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Pesticide use and risk of end-stage renal disease among licensed pesticide applicators in the Agricultural Health Study

Jill F. Lebov, MSPH, PhD,
Department of Epidemiology, University of North Carolina, Chapel Hill, NC, USA

Lawrence S. Engel, PhD,
Department of Epidemiology, University of North Carolina, Chapel Hill, NC, USA

David Richardson, PhD,
Department of Epidemiology, University of North Carolina, Chapel Hill, NC, USA

Susan L. Hogan, PhD,
Department of Medicine, Division of Nephrology and Hypertension, University of North Carolina, Chapel Hill, NC, USA

Jane A. Hoppin, ScD, and
Department of Biological Sciences, Center for Human Health and the Environment, North Carolina State University, Raleigh, NC, USA

Dale P. Sandler, PhD
Epidemiology Branch/Chronic Disease Epidemiology Group, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA

Abstract

Objectives—Experimental studies suggest a relationship between pesticide exposure and renal impairment, but epidemiological evidence is limited. We evaluated the association between exposure to 41 specific pesticides and end-stage renal disease (ESRD) incidence in the Agricultural Health Study (AHS), a prospective cohort study of licensed pesticide applicators in Iowa and North Carolina.

Methods—Via linkage to the United States Renal Data System, we identified 320 ESRD cases diagnosed between enrollment (1993-1997) and December 2011 among 55,580 male licensed pesticide applicators. Participants provided pesticide use information via self-administered questionnaires. Lifetime pesticide use was defined as the product of duration and frequency of use and then modified by an intensity factor to account for differences in pesticide application practices. Cox proportional hazards models, adjusted for age and state, were used to estimate associations between ESRD and: 1) ordinal categories of intensity-weighted lifetime use of 41 pesticides, 2) poisoning and high-level pesticide exposures, and 3) pesticide exposure resulting in a medical visit or hospitalization.

Address correspondence to: Dale P. Sandler, Ph.D. Chief, Epidemiology Branch, National Institute of Environmental Health Sciences PO Box 12233, MD A3-05, 111 T.W. Alexander Drive, Research Triangle Park, NC 27709, 919-541-4668 phone, 301-451-5473 eFAX, 301-480-3290 Branch eFAX, sandler@niehs.nih.gov.

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Results—Positive exposure-response trends were observed for the herbicides alachlor, atrazine, metolachlor, paraquat, and pendimethalin, and the insecticide chlordane. More than one medical visit due to pesticide use (HR = 2.13; 95% CI: 1.17, 3.89) and hospitalization due to pesticide use (HR = 3.05; 95% CI: 1.67, 5.58) were significantly associated with ESRD.

Conclusions—Our findings support an association between ESRD and chronic exposure to specific pesticides and suggest pesticide exposures resulting in medical visits may increase the risk of ESRD.

Keywords

Pesticide exposure; chronic kidney disease; end-stage renal disease

Introduction

In 2011, over 600,000 United States residents were receiving treatment for end-stage renal disease (ESRD), a life-threatening condition requiring dialysis or kidney transplant for survival. Although much research has been conducted on clinical precursors to ESRD, such as diabetes and hypertension, research is limited on the impact of environmental and occupational factors. Literature on the nephrotoxic effects of pesticides in humans is extremely limited, and mainly comes from case reports of both fatal and non-fatal pesticide poisoning, which have described acute nephrotoxicity with a variety of pesticide classes. [1-5] Most of the evidence regarding nephrotoxicity of pesticides is restricted to experimental animal studies. Renal damage and dysfunction has been observed in experimental animal studies with exposure to specific pesticides in a dose-dependent[6-9] and/or exposure duration-dependent[79-11] manner. A variety of pesticide classes have been shown to cause renal damage and dysfunction in animals, including organophosphate, [69] organochlorine, [1012] carbamate, [13] and pyrethroid [14] insecticides and triazine [15] and chlorophenoxy[8] herbicides.

The impact of long-term pesticide exposure on human kidney function remains largely unknown. Generally, studies conducted in El Salvador, Nicaragua, and Sri Lanka indicate an elevated prevalence of chronic kidney disease among agricultural workers [16-19] compared to those who have never worked in agriculture, particularly among male agricultural workers[20]; pesticide exposure is postulated to be a contributor to kidney disease in these regions, but existing evidence has not confirmed this hypothesis. [16-18] These studies lack specificity with regard to pesticide type and have not been able to adequately assess the long-term effects of chronic low-level or acute high-level pesticide exposure on ESRD risk. To our knowledge, the only study to assess pesticide exposure and ESRD found self-reported work in a place with frequent or daily exposure to insect or plant spray to be associated with increased ESRD risk. [21]

The Agricultural Health Study (AHS) is the largest prospective study of pesticide applicators in the United States. Linking the AHS to the United States Renal Data System (USRDS) provides a unique opportunity to evaluate the relationship between pesticide use and ESRD risk. Using this linkage, we evaluated associations between chronic and acute pesticide exposure and ESRD risk.

Methods

Population and case definition

Details of the AHS design have been described previously.[22] Briefly, the AHS recruited private pesticide applicators (mainly farmers) (N= 52,394) in North Carolina and Iowa and commercial pesticide applicators (N=4,916) in Iowa who applied for or renewed a restricted-use pesticide license between 1993 and 1997. At the licensing facility, each pesticide applicator was asked to complete a brief enrollment questionnaire. Participating applicators were also given a packet of additional questionnaires to complete at home and mail back (take-home questionnaire). Approximately 82% of eligible private applicators and 47% of eligible commercial applicators enrolled in the study. Farmworkers were not included in the AHS. At enrollment, applicators provided information on lifetime pesticide use and pesticide use practices, demographic characteristics, lifestyle factors, farm information, and medical history in a self-administered questionnaire. [22] Of enrolled applicators, 44% also completed the take-home questionnaire with additional questions about medical history and pesticide use. [23] Questionnaires are available on the AHS web site: http://aghealth.nih.gov/collaboration/questionnaires.html.

We identified ESRD cases diagnosed between study enrollment and end of follow-up (December 31, 2011) through linkage with the USRDS. The USRDS collects data on all ESRD cases in the United States through Medical Evidence Form CMS-2728, which is required for all new ESRD patients, regardless of Medicare eligibility. The USRDS derives the first ESRD service date (FSD) by taking the earliest of: a) the date of the start of dialysis for chronic renal failure, as reported on the Medical Evidence form, b) the date of a kidney transplant, or c) the date of the first Medicare dialysis claim. [24] The FSD was used to estimate age at ESRD diagnosis. Date of death was obtained from state mortality files and the National Death Index. Because the distribution of ESRD risk factors differs by gender, and because few applicators were female, we excluded female applicators (N= 1,562; 2.7%) from this analysis. We also excluded applicators under age 18 (N=127; <1.0%) and ESRD cases diagnosed prior to enrollment (N=42; 11.5% of cases). This left us with 55,580 participants for analyses of enrollment questionnaire variables, and 24,565 participants for analyses of take-home questionnaire variables.

Exposure assessment

Information provided on the enrollment and take-home questionnaires (Phase 1) was used to estimate lifetime pesticide exposure. We limited these analyses to enrollment information because recent exposure was anticipated to have a minor impact on ESRD risk, given the typical decades-long progression of this disease from chronic stage 1 to ESRD, and this information was not available for all participants. Participants provided information on years of use (duration) and average days per year of use (frequency) for 22 pesticides on the enrollment questionnaire. Duration and frequency of use data were obtained on the take-home questionnaire for 28 additional pesticides. For each pesticide, an intensity-weighted lifetime exposure metric was generated by multiplying lifetime-days of use (product of duration and frequency of use) by an intensity score that accounts for differences in exposure resulting from variation in pesticide application methods, repair of pesticide

application equipment, and use of personal protective equipment [25]. The intensity score algorithm was developed using AHS-specific pesticide exposure monitoring data, in conjunction with expert judgment from published studies on pesticide exposure, including information from the Pesticide Handlers Exposure Database.[25] We used intensity-weighted lifetime-days as our primary exposure metric. Due to the relatively small number of cases, we used the distribution of use among cases to create cut-points for intensity-weighted lifetime use of specific pesticides. For pesticides used by ≥15% of cases, we categorized non-zero intensity-weighted lifetime-days into tertiles with non-users as the referent group. For less frequently used pesticides, non-zero intensity-weighted lifetime-days of use were split at the median (<median vs. ≥ median), with non-users as the referent group. Analyses were restricted to pesticides for which there were at least 5 cases in each exposure stratum.

To assess overall pesticide use, we evaluated risk related to duration, frequency and lifetime-days of use of any pesticide. Duration and frequency of use were categorized into three levels (lowest category of use (referent), > lowest category of use to the median value, and > median). Cumulative lifetime-days of use was categorized into quartiles.

Participant report of medical visits due to pesticide use (enrollment questionnaire), unusually high personal exposure to any pesticide (take-home questionnaire), and doctor-diagnosed pesticide poisoning (take-home questionnaire) were also evaluated in relation to ESRD risk.

Statistical Analysis

We used Cox proportional hazards models to calculate hazard ratios for risk of ESRD, using age as the timescale and adjusting for state as a covariate in all models. Person-time was accrued from the date of study enrollment until the earliest of ESRD diagnosis, death, or the end of study follow-up (December 31, 2011). The proportional hazards assumption was evaluated for each model by entering a product term (exposure of interest * time on study) into each model. A product term coefficient which differed significantly from zero (chi-square p-value <0.10) indicated a potential violation of the proportional hazards assumption.

Private and commercial applicators were analyzed together because there were too few ESRD cases among the latter to analyze them separately. Race and education level were identified as additional potential confounders through directed acyclic graph analyses (DAGs) and review of prior literature. Because adjustment for these factors did not substantially change hazard ratio estimates and power was reduced due to incomplete ascertainment of education and race data, we did not adjust for these factors in the final analyses. Though diabetes and body mass index (BMI) were associated with ESRD risk in this and other studies, [2627] it was unknown whether these conditions affected pesticide use, and it is possible that use of specific pesticides may increase the risk of diabetes and BMI[28-31], which may be on the causal pathway to ESRD. Hazard ratio estimates obtained from models adjusted for diabetes and BMI were not meaningfully different from crude estimates; therefore, these two conditions were not included in final adjusted models. Hypertension was not adjusted for because it is largely asymptomatic and therefore is unlikely to have affected pesticide use practices. Additionally, in our study, there was no association between cumulative pesticide use and hypertension (data not shown).

To assess potential confounding by other pesticides, we examined pairwise correlations between pesticides that were strongly (HR in any strata ≥1.5 or ≤0.65) or significantly associated with ESRD in single pesticide adjusted exposure-response models. For pesticides with a Spearman correlation coefficient ≥0.3, we constructed models with both pesticides, using the intensity-weighted variables included in the main analyses. For pesticides that were correlated with more than one pesticide, we first evaluated each pesticide pair and then added correlated pesticides one at a time into subsequent models. We assessed model fit using Akaike information criteria (AIC) and selected that with the lowest AIC as the final model.

To assess linear exposure-response trends in intensity-weighted lifetime use, we used within-category medians as the score for each level of use for each chemical. Exposure–response trends were also evaluated for duration, frequency, and cumulative lifetime-days of use of any pesticide, and number of doctor visits related to pesticide use.

ESRD is the final stage of chronic kidney disease (CKD), which is often debilitating in later stages of the disease. Cases may have already experienced the effects of CKD prior to study enrollment, which could have influenced their pesticide use. If those with earlier stages of renal disease have reduced exposure due to modified application practices, effect estimates for specific pesticide use would be biased towards the null. This bias is commonly referred to as the healthy worker survivor effect. [32] To evaluate the potential for this effect to influence our findings, we repeated analyses, excluding person-time for all participants for the first five years after enrollment under the assumption that ESRD cases diagnosed within 5 years following study enrollment likely had poor renal health at enrollment.

To evaluate whether patterns of association were consistent across states, we entered a product term for state into pesticide use models for those pesticides for which there were at least 5 cases in each stratum of use in both states.

We used the AHS dataset releases P1REL201209, P3REL201209.00, and AHSREL201304.00. All statistical analyses were done using SAS v9.3 (Cary, NC).

Results

Of the 55,580 participants eligible for analysis, 320 (308 private and 12 commercial) were diagnosed with ESRD over an average 15.7-year follow-up period (incidence rate: 36.6 ESRD cases per 100,000 person-years). Among the subset of 24,565 participants who returned the take-home questionnaire, there were 136 cases (incidence rate: 35.1 ESRD cases per 100,000 person-years). ESRD incidence was significantly higher in North Carolina compared to Iowa, regardless of age, which follows the pattern of ESRD incidence in the general population.[24]. In age- and state-adjusted models, education level greater than high school and obesity at enrollment were associated with increased risk of ESRD (Table 1). Self-reported doctor diagnosis of diabetes, high blood pressure, and kidney disease were significantly associated with increased risk of ESRD. There was a suggestive but non-significant association between pack years of cigarettes smoked and ESRD, but applicator

type, number of years living on a farm, and alcohol consumption at enrollment were not associated with ESRD risk.

More than one doctor visit due to pesticide use and hospitalization due to pesticide use were both significantly associated with ESRD with a significant trend observed for increasing number of pesticide-related doctor visits (p *for trend*=0.038) (Table 2). ESRD risk was not associated with either self-reported unusually high personal pesticide exposure or pesticide poisoning, though only 5 ESRD cases reported a pesticide poisoning diagnosis. No exposure–response relationships were observed for duration and frequency of general pesticide use (data not shown), or for cumulative lifetime-days of general pesticide use (Table 2).

In intensity-weighted cumulative use analyses, positive associations were observed primarily among herbicides (Table 3). ESRD risk was associated with the highest tertile of intensity-weighted use of five herbicides: atrazine, metolachlor, alachlor, paraquat, and pendimethalin, compared to no use. We observed a significant (p *for trend* <0.05) exposure-response trend with increasing use levels for all of these herbicides. Although exposure-response trends were not seen for the herbicides petroleum oil or imazethapyr, ever use of these chemicals was significantly associated with risk (HR=1.63; 95% CI: 1.11, 2.41 and HR=1.46; 95% CI: 1.08, 1.99, respectively; data not shown). The proportional hazards assumption held for all exposures of interest.

Among non-herbicide pesticides, ESRD risk was associated with the highest tertile of metalaxyl (fungicide) use (HR = 1.92; 95% CI: 1.01, 3.66), with evidence of a positive exposure-response trend (Table 3). Associations for the insecticides coumaphos and parathion (organophosphates), aldicarb (carbamate), and chlordane (organochlorine) were elevated (i.e. >1.6), but did not reach statistical significance. A significant positive exposure-response trend was present for chlordane.

In analyses of correlated pesticides, we found fourteen pesticide pairs with a Spearman correlation coefficient ≥0.30. Adjustment for correlated pesticides resulted in reduced overall sample size due to missing data for each chemical. Adjusted estimates were similar in magnitude and direction, but were less precise. Patterns of exposure-response also did not change. After adjustment for correlated pesticides, the association between ESRD risk and the top tertile of intensity-weighted use remained significant only for pendimethalin, and the association became significant for chlordane (HR=1.93; 95% CI: 1.01, 3.70). Estimates for atrazine, alachlor, metolachlor, and aldicarb remained elevated but were no longer significantly associated with ESRD risk after adjustment for correlated pesticides. We did not observe a correlation coefficient ≥0.3 for the following pesticides: 2,4,5 T, chlorimuron ethyl, paraquat, petroleum oil, coumaphos, fonofos, parathion, and permethrin (for animals) (data not shown).

In sensitivity analysis evaluating the potential for a ‘healthy worker survivor effect’, we excluded 53 cases that were diagnosed with ESRD within 5 years after enrollment and 277,900 person-years. The greatest percent reductions of case numbers were observed in the ‘None’ use category for all pesticides. In general, associations for intensity-weighted

lifetime-use were in the same direction and of very similar magnitude compared to estimates in the main analyses. Of note, age- and state-adjusted estimates for the highest quantile of intensity-weighted chlordane (HR= 1.99; 95% CI: 1.07, 3.68) and coumaphos (HR=1.81, 95% CI: 1.03, 3.17) use became significant. (Supplemental Table 1).

Results did not change substantially when we restricted analyses to private applicators (data not shown). Thirteen pesticides had 5 exposed cases in each exposure stratum in both states, and were therefore included in analyses of interaction with state. P-values for interaction with state were consistently > 0.10 (data not shown), suggesting no differences by state.

Discussion

To our knowledge, this is the first study to evaluate the association between ESRD risk and cumulative lifetime use of specific pesticides. Among pesticide applicators in the AHS, we found significant positive associations between intensity-weighted use of several specific pesticides and ESRD; excluding cases that arose within 5 years after enrollment strengthened some of these associations, though estimates were less precise due to the reduction in sample size. This is also the first epidemiological study of ESRD risk associated with non-fatal pesticide poisoning, acute high-level exposure, and pesticide exposure requiring medical attention. Participants who reported doctor visits and hospitalization due to pesticide use had a significantly higher risk of ESRD diagnosis compared to those who did not, but we did not observe increased risk with applicator report of doctor-diagnosed pesticide poisoning or unusually high personal pesticide exposure.

Prior published epidemiological research on pesticide exposure and kidney disease is minimal. Results from several cross-sectional studies evaluating the relationship between agricultural work and CKD suggest a potential association between agricultural work, particularly field work, and CKD prevalence[17,20]. Studies that have evaluated overall pesticide exposure have found positive associations with CKD[17,18,35,36]. The only study to assess the relationship between ESRD risk and agricultural exposures observed an increased risk of ESRD among a large population of insured patients in the San Francisco Bay area who reported that they worked in a place with “frequent or daily exposure to insect or plant spray” (unadjusted hazard ratio: 1.78; 95% CI: 1.36-2.34).[21] In contrast, results from our analyses of general overall pesticide use did not show an association with ESRD; however few participants in this licensed applicator cohort reported no pesticide use, and evaluation of overall pesticide use may obscure associations because only some pesticides appear to be associated with ESRD.

Epidemiologic studies of renal effects of specific pesticides are rare. Hernandez et al (2006) found no difference in serum creatinine levels among greenhouse workers with higher vs. lower levels of apparent cholinesterase inhibition (used as a marker for organophosphate pesticide exposure).[37] Serum levels of several organochlorine insecticides among chronic kidney disease patients were inversely associated with kidney function, potentially indicating a renal filtration deficiency resulting in an accumulation of organochlorine pesticides in the body.[38] In our study, ESRD risk was elevated for three cholinesterase-inhibiting insecticides (the carbamate aldicarb and the organophosphates coumaphos and

parathion), with a moderate positive trend observed for coumaphos. No associations were seen with organochlorine use, except for chlordane, which was significantly positively associated with ESRD risk after adjustment for correlated pesticides and in analyses excluding cases diagnosed within five years after enrollment. Glyphosate was recently partially banned in Sri Lanka due to its hypothesized association with kidney disease, though the ban has since been lifted. Studies that informed this partial ban suggested that glyphosate exposure leads to renal failure only when combined with high-level exposure to heavy metals.[39] We found no evidence of an association between ESRD risk and glyphosate exposure.

Experimental evidence supports our findings of positive associations with exposure to the herbicides atrazine, alachlor, paraquat, and pendimethalin and the fungicide metalaxyl, with evidence of dose-response as well as renal damage and dysfunction at low dose levels. Glomerular lesions and renal tubular necrosis due to oxidative stress-induced cell damage have been observed in animal models with exposure to metalaxyl and paraquat,[4041] and kidney damage and dysfunction have been observed in rats exposed to atrazine [15] and fish exposed to alachlor.[42] There have been no reports of renal effects of pendimethalin among mammals; however, at least one formulation of pendimethalin contains monochlorobenzene as an inert ingredient, which has been shown to cause kidney damage in rats.[43] Although we observed a positive exposure-response trend for metolachlor, we found no published studies implicating this chemical in renal dysfunction or oxidative stress pathways. Sub-acute tubulointerstitial and glomerular damage, such as that observed in animal studies with prolonged low dosing of pesticides, [711] can initiate a feed-forward loop of kidney injury and progressive loss of renal function. [44] In humans, pesticide poisoning can lead to acute kidney injury,[45] which has been associated with increased risk of subsequent chronic kidney disease and ESRD. [4647]

When we adjusted for correlated pesticides, we found that estimates for atrazine, alachlor, metolachlor, and aldicarb were positively associated but no longer statistically significant. We lacked power to formally test interaction among specific pesticides. In addition, we saw significant associations for chemicals from a number of chemical groups. Given that there is no required renal toxicity testing for pesticides, we have no information regarding which chemicals we would expect to be associated with CKD. A large portion of commercial pesticide products are “other ingredients” including solvents; therefore, it is possible that one or more of these “other ingredients” are driving the risk observed here for unrelated chemicals. Unfortunately, we do not have access to what these “other ingredients” are because they are regarded as confidential business information.

A significant positive exposure-response trend was observed for pesticide-related doctor visits, and participants who reported being hospitalized due to pesticide use had three times the risk of ESRD compared to those who did not. Though information about the route and type of pesticide involved in these exposures was not available, these findings support the hypothesis that frequent and/or severe pesticide exposures may increase the risk of ESRD. We did not see an association between pesticide poisoning or self-reported unusually high pesticide exposure and ESRD; however, power to detect an association was limited because information for those exposures was available only for participants who returned the take-

home questionnaire, and pesticide poisoning was rarely diagnosed in the cohort. Pesticide poisoning is frequently under-diagnosed [48]; thus, doctor visits or hospitalization related to pesticide use may represent a more sensitive indicator for acute high-level exposure than pesticide poisoning diagnosis.

The study improves upon prior research in several ways. First, we were able to evaluate associations of ESRD risk with a wide range of specific chemicals that vary in toxicity and extent of use. The prospective design of the study mitigates concerns about differential misclassification of exposure. Whereas prior studies were limited by small sample size and exposure to few chemicals, the large size of the AHS cohort allowed us to assess exposure-response trends for many individual pesticides. Also, use of a validated exposure-intensity metric [25] allowed for a better estimate of each participant's likely pesticide exposure as opposed to non-specific pesticide use. Until now, the relationship between short-term high-level pesticide exposures and kidney disease has been evaluated only with respect to the immediate effects of pesticide poisonings. Here, we were able to evaluate measures of non-poisoning short-term high-level pesticide exposures, thereby providing an important contribution to the scientific literature regarding occupational risk factors for kidney disease. Additionally, the fact that almost all ESRD cases in the United States are captured in the USRDS reduces concerns about loss to follow-up or outcome misclassification.

Because exposure data were collected prior to disease onset and ESRD diagnosis data were obtained from a third party linkage rather than participant report, any exposure misclassification due to self-report is likely to be non-differential with respect to the outcome, which would bias estimates towards the null. Additionally, evidence suggests that report of pesticide exposure by AHS participants is reasonably reliable [49] and plausible. [50] The accuracy and reliability of reporting acute pesticide exposures has not been investigated.

Analyses of lifetime use of pesticides that were assessed only on the take-home questionnaire could be subject to selection bias if applicators who returned the take-home questionnaire were significantly different from those who did not by exposure or outcome, or by factors associated with the exposure or the outcome. State of enrollment, age, and pesticide use characteristics were similar for those who returned the take-home questionnaire compared to those who did not, and the percentage of cases was essentially the same for take-home questionnaire respondents as it was for non-respondents (0.59% vs. 0.57%). Still, differences in unmeasured factors remain a possibility, and we had limited power to evaluate associations between ESRD and lifetime use of the pesticides for which duration and frequency information was collected only on the take-home questionnaire.

Lifetime use estimates could also be biased if participants with prevalent pre-end stage kidney disease modified their pesticide application practices in the period prior to enrollment. This ‘healthy worker survivor effect’ is a common problem in occupational health studies, including among pesticide applicators, [51] frequently biasing estimates toward the null. [32] Results of our sensitivity analysis suggest a minimal impact of this potential effect on HR estimates. The median time from enrollment to ESRD diagnosis was 9.7 years. It is possible that unmeasured post-enrollment pesticide use may differ by case status; if recent exposures are stronger contributors to ESRD risk than pre-enrollment exposures, then

our results would still be biased towards the null. However, progression of renal disease from chronic stage 1 to ESRD can take several decades; if pesticide use does contribute to kidney disease incidence, it is probable that this pathway would have been initiated prior to enrollment.

Because the AHS is a cohort of US farmers in NC and IA, the risks for this cohort may be different from the risks experienced by farmworkers in the US or elsewhere. However, the AHS, with its detailed exposure characterization, limited loss to follow up over 20 years, and the ability to link to a population-based kidney disease registry, provides important human data for evaluation of the role of pesticides and kidney disease.

Lastly, in these analyses we estimated associations between a large number of exposures and ESRD. We did not employ statistical methods to adjust for multiple comparisons, such as the Bonferroni correction. Previous authors have cautioned against employing Bonferroni-type corrections in an epidemiological analysis of associations between multiple environmental or occupational exposures and disease, [52-54] and such methods have largely fallen out of use in such settings because Bonferroni adjustments are concerned with testing of a general null hypothesis which is rarely of interest. Alternatives to Bonferroni methods exist for inference in settings where multiple exposure effects are estimated, including Bayesian methods;[55] however, we have not employed such methods here, in preference for simply describing what statistical quantities have been estimated.

Conclusions

Our study provides evidence for an association between ESRD risk and chronic exposure to specific chemicals among pesticide applicators in Iowa and North Carolina. Results from this study also suggest that pesticide exposures resulting in medical visits increase the risk of incident ESRD, raising concerns that multiple high-level pesticide exposures may contribute to irreversible kidney damage and resultant disease. Efforts to better characterize the pathway between pesticide exposure and kidney disease should include assessments of earlier disease stages, rate of progression from CKD to ESRD, and other potential routes of pesticide exposure, such as spray drift and carry-home exposures. Caution should be taken in interpreting results of such studies when diagnosis dates or disease severity information is not available, because the healthy worker survivor effect may bias estimates towards the null. Additional epidemiological studies are needed to confirm the findings of our study, given the limited research on the role of pesticide exposure in the development of renal disease, and research on the direct renal toxicity of specific chemicals must be expanded to facilitate interpretation of epidemiological results.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Betrosian A, Balla M, Kafiri G, et al. Multiple systems organ failure from organophosphate poisoning. Journal of toxicology Clinical toxicology. 1995; 33(3):257–60. [PubMed: 7760452]
2. Soloukides A, Moutzouris DA, Kassimatis T, et al. A fatal case of paraquat poisoning following minimal dermal exposure. Ren Fail. 2007; 29(3):375–7. [PubMed: 17497456]
3. Wu IW. Acute renal failure induced by bentazone: 2 case reports and a comprehensive review. Journal of nephrology. 2008; 21(2):256–60. [PubMed: 18446722]
4. Memis D, Tokatlioglu D, Koyuncu O, et al. Fatal aluminium phosphide poisoning. European journal of anaesthesiology. 2007; 24(3):292–3. [PubMed: 17054805]
5. Kim, Sj, Gil, HW., Yang, JO., et al. The clinical features of acute kidney injury in patients with acute paraquat intoxication. Nephrology Dialysis Transplantation. 2009; 24(4):1226–32.
6. Shah MD, Iqbal M. Diazinon-induced oxidative stress and renal dysfunction in rats. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association. 2010; 48(12):3345–53. [PubMed: 20828599]
7. Tripathi S, Srivastav AK. Nephrotoxicity induced by long-term oral administration of different doses of chlorpyrifos. Toxicology and industrial health. 2010; 26(7):439–47. [PubMed: 20504822]
8. Uyanikgil Y, Ates U, Baka M, et al. Immunohistochemical and histopathological evaluation of 2,4-dichlorophenoxyacetic acid-induced changes in rat kidney cortex. Bull Environ Contam Toxicol. 2009; 82(6):749–55. [PubMed: 19277441]
9. Poovala VS, Huang H, Salahudeen AK. Role of reactive oxygen metabolites in organophosphate-bidrin-induced renal tubular cytotoxicity. J Am Soc Nephrol. 1999; 10(8):1746–52. [PubMed: 10446942]
10. Choudhary N, Sharma M, Verma P, et al. Hepato and nephrotoxicity in rat exposed to endosulfan. Journal of environmental biology / Academy of Environmental Biology, India. 2003; 24(3):305–8.
11. Sonne C, Wolkers H, Leifsson PS, et al. Organochlorine-induced histopathology in kidney and liver tissue from Arctic fox (Vulpes lagopus). Chemosphere. 2008; 71(7):1214–24. [PubMed: 18279914]
12. Sobel ES, Gianini J, Butfiloski EJ, et al. Acceleration of autoimmunity by organochlorine pesticides in (NZB × NZW)F1 mice. Environmental health perspectives. 2005; 113(3):323–28. [PubMed: 15743722]
13. Kaur B, Khera A, Sandhir R. Attenuation of cellular antioxidant defense mechanisms in kidney of rats intoxicated with carbofuran. Journal of biochemical and molecular toxicology. 2012; 26(10): 393–8. [PubMed: 22807346]
14. Chargui I, Grissa I, Bensassi F, et al. Oxidative stress, biochemical and histopathological alterations in the liver and kidney of female rats exposed to low doses of deltamethrin (DM): a molecular assessment. Biomedical and environmental sciences : BES. 2012; 25(6):672–83. [PubMed: 23228837]
15. Santa Maria C, Vilas MG, Muriana FG, et al. Subacute atrazine treatment effects on rat renal functions. Bull Environ Contam Toxicol. 1986; 36(3):325–31. [PubMed: 3955241]
16. Orantes CM, Miguel Almaguer MD, Brizuela EG, et al. Chronic Kidney Disease and Associated Risk Factors in the Bajo Lempa Region of El Salvador: Nefrolempa Study, 2009. MEDICC Review. 2011; 13(4):14.
17. Sanoff SL, Callejas L, Alonso CD, et al. Positive association of renal insufficiency with agriculture employment and unregulated alcohol consumption in Nicaragua. Renal failure. 2010; 32(7):766–77. [PubMed: 20662688]

18. O'Donnell JK, Tobey M, Weiner DE, et al. Prevalence of and risk factors for chronic kidney disease in rural Nicaragua. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2011; 26(9):2798–805.
19. Bandara JM, Wijewardena HV, Bandara YM, et al. Pollution of River Mahaweli and farmlands under irrigation by cadmium from agricultural inputs leading to a chronic renal failure epidemic among farmers in NCP, Sri Lanka. Environ Geochem Health. 2011; 33(5):439–53. [PubMed: 20981564]
20. Peraza S, Wesseling C, Aragon A, et al. Decreased kidney function among agricultural workers in el salvador. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2012; 59(4):531–40. [PubMed: 22300650]
21. Hsu CY, Iribarren C, McCulloch CE, et al. Risk factors for end-stage renal disease: 25-year follow-up. Archives of internal medicine. 2009; 169(4):342–50. [PubMed: 19237717]
22. Alavanja MC, Sandler DP, McMaster SB, et al. The Agricultural Health Study. Environ Health Perspect. 1996; 104(4):362–9. [PubMed: 8732939]
23. Tarone RE, Alavanja MC, Zahm SH, et al. The Agricultural Health Study: factors affecting completion and return of self-administered questionnaires in a large prospective cohort study of pesticide applicators. Am J Ind Med. 1997; 31(2):233–42. [PubMed: 9028440]
24. United States Renal Data System. USRDS 2012 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases; 2012.
25. Coble J, Thomas KW, Hines CJ, et al. An updated algorithm for estimation of pesticide exposure intensity in the agricultural health study. International Journal of Environmental Research and Public Health. 2011; 8(12):4608–22. [PubMed: 22408592]
26. Bash LD, Astor BC, Coresh J. Risk of incident ESRD: a comprehensive look at cardiovascular risk factors and 17 years of follow-up in the Atherosclerosis Risk in Communities (ARIC) Study. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2010; 55(1):31–41. [PubMed: 19932544]
27. Hsu CY, McCulloch CE, Iribarren C, et al. Body mass index and risk for end-stage renal disease. Ann Intern Med. 2006; 144(1):21–8. [PubMed: 16389251]
28. Lee DH, Steffes MW, Sjodin A, et al. Low dose organochlorine pesticides and polychlorinated biphenyls predict obesity, dyslipidemia, and insulin resistance among people free of diabetes. PloS one. 2011; 6(1):e15977. [PubMed: 21298090]
29. Lee DH, Steffes MW, Sjodin A, et al. Low dose of some persistent organic pollutants predicts type 2 diabetes: a nested case-control study. Environ Health Perspect. 2010; 118(9):1235–42. [PubMed: 20444671]
30. Starling AP, Umbach DM, Kamel F, et al. Pesticide use and incident diabetes among wives of farmers in the Agricultural Health Study. Occup Environ Med. 2014
31. Montgomery MP, Kamel F, Saldana TM, et al. Incident diabetes and pesticide exposure among licensed pesticide applicators: Agricultural Health Study, 1993-2003. Am J Epidemiol. 2008; 167(10):1235–46. [PubMed: 18343878]
32. Richardson D, Wing S, Steenland K, et al. Time-related aspects of the healthy worker survivor effect. Ann Epidemiol. 2004; 14(9):633–9. [PubMed: 15380793]
33. Coe FL, Evan A, Worcester E. Kidney stone disease. Journal of Clinical Investigation. 2005; 115(10):2598–608. [PubMed: 16200192]
34. Shafi, TaC, Josef. Disease: Definition, Epidemiology, Cost, and Outcomes Chronic Kidney Disease, Dialysis, and Transplantation. Third. Philadelphia, PA: Saunders Elsevier; 2010. Chronic Kidney Disease: Definition, Epidemiology, Cost, and Outcomes; p. 3-21.
35. Payan-Renteria R, Garibay-Chavez G, Rangel-Ascencio R, et al. Effect of chronic pesticide exposure in farm workers of a Mexico community. Archives of environmental & occupational health. 2012; 67(1):22–30. [PubMed: 22315932]
36. Raines N, Gonzalez M, Wyatt C, et al. Risk factors for reduced glomerular filtration rate in a Nicaraguan community affected by Mesoamerican nephropathy. MEDICC Rev. 2014; 16(2):16–22.

37. Hernandez AF, Amparo Gomez M, Perez V, et al. Influence of exposure to pesticides on serum components and enzyme activities of cytotoxicity among intensive agriculture farmers. Environmental research. 2006; 102(1):70–6. [PubMed: 16620808]
38. Siddharth M, Datta SK, Bansal S, et al. Study on organochlorine pesticide levels in chronic kidney disease patients: association with estimated glomerular filtration rate and oxidative stress. Journal of biochemical and molecular toxicology. 2012; 26(6):241–7. [PubMed: 22645066]
39. Jayasumana C, Gunatilake S, Senanayake P. Glyphosate, hard water and nephrotoxic metals: are they the culprits behind the epidemic of chronic kidney disease of unknown etiology in Sri Lanka? Int J Environ Res Public Health. 2014; 11(2):2125–47. [PubMed: 24562182]
40. Paolini M, Mesirca R, Pozzetti L, et al. Biomarkers of effect in evaluating metalaxyl cocarcinogenesis. Selective induction of murine CYP 3A isoform. Mutation research. 1996; 361(2-3):157–64. [PubMed: 8980701]
41. Adachi J, Tomita M, Yamakawa S, et al. 7-Hydroperoxycholesterol as a marker of oxidative stress in rat kidney induced by paraquat. Free radical research. 2000; 33(3):321–7. [PubMed: 10993486]
42. Butchiram MS, Tilak KS, Raju PW. Studies on histopathological changes in the gill, liver and kidney of Channa punctatus (Bloch) exposed to Alachlor. Journal of environmental biology / Academy of Environmental Biology, India. 2009; 30(2):303–6.
43. Kluwe WM, Dill G, Persing R, et al. Toxic responses to acute, subchronic, and chronic oral administrations of monochlorobenzene to rodents. Journal of toxicology and environmental health. 1985; 15(6):745–67. [PubMed: 4057281]
44. Hodgkins KS, Schnaper HW. Tubulointerstitial injury and the progression of chronic kidney disease. Pediatr Nephrol. 2012; 27(6):901–9. [PubMed: 21947270]
45. Reigart, JR., Roberts, JR., Agency, USEP. Recognition and management of pesticide poisonings. US Environmental Protection Agency; Washington, DC: 1999.
46. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney international. 2012; 81(5):442–8. [PubMed: 22113526]
47. Ishani A, Xue JL, Himmelfarb J, et al. Acute kidney injury increases risk of ESRD among elderly. J Am Soc Nephrol. 2009; 20(1):223–8. [PubMed: 19020007]
48. Roberts, JRaR, R, J. Recognition and Management of Pesticide Poisonings. 6. Washington, DC: U.S. Environmental Protection Agency; 2013.
49. Blair A, Tarone R, Sandler D, et al. Reliability of reporting on life-style and agricultural factors by a sample of participants in the Agricultural Health Study from Iowa. Epidemiology (Cambridge, Mass). 2002; 13(1):94–9.
50. Hoppin JA, Yucel F, Dosemeci M, et al. Accuracy of self-reported pesticide use duration information from licensed pesticide applicators in the Agricultural Health Study. Journal of exposure analysis and environmental epidemiology. 2002; 12(5):313–8. [PubMed: 12198579]
51. Gomez-Marin O, Fleming LE, Lee DJ, et al. Acute and chronic disability among U.S. farmers and pesticide applicators: the National Health Interview Survey (NHIS). Journal of agricultural safety and health. 2004; 10(4):275–85. [PubMed: 15603226]
52. Savitz DA, Olshan AF. Multiple comparisons and related issues in the interpretation of epidemiologic data. American Journal of Epidemiology. 1995; 142(9):904. [PubMed: 7572970]
53. Perneger TV. What's wrong with Bonferroni adjustments. Bmj. 1998; 316(7139):1236–38. [PubMed: 9553006]
54. Greenland S. Multiple comparisons and association selection in general epidemiology. International journal of epidemiology. 2008; 37(3):430–34. [PubMed: 18453632]
55. MacLehose RF, Dunson DB, Herring AH, et al. Bayesian Methods for Highly Correlated Exposure Data. Epidemiology (Cambridge, Mass). 2007; 18(2):199–-207. 10.1097/01.ede.0000256320.30737.c0.

What this paper adds

- Much is known about clinical risk factors for end-stage renal disease (chronic kidney disease requiring dialysis or kidney transplant for survival), but research on environmental risk factors for kidney disease is limited.
- In this study of male pesticide applicators, risk of end-stage renal disease increased with increasing cumulative exposure to several pesticides, including the herbicides metolachlor, paraquat and pendimethalin, and the insecticide chlordane.
- Risk of end-stage renal disease was significantly greater for pesticide applicators who reported multiple doctor visits due to pesticide use and hospitalization due to pesticide use, compared to those who reported no medical visits due to pesticide use.
- Exposure to certain pesticides may increase the risk of end-stage renal disease; however, additional studies are needed to support these findings.

Table 1

Association between ESRD and demographic and medical conditions among private and commercial applicators, adjusted for age and state, Agricultural Health Study (1993-1997)

Variable (at enrollment)		Non-cases (N= 55,260) N (%)	ESRD Cases (N=320) N (%)	HR (95% CI)
State (where enrolled) *	Iowa	35943 (65.0)	134 (41.9)	
	North Carolina	19317 (35.0)	186 (58.1)	2.02 (1.61, 2.53)
Applicator type*	Private	50575 (91.5)	308 (96.3)	
	Commercial	4685 (8.5)	12 (3.7)	0.75 (0.42, 1.35)
Age category (years)	18-30	6306 (11.4)	12 (3.8)	
	31-49	27380 (49.6)	58 (18.1)	1.15 (0.62, 2.15)
	50-69	18924 (34.3)	210 (65.6)	6.04 (3.38, 10.81)
	≥ 70	2650 (4.8)	40 (12.5)	10.04 (5.25, 19.20)
Race	White	52763 (97.3)	273 (85.3)	
	non-White	1440 (2.7)	47 (14.7)	4.42 (3.18, 6.13)
Education level	High school or less	22452 (41.7)	74 (24.3)	
	More than high school	31369 (58.3)	231 (75.7)	1.49 (1.14 1.95)
Number years lived or worked on a farm†	0-20	2181 (10.0)	10 (7.9)	
	21-30	2928 (13.4)	13 (10.2)	1.43 (0.62 3.28)
	>30	16668 (76.5)	104 (81.9)	0.90 (0.46 1.75)
Number of days per month drink alcohol in the last year	0	16504 (31.9)	147 (52.1)	
	1-23	31833 (61.5)	121 (42.9)	0.86 (0.66 1.11)
	≥24	3447 (6.7)	14 (5.0)	0.78 (0.45 1.36)
Number of pack-years smoked	None	28059 (53.8)	124 (43.5)	
	1-11	10956 (21.0)	45 (15.8)	0.80 (0.57 1.13)
	12-30	8708 (16.7)	67 (23.5)	1.23 (0.91 1.66)
	>30	4464 (8.6)	49 (17.2)	1.36 (0.97 1.91)
Body mass index (kg/m^2)	<25	9658 (25.5)	44 (19.8)	
	25-29.99	19341 (51.1)	108 (48.6)	1.26 (0.89 1.79)
	≥30	8823 (23.3)	70 (31.5)	2.00 (1.37 2.93)
Self-reported doctor diagnosis of:				
Diabetes	No	49616 (97.2)	192 (70.1)	
	Yes	1411 (2.8)	82 (29.9)	8.78 (6.72, 11.45)
High Blood Pressure †	No	20081 (83.6)	52 (39.4)	
	Yes	3945 (16.4)	80 (60.6)	4.66 (3.25, 6.68)
Kidney disease (not counting kidney stones)	No	50935 (99.2)	245 (88.4)	
	Yes	415 (0.8)	32 (11.6)	10.35 (7.14, 15.02)

ESRD = end-stage renal disease.

*Adjusted for age only.

†Reported on the take-home questionnaire only

Table 2

Association between ESRD risk and acute and cumulative pesticide exposure, adjusted for age and state, among male pesticide applicators, Agricultural Health Study (1993-1997)

Variable		Non-cases (N= 55,260) N (%)	ESRD Cases (N=320) N (%)	HR (95% CI)	P for trend
	None	49764 (93.4)	272 (91.3)		
	Once	2635 (4.9)	15 (5)	1.07 (0.64, 1.8)	
	More than once	884 (1.7)	11 (3.7)	2.13 (1.17, 3.89)	
Number of times ever visited a medical doctor due to pesticide use					0.0384
	No	51619 (98.9)	275 (96.2)		
Ever hospitalized due to pesticide use	Yes	572 (1.1)	11 (3.8)	3.05 (1.67, 5.58)	
	No	20112 (84.8)	115 (87.1)		
Ever experienced unusually high personal pesticide exposure *	Yes	3596 (15.2)	17 (12.9)	1.08 (0.65, 1.81)	
	No	23506 (98.0)	126 (96.2)		
Ever diagnosed with Pesticide poisoning *	Yes	484 (2.0)	5 (3.8)	1.59 (0.65, 3.89)	
	0-64	13850 (27.1)	78 (28.0)		
	65-225	15637 (30.6)	69 (24.7)	0.89 (0.64, 1.24)	
	226-457	7307 (14.3)	41 (14.7)	0.95 (0.65, 1.39)	
Cumulative lifetime-days personally mixed or applied pesticides	>457	14314 (28.0)	91 (32.6)	1.07 (0.79, 1.44)	
					0.4667

ESRD = end-stage renal disease

* Question asked only on the take-home questionnaire: N (non-cases) = 24,429 and N (cases) =136.

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Table 3

Intensity-weighted lifetime-days of use of specific pesticides and ESRD risk, adjusted for age and state, among male pesticide applicators in the Agricultural Health Study (1993-1997)

		Non-cases N=55,260	ESRD Cases N=320	HR (95% CI)	P for trend
Pesticide	**Intensity-weighted lifetime-days**	**N (%)**	**N (%)**		
FUMIGANTS					
Methyl Bromide	<490	3180 (6)	17 (5.7)	0.63 (0.38, 1.04)	
	490-1873	2449 (4.6)	20 (6.8)	0.87 (0.54, 1.40)	
	≥1874	2038 (3.8)	20 (6.8)	0.97 (0.61, 1.57)	
					0.9304
FUNGICIDES					
Chlorothalonil *	<588	1341 (2.5)	13 (4.4)	1.47 (0.84, 2.59)	
	588-3254	1483 (2.8)	14 (4.7)	1.38 (0.80, 2.40)	
	≥3255	1330 (2.5)	14 (4.7)	1.54 (0.89, 2.67)	
					0.1119
Metalaxyl *	<294	1315 (5.6)	11 (8.7)	1.62 (0.86, 3.06)	
	294-1679	1531 (6.6)	12 (9.5)	1.58 (0.83, 3.01)	
	≥ 1680	1339 (5.7)	13 (10.3)	1.92 (1.01, 3.66)	
					0.067
HERBICIDES					
Phenoxy herbicides					
2,4-D *	<1721	15671 (29.8)	67 (22.9)	0.74 (0.54, 1.02)	
	1721-6614	12980 (24.7)	66 (22.5)	0.87 (0.62, 1.2)	
	≥ 6615	10788 (20.5)	71 (24.2)	1.00 (0.73, 1.39)	
					0.3247
2,4,5,T *	<780	2425 (10.3)	12 (9.4)	0.60 (0.33, 1.09)	
	≥ 780	1776 (7.6)	13 (10.2)	0.83 (0.46, 1.48)	
					0.5508

Pesticide	Intensity-weighted lifetime-days	Non-cases N=55,260 N (%)	ESRD Cases N=320 N (%)	HR (95% CI)	P for trend
Triazine herbicides					
Atrazine	<1302	13386 (25.3)	67 (22.3)	1.10 (0.80, 1.52)	
	1302-6439	14134 (26.7)	67 (22.3)	1.00 (0.73, 1.39)	
	≥ 6440	9065 (17.1)	72 (24)	1.51 (1.11, 2.06)	
					0.023
Cyanazine	<780	7791 (15.7)	27 (10.6)	0.82 (0.54, 1.26)	
	780-2787	6479 (13.1)	29 (11.4)	1.07 (0.71, 1.62)	
	≥ 2788	6201 (12.5)	28 (11)	1.16 (0.76, 1.77)	
					0.3698
Metribuzin [a]	<455	3555 (15.1)	14 (10.9)	0.90 (0.50, 1.62)	
	455-1322	2497 (10.6)	15 (11.6)	1.39 (0.79, 2.45)	
	≥ 1323	2627 (11.2)	16 (12.4)	1.49 (0.86, 2.59)	
					0.1075
Dinitroaniline herbicides					
Pendimethalin *	<793	4318 (18.3)	14 (11)	0.7 (0.4, 1.23)	
	793-3023	2829 (12)	14 (11)	1.19 (0.67, 2.1)	
	≥ 3024	1779 (7.6)	15 (11.8)	2.15 (1.23, 3.77)	
					0.0041
Trifluralin	<1008	8255 (16.8)	37 (14.7)	0.95 (0.66, 1.38)	
	1008-3417	8060 (16.4)	39 (15.5)	1.10 (0.76, 1.59)	
	≥ 3418	9425 (19.1)	38 (15.1)	0.91 (0.63, 1.31)	
					0.6499
Chloroacetanilide herbicides					
Metolachlor	<1006	9206 (18.7)	38 (14.5)	1.02 (0.71, 1.46)	
	1006-3827	7157 (14.5)	38 (14.5)	1.39 (0.96, 2.00)	
	≥ 3828	6443 (13.1)	40 (15.3)	1.53 (1.08, 2.18)	
					0.0121
Alachlor	<1008	9683 (19.7)	46 (17.6)	1.04 (0.74, 1.48)	

Pesticide	Intensity-weighted lifetime-days	Non-cases N=55,260 N (%)	ESRD Cases N=320 N (%)	HR (95% CI)	P for trend
	1008-5486	9776 (19.9)	47 (18)	1.02 (0.73, 1.44)	
	≥ 5487	6111 (12.4)	49 (18.8)	1.56 (1.12, 2.18)	
					0.0077
all other herbicides					
Dicamba	<473	6981 (14.2)	32 (12.4)	1.01 (0.67, 1.51)	
	473-2603	9899 (20.2)	29 (11.2)	0.66 (0.43, 1.01)	
	≥ 2604	7766 (15.8)	34 (13.1)	1.05 (0.71, 1.57)	
					0.7251
Chlorimuron-ethyl *	<351	3368 (14.3)	12 (9.3)	0.90 (0.49, 1.65)	
	351-787	1361 (5.8)	14 (10.9)	2.47 (1.4, 4.34)	
	≥ 788	2863 (12.2)	13 (10.1)	1.06 (0.59, 1.9)	
					0.5893
EPTC	<15	4525 (9.3)	11 (4.4)	0.64 (0.35, 1.19)	
	15-55	2753 (5.6)	12 (4.8)	1.18 (0.65, 2.13)	
	>55	2713 (5.6)	12 (4.8)	1.25 (0.69, 2.24)	
					0.3894
Paraquat *	<638	1881 (8)	11 (8.5)	1.15 (0.61, 2.15)	
	638-2087	1034 (4.4)	10 (7.7)	1.82 (0.93, 3.58)	
	≥ 2088	1012 (4.3)	12 (9.2)	2.23 (1.18, 4.21)	
					0.0121
Petroleum Oil *	<784	1950 (8.3)	11 (8.5)	1.27 (0.68, 2.38)	
	784-2024	1006 (4.3)	12 (9.3)	3.20 (1.75, 5.85)	
	≥ 2025	1969 (8.4)	12 (9.3)	1.42 (0.78, 2.59)	
					0.1906
Imazethapyr	<350	6748 (13.8)	29 (11.2)	1.34 (0.87, 2.07)	
	350-839	4819 (9.8)	29 (11.2)	2.03 (1.31, 3.15)	
	≥ 840	9393 (19.2)	31 (12)	1.26 (0.83, 1.93)	
					0.3169
Glyphosate	<600	12104 (22.9)	70 (23.4)	0.91 (0.67, 1.26)	

Pesticide	Intensity-weighted lifetime-days	Non-cases N=55,260 N (%)	ESRD Cases N=320 N (%)	HR (95% CI)	P for trend
	600-2687	14471 (27.3)	72 (24.1)	0.75 (0.54, 1.03)	
	≥ 2688	13375 (25.3)	74 (24.7)	0.85 (0.62, 1.17)	
					0.5843
Butylate *	<1006	3237 (13.8)	13 (10.2)	0.78 (0.43, 1.41)	
	≥ 1006	2888 (12.3)	12 (9.4)	0.87 (0.48, 1.60)	
					0.6548
INSECTICIDES					
Organochlorines					
Aldrin *	<327	1292 (5.5)	12 (9.8)	1.27 (0.68, 2.37)	
	327-1018	1196 (5.1)	11 (9)	1.21 (0.63, 2.31)	
	≥ 1019	1227 (5.2)	12 (9.8)	1.23 (0.66, 2.29)	
					0.5243
Chlordane *	<560	2581 (11)	11 (8.7)	0.57 (0.30, 1.06)	
	560-1224	805 (3.4)	10 (7.9)	1.44 (0.75, 2.78)	
	≥ 1225	874 (3.7)	13 (10.2)	1.70 (0.95, 3.06)	
					0.0409
DDT *	<438	1904 (8.2)	16 (12.7)	0.80 (0.46, 1.38)	
	438-2327	1689 (7.2)	16 (12.7)	0.82 (0.47, 1.42)	
	≥ 2328	1328 (5.7)	15 (11.9)	0.99 (0.56, 1.74)	
					0.9263
Heptachlor *	>408	1235 (5.2)	11 (8.7)	1.29 (0.68, 2.46)	
	≥ 408	1433 (6.1)	15 (11.9)	1.44 (0.82, 2.52)	
					0.2068
Toxaphene *	<1006	1554 (6.6)	8 (6.5)	0.69 (0.34, 1.42)	
	≥ 1006	975 (4.1)	9 (7.3)	0.99 (0.49, 1.99)	
					0.9583
Organophosphates					

Pesticide	Intensity-weighted lifetime-days	Non-cases N=55,260 N (%)	ESRD Cases N=320 N (%)	HR (95% CI)	P for trend
Terbufos	<827	7124 (14.4)	28 (11)	1.0 (0.66, 1.51)	
	827-2159	4413 (8.9)	27 (10.6)	1.41 (0.93, 2.13)	
	≥ 2160	6833 (13.8)	29 (11.4)	0.97 (0.65, 1.44)	
					0.9823
Fonofos	<588	3761 (7.6)	10 (3.9)	0.62 (0.33, 1.19)	
	588-1619	2834 (5.7)	11 (4.3)	0.9 (0.48, 1.66)	
	≥ 1620	3670 (7.4)	12 (4.7)	0.7 (0.39, 1.27)	
					0.257
Chlorpyrifos	<438	5989 (13.1)	29 (11)	0.85 (0.57, 1.26)	
	438-2139	7603 (16.7)	28 (10.6)	0.65 (0.43, 0.97)	
	≥ 2140	6078 (13.3)	29 (11)	0.84 (0.57, 1.25)	
					0.3738
Malathion*	<644	6577 (28.2)	27 (21.4)	0.87 (0.54, 1.42)	
	644-1743	3567 (15.3)	28 (22.2)	1.47 (0.91, 2.36)	
	≥ 1744	4403 (18.9)	28 (22.2)	1.01 (0.62, 1.63)	
					0.9247
Parathion*	<1392	1022 (4.4)	8 (6.5)	1.11 (0.53, 2.29)	
	≥1392	687 (2.9)	8 (6.5)	1.64 (0.79, 3.43)	
					0.1856
Diazinon*	<1184	3124 (13.4)	11 (8.7)	0.57 (0.31, 1.07)	
	≥1184	1762 (7.5)	14 (11.1)	1.11 (0.62, 1.97)	
					0.6733
Phorate*	<408	2514 (10.7)	10 (8.3)	0.76 (0.39, 1.51)	
	408-2169	2625 (11.2)	12 (9.9)	0.87 (0.47, 1.63)	
	≥ 2170	1486 (6.3)	12 (9.9)	1.47 (0.80, 2.71)	
					0.1941
Coumaphos	<957	2100 (4.3)	14 (5.6)	1.29 (0.75, 2.22)	
	≥957	1651 (3.4)	14 (5.6)	1.63 (0.95, 2.79)	
					0.0689

Pesticide	Intensity-weighted lifetime-days	Non-cases N=55,260 N (%)	ESRD Cases N=320 N (%)	HR (95% CI)	P for trend
Dichlorvos	<3136	2987 (6.1)	10 (4.1)	0.78 (0.41, 1.47)	
	≥ 3136	1682 (3.4)	10 (4.1)	1.41 (0.74, 2.67)	
					0.2862
Pyrethroids					
Permethrin for crops	<368	2737 (5.6)	11 (4.3)	1.06 (0.58, 1.94)	
	368-2572	2611 (5.3)	11 (4.3)	0.99 (0.54, 1.82)	
	≥ 2573	1576 (3.2)	11 (4.3)	1.50 (0.82, 2.77)	
					0.201
Permethrin for animals	<646	2709 (5.4)	13 (5.1)	1.60 (0.91, 2.83)	
	≥ 646	3225 (6.5)	12 (4.7)	1.24 (0.69, 2.22)	
					0.4335
Carbamates					
Carbofuran	<696	5740 (11.7)	21 (8.4)	0.65 (0.41, 1.03)	
	696-2299	3753 (7.6)	21 (8.4)	0.88 (0.56, 1.39)	
	≥ 2300	3210 (6.5)	22 (8.8)	1.06 (0.68, 1.65)	
					0.755
Carbaryl*	<919	4818 (20.6)	18 (14.4)	0.57 (0.34, 0.97)	
	919-6874	3353 (14.4)	17 (13.6)	0.59 (0.33, 1.05)	
	≥ 6875	1649 (7.1)	19 (15.2)	1.05 (0.58, 1.88)	
					0.3186
Aldicarb*	<1323	878 (3.7)	8 (6.3)	1.66 (0.79, 3.5)	
	≥ 1323	856 (3.6)	7 (5.5)	1.71 (0.77, 3.79)	
					0.1876

*Indicates pesticide with duration and frequency information only available on the take-home questionnaire: N (non-cases) = 24,429 and N (cases) =136.