67 (18.9)	Ref	0.52

(*continued on next page*)

Table 4 (*continued*)

		Pesticide exposure through enrollment				Pesticide exposure through Phase 2				
Pesticide	Lifetime days[a]	No PD, n (%)	PD, n (%)	HR (95% CI)[b]	p[c]	Lifetime days[a]	No PD, n (%)	PD, n (%)	HR (95% CI)[b]	p[c]
	>0–≤1269	8944 (25.3)	84 (23.9)	1.07 (0.78, 1.47)		>0–≤1440	9486 (26.6)	97 (27.3)	1.08 (0.79, 1.49)	
	>1269–≤5104	9303 (26.3)	97 (27.6)	1.04 (0.76, 1.43)		>1440–≤5394	9767 (27.4)	86 (24.2)	0.87 (0.62, 1.22)	
	>5104	9035 (25.5)	99 (28.1)	0.96 (0.7, 1.31)		>5394	9432 (26.5)	105 (29.6)	0.93 (0.67, 1.29)	
2,4,5-T[d]	Never use	13,328 (80.9)	143 (71.9)	Ref	0.71	–	–	–	–	
	>0–≤289	1068 (6.5)	20 (10.1)	1.21 (0.75, 1.95)						
	>289–≤1006	1069 (6.5)	20 (10.1)	1.27 (0.78, 2.05)						
	>1006	1007 (6.1)	16 (8)	1.11 (0.65, 1.89)						
Atrazine	Never use	9709 (27.3)	95 (27)	Ref	0.64	Never use	8473 (23.8)	87 (24.7)	Ref	0.53
	>0–≤1050	8525 (23.9)	87 (24.7)	1.14 (0.84, 1.54)		>0–≤1221	8960 (25.2)	97 (27.6)	1.17 (0.86, 1.59)	
	>1050–≤4456	8826 (24.8)	85 (24.1)	0.99 (0.73, 1.34)		>1221–≤4666	9250 (26)	83 (23.6)	0.95 (0.69, 1.3)	
	>4456	8556 (24)	85 (24.1)	0.99 (0.73, 1.34)		>4666	8943 (25.1)	85 (24.1)	0.98 (0.72, 1.34)	
Cyanazine	Never use	19,018 (57.2)	174 (57.4)	Ref	0.79	Never use	18,910 (56.9)	173 (57.1)	Ref	0.66
	>0–≤560	4706 (14.2)	40 (13.2)	0.84 (0.59, 1.20)		>0–≤588	4808 (14.5)	39 (12.9)	0.81 (0.57, 1.17)	
	>560–≤2268	4850 (14.6)	45 (14.9)	0.91 (0.64, 1.28)		>588–≤2279	4792 (14.4)	46 (15.2)	0.94 (0.66, 1.32)	
	>2268	4665 (14)	44 (14.5)	1.00 (0.71, 1.42)		>2279	4716 (14.2)	45 (14.9)	1.03 (0.73, 1.45)	
Metribuzin	Never use	9599 (59.7)	115 (61.5)	Ref	0.33	Never use	9513 (58)	115 (60.8)	Ref	0.37
	>0–≤319	2148 (13.4)	30 (16)	1.10 (0.71, 1.69)		>0–≤341	2358 (14.4)	31 (16.4)	1.01 (0.65, 1.56)	
	>319–≤1024	2193 (13.6)	21 (11.2)	0.77 (0.47, 1.27)		>341–≤1054	2259 (13.8)	21 (11.1)	0.75 (0.46, 1.23)	
	>1024	2128 (13.2)	21 (11.2)	0.81 (0.49, 1.33)		>1054	2260 (13.8)	22 (11.6)	0.81 (0.50, 1.34)	

Abbreviation: 2,4-D, 2,4-Dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-Trichlorophenoxyacetic acid; 2,4,5-T,P, 2-(2,4,5-trichlorophenoxy) propionic acid; CI, Confidence Intervals; DDT, Dichlorodiphenyltrichloroethane; EPTC, S-Ethyl dipropylthiocarbamate; HR, Hazard Ratio.

[a] Tertile cut-off and n (%) may differ between Phase 1 and Phase 2 exposure because of difference in exposure information and missingness.

[b] HR adjusted for sex, state of residence, smoking status, education, and ever-use of correlated pesticides (other pesticides whose ever-use variable had Spearman correlation ≥ 0.40 with the ever-use variable of the target pesticide).

[c] P-value for test for trend.

[d] HR not presented if, at Phase 2, pesticide exposure since enrollment was not reported.

[e] HR allowed to vary by the median age (i.e., 63 years) for pesticides that did not meet proportional hazards assumption ($p \leq 0.10$).

[f] Proportional hazards assumption not met for those in italics, but there was no adequate sample size to provide stratified estimates by the median age.

[g] HR not presented as there were less than 5 exposed cases.

Our study also suggests that use of chemical resistant gloves may have conferred some protection against PD in pesticide applicators using certain herbicides. Chemical resistant gloves, but not other types of gloves, have been shown in the AHS to offer protection from pesticide exposure (Hines et al., 2011; Thomas et al., 2010). In FAME, associations of several pesticides including permethrin and paraquat with PD risks were greater in those who used chemical-resistant gloves less than 50% of the time compared to those who used >50% (Furlong et al., 2015).

4.1. Limitations and strengths

Our study has several limitations. First, pesticide-use data were self-reported; thus, some exposure misclassification is likely. However, AHS farmers have been shown to report both reliable and valid pesticide usage (Blair et al., 2002; Hoppin et al., 2002); for lifetime exposures, we used exposure intensity, which correlates better with urinary biomarkers of pesticides than uncorrected days of use (Coble et al., 2011; Hines et al., 2011). Due to our prospective design, exposure misclassification was likely non-differential for PD. Non-differential misclassification might have biased effect estimates towards the null for binary pesticide-use variables; but, for polytomous categories, directionality of bias is uncertain (Rothman et al., 2008).

Second, in the current analyses, although we incorporated pesticide usage through the first follow-up for applicators, we could not do so for spouses and we could not account for more proximal exposures for applicators because data were not available for all participants due to cohort attrition. The time duration from Phase 2 (when exposures were updated for this analysis) to Phase 4 (i.e., end of follow-up) was 13 years on average. Failure to account for exposure occurring during this window could have heightened exposure misclassification, for those pesticides that are still on the market.

Third, our effort to validate all potential PD cases using medical records suffered from low response from both participants (or their proxies) and their physicians, so we relied on PD self-report. We attempted to minimize potential PD misclassification by restricting analysis to individuals providing consistent responses on PD across surveys and for those with relevant questionnaire data, restricting to cases with supporting data on neurological symptoms and medication use. We did find that those medical records we obtained were in high agreement with self-reported PD. Further, agreement between PD self-report and clinical diagnostic evaluation was found to be high in FAME (84%) (Tanner et al., 2011) as well in other studies (Jain et al., 2015), indicating PD self-reports are, in general, reasonably reliable. Furthermore, we observed reduced PD risk in smokers [age and sex adjusted HR: 0.75 (95%CI: 0.61, 0.91) for former smoking and 0.55 (95%CI: 0.38, 0.81) for current smoking] in the current study, which is consistent with prior literature (Hernan et al., 2002) and thus indirectly supports the validity of PD self-reports in the AHS.

Fourth, we were unable to account for possible PD in participants who were lost to follow-up, although we were able to identify participants who had PD recorded on their death certificates (but did not report PD in surveys). We included such cases in our analysis if their proxy provided adequate information in the validation screener to support a PD diagnosis. We had similar results in analyses using inverse probability weighting to make inference on all enrolled participants. Nevertheless, we cannot completely rule out selection bias due to loss-to-follow up or bias due to selective mortality before enrollment resulting from higher pesticide exposures. Fifth, we found inverse associations for some pesticides which may be due to reverse causality – for instance, if individuals with symptomatic but undiagnosed PD accumulate less exposure due to reduced farming activities compared to those individuals that are "healthy" and continue farming. We know of no reason why this reverse causality would apply only to certain pesticides.

Sixth, we also did not adjust for multiple comparisons given the exploratory nature of our study and therefore some of the observed associations may be false positives and thus our findings should be interpreted with caution. Seventh, participants were exposed to multiple pesticides. Although we adjusted for several correlated pesticides, we cannot rule out lack of complete control of confounding due to other pesticides. Lastly, our current analytical approach focusing on a single exposure fails to account for the overall PD risk associated with multiple pesticide exposures. Pesticide use in the AHS is not easily addressed using current methods for the analysis of chemical mixtures. Applicators report a lifetime of use, with one or two possibly different pesticides being used in any given year. Chemicals used may have changed over time in relation to specific crops planted, environmental conditions, changes in availability of banned or restricted chemicals, pesticide costs and economic constraints, and much more. The development and application of new methods to address this complex and unique mixture situation is warranted.

Countering these limitations, the strengths for the current investigation include large sample size, prospective design, long-term follow-up, comprehensive information on lifetime use of pesticides, and detailed information on PD risk factors. Although we found evidence of increased PD risk for a few pesticides, most pesticides were not associated with PD nor, for the most part, were pesticides/groups that were previously implicated for PD. Continued research on pesticide-PD risk that can focus on specific chemicals is important because of continued widespread use of pesticides worldwide.

Credit author statement

Srishti Shrestha and Dale P. Sandler conceptualized the investigation, led the analysis and prepared the first draft of the manuscript. Srishti Shrestha and Marie Richards-Barber conducted data analysis. Dale P. Sandler provided supervision and funding acquisition. Dale P. Sandler, Christine G. Parks, and Laura E. Beane Freeman were involved in project administration. All the authors were involved in data interpretation and in reviewing, critiquing, and editing the manuscript, and provided final manuscript approval.

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Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2020.110186.

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BEFORE THE UNITED JUDICIAL PANEL ON MULIDISTRICT LITIGATION

IN RE: Paraquat Products Liability Litigation **MDL No. 3004**

PROOF OF SERVICE

In compliance with Rule 4.1(a) of the Rules of Procedure for the United States Judicial Panel on Multidistrict Litigation, I hereby certify that copies of the foregoing Syngenta's Response to the Motion to Transfer Related Actions for Coordinated Pretrial Proceedings were served on all parties in the following cases electronically via ECF, or as indicated below, on April 29, 2021.

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Holyfield et al v. Chevron U.S.A. Inc., et al, E.D. Missouri, No. 1:20-cv-00165

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Adams v. Syngenta Crop Protection LLC et al, E.D. Missouri, No. 2:21-cv-00029

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Tenneson, Todd v. Syngenta Crop Protection LLC et al, W.D. Wisconsin, No. 3:21-cv-00231

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Gamwell v. Syngenta Crop Protection LLC et al, D. Minnesota, No. 0:21-cv-01063

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