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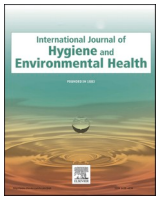

Prenatal ambient pesticide exposure and childhood retinoblastoma

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ABSTRACT

Background: Retinoblastoma is a rare tumor of the retina, most commonly found in young children. Due to the rarity of this childhood cancer, few studies have been able to examine prenatal pesticide exposure as a risk factor.
Objective: To examine the relationship between childhood retinoblastoma and prenatal exposure to pesticides through residential proximity to agricultural pesticide applications.
Methods: We conducted a population-based case-control study using cases aged 5 and younger identified from the California Cancer Registry, and controls randomly selected from California birth certificates. Frequency matching cases to controls by age resulted in 221 cases of unilateral retinoblastoma and 114 cases of bilateral retinoblastoma, totaling 335 cases and 123,166 controls. Based on addresses from birth certificates we employed Pesticide Use Reports and land use information within a geographic information system approach to individually assess exposures to specific pesticides within 4000 m of the residence reported on birth certificates. The associations between retinoblastoma (all types combined and stratified by laterality) and individual pesticides were expressed as odds ratios estimates obtained from unconditional logistic regression models including a single pesticide, and from a hierarchical logistic regression model including all pesticides.
Results: We found that exposures to acephate (OR: 1.70, 95% CI: 1.20, 2.41) and bromacil (OR: 1.87, 95% CI: 1.07, 3.26) were associated with increased risk for unilateral retinoblastoma. In addition to acephate, we found that pymetrozine (OR: 1.45, 95% CI: 1.00, 2.08) and kresoxim-methyl (OR: 1.60, 95% CI: 1.00, 2.56) were associated with retinoblastoma (all types combined).
Conclusion: Our findings suggest that certain types of prenatal ambient pesticide exposure from residing near agricultural fields may play a role in the development of childhood retinoblastoma.

1. Introduction

Retinoblastoma is a rare tumor of the retina, affecting an estimated 8000 children per year globally (Dimaras et al., 2015). Accounting for roughly 3% of all childhood cancers, it is the most common eye cancer in children (Yun et al., 2011). Though the survival rate is greater than 95% in high-income countries, survivors may face visual impairments, declines in neurocognitive development, and elevated risk for subsequent primary malignancies in adulthood (Yun et al., 2011; Dimaras et al., 2015; Willard et al., 2014; MacCarthy et al., 2009). In low-income countries, the tumor is associated with much lower survival (about 30%) likely due to later diagnosis and difficulty in accessing specialty care (Dimaras et al., 2010; Nyawira et al., 2013; Dean et al., 2014).

Retinoblastoma usually presents in children ages 5 and younger, as the result of biallelic mutation of the retinoblastoma tumor-suppressor (*RB1*) gene (Yun et al., 2011). Following a two-hit model of gene inactivation, retinoblastoma presents either unilaterally or bilaterally (Knudson, 1971). Most cases of bilateral retinoblastoma result from a germline mutation of the *RB1* gene (first hit) followed by a somatic mutation (second hit) post-conception. For bilateral retinoblastoma, this

Abbreviations: CI, confidence interval; CDWR, California Department of Water Resources; CNS, Central nervous system; EPA, Environmental Protection Agency; GIS, Geographic Information System; GRAPES, GIS-based Residential Ambient Pesticide Estimation System; OP, organophosphate; OR, odds ratio; PAN, Pesticide Action Network; PLSS, Public Land Survey System; PUR, Pesticide Use Reports; *RB1*, Retinoblastoma tumor suppressor; SES, socioeconomic status; SIR, standardized incidence ratio.

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first hit is acquired from a parent, in whom the mutation occurs in the germinal cells some time prior to conception (Omidakhsh et al., 2017). For unilateral retinoblastoma, which comprises 73% of all cases, both *RB1* mutations occur somatically in a retinal cell post-conception (Broaddus et al., 2009). This timeline, along with the early childhood occurrence, suggests that perinatal exposures are relevant in the etiology of retinoblastoma (Heck et al., 2015; Bunin et al., 1989). Furthermore, the difference in the timing of the *RB1* mutation between the subtypes suggests that pesticide exposures may impact unilateral and bilateral retinoblastoma cases differentially.

A number of environmental risk factors for retinoblastoma have been suggested, including air pollution, sunlight, X-rays, and various parental occupational exposures (Heck et al., 2013, 2015; Ghosh et al., 2013; Hooper, 1999; Jemal et al., 2000; Lombardi et al., 2013; Bunin et al., 1989, 1990; Abdolahi et al., 2013; Omidakhsh et al., 2021). Among these occupational exposures, pesticides have been associated with retinoblastoma risk albeit somewhat inconsistently. Some retinoblastoma studies focusing on parental pesticide exposure examined parents working as pesticide applicators or other agricultural workers, while others examined residential exposure from living on farms or using pesticides in homes and gardens (Flower et al., 2004; Rodvall et al., 2003; MacCarthy et al., 2009; Abdolahi et al., 2013; Fear et al., 1998; Pearce et al., 2006; Kristensen et al., 1996; Omidakhsh et al., 2017; Bunin et al., 1989).

Due to the rarity of retinoblastoma, most of the previous studies have been underpowered and consequently limited from estimating risk separately for unilateral and bilateral disease. Furthermore, pesticide exposure information in these studies is only available in broad categories that assess all pesticides together or characterize them broadly by type (e.g. agrochemicals, insecticides). The different exposure definitions across prior studies may have also led to the inconsistent results. Here, we therefore aim to expand upon the literature by separately assessing risk for unilateral and bilateral retinoblastoma and use information on a large number of specific pesticides applied commercially on fields in California.

2. Materials and methods

2.1. Study population

Retinoblastoma cases (International Classification of Childhood Cancer code 050) (Steliarova-Foucher et al., 2005) aged 5 and younger were drawn from California Cancer Registry records of incident cancer diagnosed in 1988–2013. Case ascertainment in the California Cancer Registry is extensive. Since 1985, California state law has required that all cancers diagnosed in California be reported to the California Cancer Registry (California Cancer Registry, 2018). The state registry is internally validated by the California Department of Public Health and meets data standards for the National Program of Cancer Registries and the National Cancer Institute's Surveillance, Epidemiology, and End Results program. Cases were linked with birth certificates based on exact matches for name, date of birth, and social security number when available, using a probabilistic linkage program, which achieved an 89% matching success for all childhood cancer cases (n = 13,674). The 11% of cases that did not match with a birth certificate were likely not born in California (Urayama et al., 2009). Controls were randomly selected from California birth certificate data and 20:1 frequency-matched by birth year to all childhood cancer cases during the study period (n = 270,941). The median age at diagnosis for all retinoblastoma cases combined was 1 year old, with a median birth year of 2004 for both cases and controls included in this study. Unilateral retinoblastoma cases had a mean age at diagnosis of 14 months old, and bilateral retinoblastoma cases had a mean age at diagnosis of 5 months old.

Controls who died before the age of 6 (n = 1215), and observations with unknown sex (n = 3), gestational age less than 20 weeks (n = 680), or birth weight less than 500 g (n = 131) were excluded from the sample. Since exposure data is not available for most other states, observations with birth addresses outside of California were also excluded (n = 488). Inclusion criteria for the parent study was birth in California during the study period. For the present analysis, an additional inclusion criterion was residence in the study area, assessed by birth certificate address.

We limited analysis to birth years 1998–2011, since prior to 1998, full residential addresses were not available in the electronic birth certificate dataset. Furthermore, we restricted the sample of cases and controls to mothers living within 4000 m of a site to which at least one pesticide—among the more than 600 pesticides applied in California agriculture—was applied during their pregnancy assuming they lived at the address recorded on the birth record. This restriction is intended to limit exposure misclassification due to differences in exposure environments between children living in proximity to agriculture and children living in urban environments. Agricultural pesticide use is generally rare in urban areas, but non-agricultural commercial pesticide use such as home fumigation or applications to parks and roadways can nevertheless be extensive and in California, is only reported at the county level. This restriction also is likely to generate a rural study sample that is more homogeneous with regard to other unmeasured social and environmental factors such as parental occupation or air pollution exposures. Our resulting study population contained 221 cases of unilateral retinoblastoma and 114 cases of bilateral retinoblastoma, totaling to 335 cases and 123,166 controls.

2.2. Ethics approval and consent to participate

Ethics approval for the current study was obtained from the University of California Los Angeles, Office of the Human Subjects Research Protection Program and the California State Committee for the Protection of Human Subjects. As this study involved secondary analysis of existing registry data, patient consent was not required.

2.3. Pesticide exposure assessment

The California Department of Pesticide Regulation has mandated since 1990 that all agricultural use of pesticides be reported in the form of Pesticide Use Reports (PUR). These reports identify the quantities in which specific pesticides are applied, the sites and times at which these applications take place, as well as which crops are treated. Land-use data is collected through California's Public Land Survey System (PLSS), which records the exact locations of the crops that are reported in the PUR data. Our study's GIS-based Residential Ambient Pesticide Estimation System (GRAPES) maps the PUR data onto the PLSS grid according to land use information provided by the California Department of Water Resources (CDWR) and allows us to more precisely locate pesticide applications (Cockburn et al., 2011). CDWR provides digitally accessible land-use maps dating back to 1986; therefore, pesticide exposure information is available for the entire study period (California Department of Water Resources, 2022).

Regarding geocoding accuracy, 54% of residential addresses were geocoded via exact parcel centroid point, address range interpolation was used for 39% of the addresses, and 7% of the addresses were geocoded by USPS zip area centroid. To assess potential misclassification due to geocoding inaccuracy, we performed a sensitivity analysis that dichotomized results by geocoding quality type. Cases and controls were geocoded, blind to case-control status, using the Texas A&M geocoding service (Texas A&M Geoservices, 2019).

We defined exposure to each pesticide as ever pesticide exposure, to any of the 600+ PUR pesticides, during pregnancy within a 4000 m buffer of the maternal address listed on the birth certificate. Using date of last menstrual period and date of birth from the birth certificate, we were able to assess whether mothers were exposed to specific pesticides at any point during the pregnancy.

Out of all agricultural pesticides used in our study area, we selected 132 pesticides classified as possibly or probably carcinogenic by the

Environmental Protection Agency (EPA, 2012), and are reporting results for 58 of these pesticides to which a minimum of 20 cases were considered exposed during the study period.

2.4. Statistical analysis

Following the analytic strategy suggested by Momoli et al. (2010), we used unconditional logistic regression models to estimate odds ratios (OR) and 95% confidence intervals (CI) for associations between each of the selected pesticides and all types combined retinoblastoma. We further stratified analyses by laterality using the same controls and tested for heterogeneity between the two subtypes using methods developed by Wang et al. (2016). Based on previous literature, we adjusted all models for birth year, child's sex, maternal age, neighborhood socioeconomic status (SES), and maternal race/ethnicity (Heck et al., 2012; Omidakhsh et al., 2017; Bunin et al., 1989). Neighborhood SES was measured with an index developed by Yost et al. (2001), which summarizes the following census-group-level socioeconomic indicators into one 5-level variable: education, median household income, percent living 200% below poverty, percent blue-collar workers, percent older than 16 years without employment, median rent, and median house value. To account for individual SES, we also attempted adjusting for maternal education (Supplementary Table 1). Additionally, we tested the inclusion of maternal birthplace and paternal age in our model, which have been associated with retinoblastoma and may be associated with pesticide exposure (Heck et al., 2012). However, these variables did not change estimates by more than 5% and were not included in the final models. Maternal smoking may be related to retinoblastoma (Azary et al., 2016). In a subanalysis among the children for whom data were available, we additionally adjusted for maternal smoking, as ascertained by cotinine in neonatal dried blood spots (Supplementary Table 2). This did not change results and was left out of final models.

We used single-pesticide models to separately estimate the OR and 95% CI for each pesticide without adjusting for exposure to any of the other pesticides. In order to co-adjust for the other selected pesticide exposures and account for multiple comparisons, we built a multiple-pesticide model via a semi-Bayesian hierarchical logistic regression model with a pre-specified second-stage variance of 0.5, representing a 16-fold uncertainty about the 95% CI for the prior OR estimates. This semi-Bayesian approach assumes that individual pesticide effect estimates for retinoblastoma follow separate prior (or second-stage) normal distributions with separate group means for each subset (or class) to which each pesticide belongs. In other words, we assumed that pesticides belonging to a specific subset would have a common category-specific prior effect on retinoblastoma, and the semi-Bayesian hierarchical regression model would shrink the estimated individual pesticide effects within the subset towards their common category specific effect (group mean) to produce a weighted posterior effect estimate for each individual pesticide (Greenland, 1992, 1994).

We performed this analysis using two separate approaches for generating the pesticide subset categorization scheme. First, each pesticide was assumed to belong to its respective chemical class, as categorized by the Pesticide Action Network (PAN) database (Kegley et al., 2011): 2,6-dinitroaniline, amide, anilide, azole, chloroacetanilide, dicarboximide, halogenated organic, n-methyl carbamate, organochlorine, organophosphate (OP), pyrethroid, substituted benzene, triazine, or urea. Alternatively, we assumed that each pesticide belongs to subsets of pesticide applications that are highly correlated with each other in our controls. Specifically, we conducted factor analysis using principal components extraction with varimax rotation for exposures among control subjects to generate subsets of correlated pesticide applications in pregnancy based on factor loadings >0.60. Both approaches yielded similar posterior OR estimates; therefore, here we present results from the hierarchical logistic regression model based on the first assumption of the chemical classes. Analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

Among our study population of 335 cases and 123,166 controls, there were 46 pesticides to which at least 20 unilateral cases were exposed, and 34 pesticides to which at least 20 bilateral cases were exposed. Overall, there were 58 pesticides examined, to which at least 20 total cases (all subtypes) were exposed. Table 1 shows the demographics of the study population. For both subtypes, retinoblastoma cases were more likely to be male than controls. A greater proportion of bilateral retinoblastoma occurred among children of Hispanic mothers and mothers over the age of 30.

Most of the pesticides that loaded onto the same factor had correlation coefficients ranging from 0.5 to 0.75, with the highest correlation between any two pesticides being 0.63. This correlation structure is depicted in greater detail by Lombardi et al. (2021). Our sensitivity analysis to assess exposure misclassification resulted in increased point estimates when observations were restricted to only those geocoded by exact parcel centroid—the highest resolution geocode type; and resulted in estimates that were closer to the null for observations with lower resolution geocodes.

Fig. 1 shows estimated posterior ORs for all retinoblastoma cases combined obtained from the multiple-pesticide model; sample sizes and percent exposed to each pesticide, along with estimated ORs from single-pesticide models are shown in Supplementary Table 3. Acephate was the pesticide to which the largest proportion (63%) of cases were exposed, while flonicamid was the pesticide to which the smallest proportion was exposed. We obtained elevated OR estimates for all retinoblastoma with exposure to acephate, pymetrozine, and oxythioquinox in single-pesticide models. When we adjusted for exposures to other pesticides in the hierarchical logistic regression model, acephate (OR: 1.59, 95% CI: 1.19, 2.12) remained positively associated with retinoblastoma, as did pymetrozine (OR: 1.45, 95% CI: 1.00, 2.08) and oxythioquinox (OR: 1.48, 95% CI: 0.97, 2.26) although the 95% CIs included null. Effect estimates for kresoxim-methyl (OR: 1.60, 95% CI: 1.00, 2.56) and captan (OR: 1.31, 95% CI: 0.95, 1.80) were shifted further away from the null in the hierarchical logistic regression model. We observed an inverse association between retinoblastoma and exposure to hydramethylnon (OR: 0.59, 95% CI: 0.35, 0.98) in the hierarchical logistic regression model for all retinoblastoma.

Fig. 2 presents associations between prenatal pesticide exposure and retinoblastoma, stratified by laterality. The effect estimates and distributions for unilateral and bilateral retinoblastoma are presented in Supplementary Table 4 and Supplementary Table 5, respectively. For the unilateral subtype, we observed elevated odds with exposure to acephate (OR: 1.70, 95% CI: 1.20, 2.41), in addition to several other elevated OR estimates in the single-pesticide models; however, only exposure to bromacil (OR: 1.87, 95% CI: 1.07, 3.26) showed an association in the multiple-pesticide adjusted model. We observed several additional elevated OR estimates with wide confidence intervals for bilateral retinoblastoma in the single-pesticide and multiple-pesticide adjusted models.

4. Discussion

In this case-control study, we observed elevated associations with childhood retinoblastoma for maternal ambient exposure to several pesticides during pregnancy. In analyses for all types of retinoblastoma, we estimated elevated odds with exposure to acephate, pymetrozine, and kresoxim-methyl. After stratifying by laterality, unilateral retinoblastoma was still associated with exposure to acephate and newly with bromacil. Similar to one of the previous studies examining prenatal pesticide exposure and retinoblastoma, our CIs for bilateral disease estimates were wider than those for unilateral retinoblastoma due to the smaller number of cases (Omidakhsh et al., 2017). We observed an elevated estimate for diazinon in the single-pesticide model for bilateral retinoblastoma; however, our results did not suggest any pesticide

Table 1
Demographic characteristics of children in California born in 1998–2011 exposed to at least one pesticide during pregnancy.

Characteristic	Retinoblastoma (all types) N = 335	Unilateral Retinoblastoma N = 221	Bilateral Retinoblastoma N = 114	Controls N = 123,166
Sex of Child, n (%)				
Male	187 (55.8)	121 (54.8)	66 (57.9)	62738 (50.9)
Female	148 (44.2)	100 (45.2)	48 (42.1)	60428 (49.1)
Maternal Race/Ethnicity, n (%)				
Hispanic	176 (52.5)	113 (51.1)	63 (55.3)	63230 (51.3)
Other†	73 (21.8)	53 (24.0)	20 (17.5)	23877 (19.4)
White non-Hispanic	86 (25.7)	55 (24.9)	31 (27.2)	36059 (29.3)
Maternal Age, n (%)				
19 or less	22 (6.6)	15 (6.8)	7 (6.1)	12038 (9.8)
20-24	73 (21.8)	54 (24.4)	19 (16.7)	28157 (22.9)
25-29	95 (28.4)	66 (29.9)	29 (25.4)	33096 (26.9)
30-34	88 (26.3)	51 (23.1)	37 (32.5)	29743 (24.1)
35 and older	57 (17.0)	35 (15.8)	22 (19.3)	20128 (16.3)
Missing				4
Census-based SES[a] index level, n (%)				
1 (lower SES)	89 (26.6)	59 (26.7)	30 (26.3)	32206 (26.2)
2	80 (23.9)	48 (21.7)	32 (28.1)	29472 (24.0)
3	72 (21.5)	54 (24.4)	18 (15.8)	24930 (20.3)
4	51 (15.2)	29 (13.1)	22 (19.3)	19625 (16.0)
5 (higher SES)	43 (12.8)	31 (14.0)	12 (10.5)	16788 (13.6)
Missing				145
Maternal Education, n (%)				
8 or less years	25 (7.7)	13 (6.0)	12 (11.1)	12849 (10.7)
9–11 years	65 (20.1)	39 (18.1)	26 (24.1)	22186 (18.5)
12 years	94 (29.0)	69 (31.9)	25 (23.1)	33176 (27.6)
13–15 years	72 (22.2)	54 (25.0)	18 (16.7)	25110 (20.9)
16 or more years	68 (21.0)	41 (19.0)	27 (25.0)	26854 (22.3)
Missing	11	5	6	2991
Maternal Smoking Status, n (%)[b]				
Yes	28 (12.2)	17 (14.4)	11 (9.8)	22 (5.9)
No	202 (87.8)	101 (85.6)	101 (90.2)	353 (94.1)

† Other races, in order of frequency among cases, included Filipino, Black, Vietnamese, Indian, Japanese, Cambodian, Chinese, Hmong, and American Indian.

[a] Neighborhood SES was measured with an index developed by Yost et al. (2001), which summarizes the following census-group-level socioeconomic indicators into one 5-level variable: education, median household income, percent living 200% below poverty, percent blue-collar workers, percent older than 16 years without employment, median rent, and median house value.

[b] Maternal smoking status was ascertained by cotinine presence in neonatal dried blood spots—this information was only available for a subset of 230 cases and 375 controls. The listed percentages for this variable use the type-specific totals within the subset as denominators.

associations in the multiple-pesticide model for the bilateral subtype. Collapsing the subtypes into an 'all retinoblastoma' category improved sample size but precluded analysis of potential exposure effect differences based on subtypes.

Many studies that previously linked pesticides to eye cancers have been underpowered or did not examine retinoblastoma, specifically (Rodvall et al., 2003; Fear et al., 1998; Kristensen et al., 1996). Moreover, exposure classification in these studies has been relatively crude, with pesticide exposure mostly being defined in terms of parental employment (Bunin et al., 1990; Abdolahi et al., 2013; Omidakhsh et al., 2021; Fear et al., 1998; Pearce et al., 2006). This study is the first, to our knowledge, to examine risk for childhood retinoblastoma with ambient exposure to specific pesticides during pregnancy.

For the pesticides found to be positively associated with retinoblastoma in our study, data on carcinogenicity is still limited. Pymetrozine and bromacil have both been found to cause skeletal malformations in rats and rabbits (EPA 1996, 2000). Early skeletal and ectodermal cells share genetic signaling networks, suggesting that skeletal malformation may be linked with abnormal neuroectodermal tissue (Richtsmeier and Flaherty, 2013). Retinoblastomas originate in the germinal neuroectodermal layer along with embryonal central nervous system (CNS) tumors and neuroblastomas (Gatta et al., 2012; Kohe et al., 2018; Ortega-García et al., 2011). This also suggests that retinoblastomas and CNS tumors may have overlapping etiologies. A growing number of studies have found associations between residential pesticide exposures and CNS tumors occurring in childhood (Van Maele-Fabry et al., 2017).

In a previous study by Pearson et al. both bromacil and kresoxim-methyl were associated with childhood CNS tumors (Pearson et al., 2016). Other studies found that kresoxim-methyl alters neural transcription, induces neuronal death, and facilitates oxidation in neuroblastoma cells (Regueiro et al., 2015; Flampouri et al., 2018; EPA, 2001).

Acephate, which showed a strong association with unilateral retinoblastoma, is an organophosphate (OP) insecticide that can cause brain cholinesterase inhibition in humans, overstimulating the nervous system (Maroni et al., 1990). OP metabolites have been found in cord blood and meconium samples from mothers and infants exposed during pregnancy, indicating vertical transmission of the exposure to the developing fetus (Ostrea et al., 2009). A study in mice also found that acephate induced chromosomal aberrations at sub-acute doses, with a dose-response effect; and the authors concluded that the pesticide may be considered a potential mutagen (Behera and Bhunya, 1989). Lastly, there is very little data available concerning the carcinogenicity of either oxythioquinox or captan to date; however, both can cause irreversible eye damage (EPA, 1999a, 1999b). Oxythioquinox was voluntarily removed from the market in 2001, prior to EPA completing human health risk assessment. Captan continues to be commonly used on edible crops and ornamental plants. At the present time, no safe level of exposure has been identified for these pesticides.

Our finding of a decreased OR estimate for hydramethylnon was unexpected. Due to the large number of pesticides being examined and the small number of exposed cases, it is possible that this finding is the result of chance. It is also possible that the decreased OR estimate is the result of pesticide correlation due to co-application with a reproductively highly toxic pesticide we did not investigate here that contributes to early loss of susceptible fetuses, as we pre-selected only for pesticides with potential carcinogenicity according to EPA.

Pesticide applications and exposures are highly correlated. For

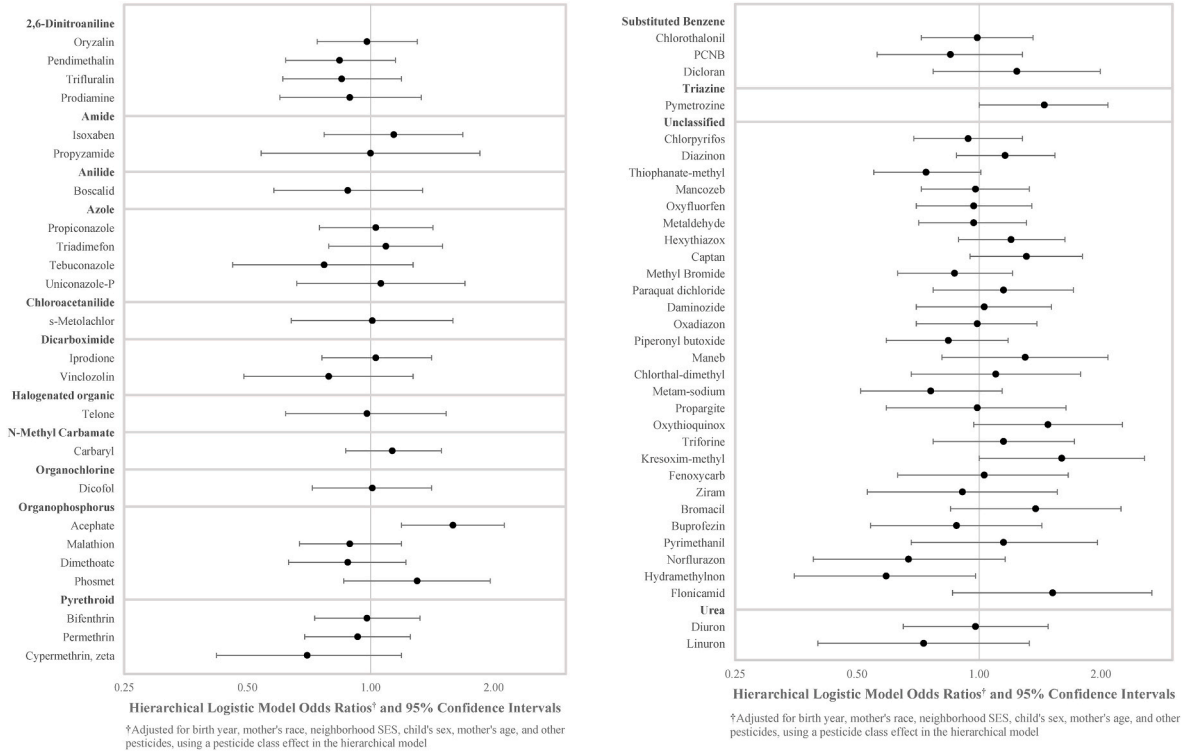

Fig. 1. Fig. 1. Estimated Odds Ratios and 95% Confidence Intervals from the Hierarchical Logistic Regression Model for all cases combined.

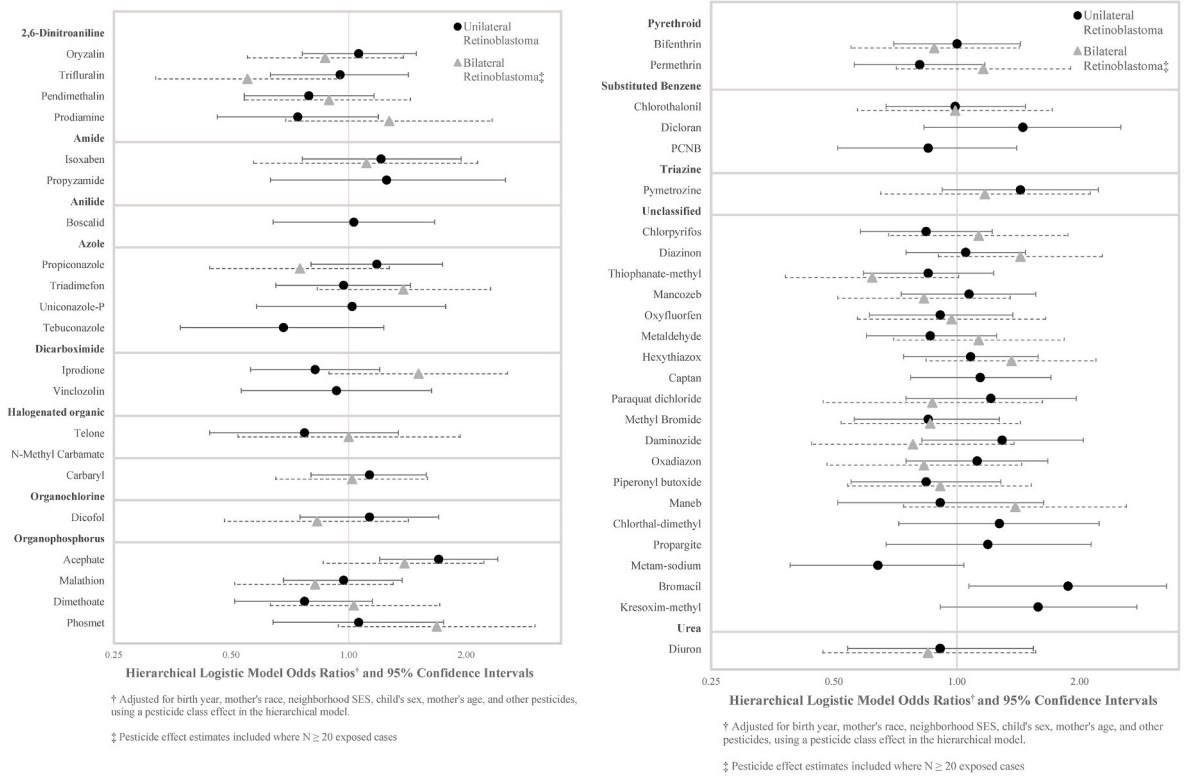

Fig. 2. Fig. 2. Estimated Odds Ratios and 95% Confidence Intervals from the Hierarchical Logistic Regression Model, stratified by laterality.

example, correlations in our data reflect commonly practiced co-applications, such as maneb with paraquat (Lombardi et al., 2021; Costello et al., 2009). We attempted to address these correlated exposure patterns by using a semi-Bayesian hierarchical logistic modelling approach.

The Agricultural Health Study observed an elevated point estimate with wide confidence intervals for retinoblastoma in children of the pesticide applicators enrolled in Iowa (SIR: 1.63, 95% CI: 0.41–6.53),

while another cohort study found observed a slightly decreased risk estimate with wide confidence intervals for eye cancers in such children (SIR: 0.76, 95% CI: 0.09–2.75) (Flower et al., 2004; Rodvall et al., 2003). Two other studies reported null effects for retinoblastoma (OR: 1.65, 95% CI: 0.51–5.33) and eye cancers (OR: 0.71, 95% CI: 0.15–2.08) with parental occupational pesticide exposure (Pearce et al., 2006; Fear et al., 1998). One of the few studies distinguishing between subtypes reported a null association between unilateral retinoblastoma and parental occupational exposure to agrochemicals (OR: 1.00, 95% CI: 0.51–1.96), while another reported a positive association between bilateral disease and paternal occupational pesticide exposure (OR: 2.12, 95% CI: 1.25–3.61) (MacCarthy et al., 2009; Abdolahi et al., 2013). Most of these studies assessed parental exposure based on occupation-industry group, which may misclassify pesticide exposures (Daniels et al., 2001). The only two previous retinoblastoma studies to report on residential pesticide use both suggested increased risks for unilateral disease with parental use of insecticides (OR: 2.80, 95% CI: 1.1–67); (OR: 2.70, 95% CI: 0.6–15.6) (Omidakhsh et al., 2017; Bunin et al., 1989). However, these studies also assessed exposures retrospectively from parental interviews, which may be biased due to differential exposure reporting between case parents and control parents (Rull et al., 2006).

While studies have linked residential proximity to agricultural pesticide applications with other childhood cancers, few have examined risks for retinoblastoma. A cohort study in Norway observed an increased risk estimate for eye cancers in children of farm residents (OR: 3.17, 95% CI: 0.93–10.9), but only two of the four exposed cases were retinoblastomas (Kristensen et al., 1996). A case-control study in Texas found no association between retinoblastoma and proximity to agricultural land use (OR: 0.90, 95% CI: 0.5–1.5) (Carozza et al., 2009).

Unilateral and bilateral retinoblastoma are both induced by inactivation of the *RB1* gene; however, the two subtypes are initiated by slightly different molecular genetic processes. Children with bilateral retinoblastoma have inherited a defective *RB1* allele from one parent, and the second *RB1* allele is inactivated during DNA replication of progenitor cells in the fetal retina. Unilateral retinoblastoma occurs when both *RB1* alleles are inactivated in the same retinal progenitor cell (Dyer, 2004). Since only a 'second hit' is required for disease to occur in children born with a defective *RB1* gene, approximately 90% of those who inherit the gene mutation develop retinoblastoma (Draper et al., 1992). The likelihood of both alleles being inactivated post-conception is much lower. This etiology is consistent with expecting bilateral cases to be affected by or susceptible to pesticide exposures differently from unilateral cases. Thus, it is not entirely surprising that pesticides associated with unilateral retinoblastoma may not also be associated with bilateral retinoblastoma as the underlying pathophysiological mechanisms differ; specifically, the elevated risks for bilateral retinoblastoma with prenatal exposure to pesticides correspond to a 'second hit' model (Knudson, 1971); while for unilateral retinoblastoma both hits occur post-conception.

Though the germline *RB1* mutation inherited by children who develop bilateral retinoblastoma may arise de novo in either parent preconceptionally, it most commonly arises in the father (Kato et al., 1994). Since we assigned exposure based on maternal address listed on the birth certificate, a potential limitation of this study is that we were not able to address preconception residential pesticide exposure affecting the parental germline, and we had no information on whether the parents cohabitated prior to or during the pregnancy. Also, birth certificate addresses may not be the same as prenatal residential addresses if mothers moved during pregnancy. These instances would likely result in exposure misclassification, with true exposures via the new residence being unaccounted for and pesticide applications near the previous residence being falsely classified as exposures. However, a previous sensitivity analysis by our group showed that pesticide exposure estimates did not vary substantially when full residential histories were available. When comparing use of birth certificate address to use of residential addresses from a public-record database for assignment of early life pesticide exposures, there was moderate to strong correlation between exposure assignments (Spearman correlation = 0.76–0.83) (Ling et al., 2019).

Exposure misclassification may also be introduced by geocoding inaccuracy. Our sensitivity analysis by geocoding accuracy suggests that the inclusion of data with lower resolution geocodes resulted in small biases towards the null. This result is to be expected, since exposures determined by lower resolution geocoding types, such as zip area centroid, may be less accurately classified than exposures determined with finer geocode accuracy. However, it would be inappropriate to exclude the observations with lower resolution geocodes from our analysis, as suggested by a study by Thompson et al. (2021).

Pregnant mothers may have also been exposed to pesticides through their occupation, which has been assessed in most of the cited previous literature on retinoblastoma and pesticide exposure. Unfortunately, parental occupation information was not available on California birth certificates. At the population level, between 6% and 10% of rural California residents are employed in 'agriculture, forestry, fishing, hunting, mining industries' (USDA Economic Research Service, 2007). Information regarding the proportion of this population that is employed in agriculture, specifically, is sparse. Nonetheless, the unavailability of occupational information on birth certificates precluded adjustment for potential occupational pesticide exposures in our analysis.

Despite these limitations, this study also has several strengths. Among the studies that have investigated retinoblastoma and pesticide exposure thus far, this population-based study has the largest number of cases yet. This allowed us to stratify by laterality in order to separately investigate risk factors for unilateral and bilateral retinoblastoma and resulted in fairly stable estimates, at least for the unilateral cases. Furthermore, our objective and spatially refined assessment of exposure using statewide reports allowed us to access information on individual pesticides that was not subject to recall bias. In addition to these strengths, our exposure assessment is validated by previous studies that have demonstrated pesticide volatilization as a potential mechanism of exposure. A study in Northern California found strong associations between regional agricultural pesticide application and outdoor air concentrations up to 5000 m away, even days after the original application (Harnly et al., 2005). Volatilized pesticides may also drift into homes and persist in dust, as suggested by associations observed between household pesticide dust concentrations and nearby agricultural application (Harnly et al., 2009).

5. Conclusions

In conclusion, this case-control study is among the first to focus on specific pesticide exposures as they individually relate to unilateral and bilateral retinoblastoma. Future studies are needed to also assess agriculturally common pesticide mixtures and mixture effects. The associations we observed between retinoblastoma and residential proximity to applications for specific pesticides that have previously raised concern as to their carcinogenic potential contribute to the growing body of knowledge concerning prenatal pesticide exposure and rare childhood cancers of the nervous system. Strategies for reducing exposure in those living near agricultural fields should be considered as a protective health measure.

Consent for publication

Not applicable.

Availability of data and materials

The datasets in the current study are used under the approval of the California Committee for the Protection of Human Subjects. Approvals would be necessary to share data.

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Authors' contributions

JEH and BR supervised and substantially conducted the conception, design, and interpretation of data, in addition to reviewing and editing the manuscript for the current study. ST performed the formal analyses, produced visualizations, and wrote the manuscript. MC oversaw geocoding methodology in addition to reviewing and editing the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2022.114025.

References

Abdolahi, A., van Wijngaarden, E., McClean, M.D., et al., 2013. A case-control study of paternal occupational exposures and the risk of childhood sporadic bilateral retinoblastoma. Occup. Environ. Med. 70, 372–379. https://doi.org/10.1136/oemed-2012-101062.

Azary, S., Ganguly, A., Bunin, G.R., Lombardi, C., Park, A.S., Ritz, B., Heck, J.E., 2016 Mar 18. Sporadic retinoblastoma and parental smoking and alcohol consumption before and after conception: a report from the children's Oncology group. PLoS One 11 (3), e0151728. https://doi.org/10.1371/journal.pone.0151728.

Behera, B.C., Bhunya, S.P., 1989. Studies on the genotoxicity of asataf (acephate), an organophosphate insecticide, in a mammalian in vivo system. Mutat. Res. 223 (3), 287–293. https://doi.org/10.1016/0165-1218(89)90121-3.

Broaddus, E., Topham, A., Singh, A.D., 2009. Incidence of retinoblastoma in the USA: 1975-2004. Br. J. Ophthalmol. 93, 21–23. https://doi.org/10.1136/bjo.2008.138750.

Bunin, G.R., Meadows, A.T., Emanuel, B.S., Buckley, J.D., Woods, W.G., Hammond, G.D., 1989. Pre- and postconception factors associated with sporadic heritable and nonheritable retinoblastoma. Cancer Res. 49, 5730–5735.

Bunin, G.R., Petrakova, A., Meadows, A.T., et al., 1990. Occupations of parents of children with retinoblastoma: a report from the Children's Cancer Study Group. Cancer Res. 50, 7129–7133.

California Cancer Registry, 2018. About California cancer registry. https://www.ccrcal.org/learn-about-ccr/about-cancer-registries/. (Accessed 12 May 2022).

California Department of Water Resources, 2022. Land Use Surveys. Sacramento, CA. https://water.ca.gov/programs/water-use-and-efficiency/land-and-water-use/land-use-surveys. (Accessed 6 April 2022).

Carozza, S.E., Li, B., Wang, Q., Horel, S., Cooper, S., 2009. Agricultural pesticides and risk of childhood cancers. Int. J. Hyg Environ. Health 212 (2), 186–195. https://doi.org/10.1016/j.ijheh.2008.06.002.

Cockburn, M., Mills, P., Zhang, X., Zadnick, J., Goldberg, D., Ritz, B., 2011. Prostate cancer and ambient pesticide exposure in agriculturally intensive areas in California. Am. J. Epidemiol. 173 (11), 1280–1288. https://doi.org/10.1093/aje/kwr003.

Costello, S., Cockburn, M., Bronstein, J., Zhang, X., Ritz, B., 2009. Parkinson's disease and residential exposure to maneb and paraquat from agricultural applications in the central valley of California. Am. J. Epidemiol. 169 (8), 919–926. https://doi.org/10.1093/aje/kwp006.

Daniels, J.L., Olshan, A.F., Teschke, K., Hertz-Picciotto, I., Savitz, D.A., Blatt, J., 2001. Comparison of assessment methods for pesticide exposure in a case-control interview study. Am. J. Epidemiol. 153, 1227–1232. https://doi.org/10.1093/aje/153.12.1227.

Dean, M., Bendfeldt, G., Lou, H., Giron, V., Garrido, C., Valverde, P., et al., 2014. Increased incidence and disparity of diagnosis of retinoblastoma patients in Guatemala. Cancer Lett. 351, 59–63. https://doi.org/10.1016/j.canlet.2014.04.023.

Dimaras, H., Dimba, E.A.O., Gallie, B.L., 2010. Challenging the global retinoblastoma survival disparity through a collaborative research effort. Br. J. Opthalmol. 94, 1415–1416. https://doi.org/10.1136/bjo.2009.174136.

Dimaras, H., Corson, T.W., Cobrinik, D., White, A., Zhao, J., Munier, F.L., Abramson, D. H., Shields, C.L., Chantada, G.L., Njuguna, F., Gallie, B.L., 2015. Retinoblastoma. Nat. Rev. Dis. Prim. 1, 15021 https://doi.org/10.1038/nrdp.2015.21.

Draper, G.J., Sanders, B.M., Brownbill, P.A., Hawkins, M.M., 1992. Patterns of risk of hereditary retinoblastoma and applications to genetic counselling. Br. J. Cancer 66 (1), 211–219. https://doi.org/10.1038/bjc.1992.244.

Dyer, M.A., 2004. Mouse models of childhood cancer of the nervous system. J. Clin. Pathol. 57 (6), 561–576. https://doi.org/10.1136/jcp.2003.009910. Erratum in: J. Clin. Pathol. 2004;57(8):896.

EPA United States Environmental Protection Agency, 1996. Bromacil. Prevention, Pesticides, and Toxic Substances. https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/fs_PC-012301_1-Aug-96.pdf. (Accessed 15 February 2021).

EPA, 1999a. Oxythioquinox. Prevention, Pesticides, and Toxic Substances. https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/fs_PC-103301_1-Sep-01.pdf. (Accessed 16 February 2021).

EPA, 1999b. Reregistration Eligibility decision, captan. https://archive.epa.gov/pesticides/reregistration/web/pdf/0120red.pdf. (Accessed 28 April 2021).

EPA, 2000. Fact Sheet for Pymetrozine. Office of Prevention, Pesticides, and Toxic Substances. EPA. https://nepis.epa.gov/Exe/ZyPDF.cgi/P100BIBS.PDF. (Accessed 15 February 2021).

EPA, 2001. Acephate Facts. Prevention, Pesticides, and Toxic Substances. https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/fs_PC-103301_1-Sep-01.pdf. (Accessed 15 February 2021).

EPA, 2012. List of Chemicals Evaluated for Carcinogenic Potential. http://www.epa.gov/opp00001/carlist/. (Accessed 27 August 2013).

Fear, N.T., Roman, E., Reeves, G., Pannett, B., 1998. Childhood cancer and paternal employment in agriculture: the role of pesticides. Br. J. Cancer 77 (5), 825–829. https://doi.org/10.1038/bjc.1998.134.

Flampouri, E., Theodosi-Palimeri, D., Kintzios, S., 2018. Strobilurin fungicide kresoxim-methyl effects on a cancerous neural cell line: oxidant/antioxidant responses and in vitro migration. Toxicol. Mech. Methods 28 (9), 709–716. https://doi.org/10.1080/15376516.2018.1506848.

Flower, K.B., Hoppin, J.A., Lynch, C.F., et al., 2004. Cancer risk and parental pesticide application in children of Agricultural Health Study participants. Environ. Health Perspect. 112, 631–635. https://doi.org/10.1289/ehp.6586.

Gatta, G., Ferrari, A., Stiller, C.A., Pastore, G., Bisogno, G., Trama, A., Capocaccia, R., RARECARE Working Group., 2012. Embryonal cancers in Europe. Eur. J. Cancer 48 (10), 1425–1433. https://doi.org/10.1016/j.ejca.2011.12.027. Epub 2012 Feb 20.

Texas A&M Geoservices, 2019. Geocoding Platform Technical Details. http://geoservices.tamu.edu/Services/Geocode/About/.

Ghosh, J.K., Heck, J.E., Cockburn, M., Su, J., Jerrett, M., Ritz, B., 2013. Prenatal exposure to traffic-related air pollution and risk of early childhood cancers. Am. J. Epidemiol. 178, 1233–1239. https://doi.org/10.1093/aje/kwt129.

Greenland, S., 1992. A semi-Bayes approach to the analysis of correlated multiple associations, with an application to an occupational cancer-mortality study. Stat. Med. 11 (2), 219–230. https://doi.org/10.1002/sim.4780110208.

Greenland, S., 1994. Hierarchical regression for epidemiologic analyses of multiple exposures. Suppl 8 Environ. Health Perspect. 102 (Suppl. 8), 33–39. https://doi.org/10.1289/ehp.94102s833.

Harnly, M., McLaughlin, R., Bradman, A., Anderson, M., Gunier, R., 2005. Correlating agricultural use of organophosphates with outdoor air concentrations: a particular concern for children. Environ. Health Perspect. 113, 1184–1189. https://doi.org/10.1289/ehp.7493.

Harnly, M.E., Bradman, A., Nishioka, M., McKone, T.E., Smith, D., McLaughlin, R., Kavanaugh-Baird, G., Castorina, R., Eskenazi, B., 2009. Pesticides in dust from homes in an agricultural area. Environ. Sci. Technol. 43 (23), 8767–8774. https://doi.org/10.1021/es9020958.

Heck, J.E., Lombardi, C.A., Meyers, T.J., Cockburn, M., Wilhelm, M., Ritz, B., 2012. Perinatal characteristics and retinoblastoma. Cancer Causes Control 23 (9), 1567–1575. https://doi.org/10.1007/s10552-012-0034-7.

Heck, J.E., Wu, J., Lombardi, C., et al., 2013. Childhood cancer and traffic-related air pollution exposure in pregnancy and early life. Environ. Health Perspect. 121, 1385–1391. https://doi.org/10.1289/ehp.1306761.

Heck, J.E., Park, A.S., Qiu, J., Cockburn, M., Ritz, B., 2015. Retinoblastoma and ambient exposure to air toxics in the perinatal period. J. Expo. Sci. Environ. Epidemiol. 25, 182–186. https://doi.org/10.1038/jes.2013.84.

Hooper, M.L., 1999. Is sunlight an aetiological agent in the genesis of retinoblastoma? Br. J. Cancer 79, 1273–1276. https://doi.org/10.1038/sj.bjc.6690204.

Jemal, A., Devesa, S.S., Fears, T.R., Fraumeni Jr., J.F., 2000. Retinoblastoma incidence and sunlight exposure. Br. J. Cancer 82, 1875–1878. https://doi.org/10.1054/bjoc.2000.1215.

Kato, M.V., Ishizaki, K., Shimizu, T., Ejima, Y., Tanooka, H., Takayama, J., Kaneko, A., Toguchida, J., Sasaki, M.S., 1994. Parental origin of germ-line and somatic mutations in the retinoblastoma gene. Hum. Genet. 94 (1), 31–38. https://doi.org/10.1007/BF02272838.

Kegley, S.E., Hill, B.R., Orme, S., Choi, A.H., 2011. PAN Pesticide Database. Pesticide Action Network (North America).

Knudson, A.G., 1971. Mutation and cancer: statistical study of retinoblastoma. Proc. Natl. Acad. Sci. U.S.A. 68, 820–823. https://doi.org/10.1073/pnas.68.4.820.

Kohe, S.E., Bennett, C.D., Gill, S.K., Wilson, M., McConville, C., Peet, A.C., 2018. Metabolic profiling of the three neural derived embryonal pediatric tumors retinoblastoma, neuroblastoma and medulloblastoma, identifies distinct metabolic profiles. Oncotarget 9 (13), 11336–11351. https://doi.org/10.18632/oncotarget.24168.

Kristensen, P., Andersen, A., Irgens, L.M., Bye, A.S., Sundheim, L., 1996. Cancer in offspring of parents engaged in agricultural activities in Norway. Int. J. Cancer 65, 39–50. https://doi.org/10.1002/(SICI)1097-0215(19960103)65:1<39::AID-IJC8>3.0.CO;2-2.

Ling, C., Heck, J.E., Cockburn, M., Liew, Z., Marcotte, E., Ritz, B., 2019. Residential mobility in early childhood and the impact on misclassification in pesticide exposures. Environ. Res. 173, 212–220. https://doi.org/10.1016/j.envres.2019.03.039.

Lombardi, C., Heck, J.E., Cockburn, M., Ritz, B., 2013. Solar UV radiation and cancer in young children. Cancer Epidemiol. Biomarkers Prev. 22 (6), 1118–1128. https://doi.org/10.1158/1055-9965.EPI-12-1316.

Lombardi, C., Thompson, S., Ritz, B., Cockburn, M., Heck, J.E., 2021. Residential proximity to pesticide application as a risk factor for childhood central nervous system tumors. Environ. Res. 31 (197), 111078 https://doi.org/10.1016/j.envres.2021.111078.

MacCarthy, A., Bunch, K.J., Fear, N.T., King, J.C., Vincent, T.J., Murphy, M.F., 2009. Paternal occupation and retinoblastoma: a case-control study based on data for Great Britain 1962–1999. Occup. Environ. Med. 66, 644–649.

Maroni, M., Catenacci, G., Galli, D., Cavallo, D., Ravazzani, G., 1990. Biological monitoring of human exposure to acephate. Arch. Environ. Contam. Toxicol. 19 (5), 782–788. https://doi.org/10.1007/BF01183993.

Momoli, F., Abrahamowicz, M., Parent, M.E., Krewski, D., Siemiatycki, J., 2010. Analysis of multiple exposures: an empirical comparison of results from conventional and semi-bayes modeling strategies. Epidemiology 21 (1), 144–151.

Nyawira, G., Kahaki, K., Kariuki-Wanyoike, M., 2013. Survival among retinoblastoma patients at the Kenyatta National Hospital, Kenya. J Ophthalmol. Eastern Central Southern Africa 15–19.

Omidakhsh, N., Ganguly, A., Bunin, G.R., von Ehrenstein, O.S., Ritz, B., Heck, J.E., 2017. Residential pesticide exposures in pregnancy and the risk of sporadic retinoblastoma: a report from the Children's Oncology Group. Am. J. Ophthalmol. 176, 166–173.

Omidakhsh, N., Hansen, J., Ritz, B., Coleman, A.L., McKean-Cowdin, R., Olsen, J., Heck, J.E., 2021. Parental occupation and risk of childhood retinoblastoma in Denmark. J. Occup. Environ. Med. 63 (3), 256–261. https://doi.org/10.1016/j.ajo.2017.01.016.

Ortega-García, J.A., López-Hernández, F.A., Fuster-Soler, J.L., Martínez-Lage, J.F., 2011. Space-time clustering in childhood nervous system tumors in the Region of Murcia, Spain, 1998-2009. Childs. Nerv. Syst. 27 (11), 1903–1911. https://doi.org/10.1007/s00381-011-1483-0.

Ostrea Jr., E.M., Bielawski, D.M., Posecion Jr., N.C., Corrion, M., Villanueva-Uy, E., Bernardo, R.C., Jin, Y., Janisse, J.J., Ager, J.W., 2009. Combined analysis of prenatal (maternal hair and blood) and neonatal (infant hair, cord blood and meconium) matrices to detect fetal exposure to environmental pesticides. Environ. Res. 109 (1), 116–122. https://doi.org/10.1016/j.envres.2008.09.004.

Pearce, M.S., Hammal, D.M., Dorak, M.T., McNally, R.J., Parker, L., 2006. Paternal occupational exposure to pesticides or herbicides as risk factors for cancer in children and young adults: a case-control study from the North of England. Arch. Environ. Occup. Health 61 (3), 138–144. https://doi.org/10.3200/AEOH.61.3.138-144.

Pearson, B.L., Simon, J.M., McCoy, E.S., Salazar, G., Fragola, G., Zylka, M.J., 2016. Identification of chemicals that mimic transcriptional changes associated with autism, brain aging and neurodegeneration. Nat. Commun. 7, 11173 https://doi.org/10.1038/ncomms11173.

Regueiro, J., Olguín, N., Simal-Gándara, J., Suñol, C., 2015. Toxicity evaluation of new agricultural fungicides in primary cultured cortical neurons. Environ. Res. 140, 37–44. https://doi.org/10.1016/j.envres.2015.03.013.

Richtsmeier, J.T., Flaherty, K., 2013. Hand in glove: brain and skull in development and dysmorphogenesis. Acta Neuropathol. 125 (4), 469–489. https://doi.org/10.1007/s00401-013-1104-y.

Rodvall, Y., Dich, J., Wiklund, K., 2003. Cancer risk in offspring of male pesticide applicators in agriculture in Sweden. Occup. Environ. Med. 60, 798–801. https://doi.org/10.1136/oem.60.10.798.

Rull, R.P., Ritz, B., Shaw, G.M., 2006. Validation of self-reported proximity to agricultural crops in a case-control study of neural tube defects. J. Expo. Sci. Environ. Epidemiol. 16 (2), 147–155. https://doi.org/10.1038/sj.jea.7500444.

Steliarova-Foucher, E., Stiller, C., Lacour, B., Kaatsch, P., 2005 Apr 1. International classification of childhood cancer. Cancer 103 (7), 1457–1467 third ed.

Thompson, L.K., Langholz, B., Goldberg, D.W., Wilson, J.P., Ritz, B., Tayour, C., Cockburn, M., 2021. Area-based geocoding: an approach to exposure assessment incorporating positional uncertainty. GeoHealth 5 (12), e2021GH000430.

Urayama, K.Y., Von Behren, J., Reynolds, P., Hertz, A., Does, M., Buffler, P.A., 2009. Factors associated with residential mobility in children with leukemia: implications for assigning exposures. Ann. Epidemiol. 19 (11), 834–840. https://doi.org/10.1016/j.annepidem.2009.03.001.

USDA (U.S. Department of Agriculture) Economic Research Service, 2007. California-rural Definitions: State-Level Maps. https://www.ers.usda.gov/webdocs/DataFiles/53180/25559_CA.pdf?v=300.1. (Accessed 19 May 2022).

Van Maele-Fabry, G., Gamet-Payrastre, L., Lison, D., 2017. Residential exposure to pesticides as risk factor for childhood and young adult brain tumors: a systematic review and meta-analysis. Environ. Int. 106, 69–90. https://doi.org/10.1016/j.envint.2017.05.018.

Wang, M., Spiegelman, D., Kuchiba, A., Lochhead, P., Kim, S., Chan, A.T., Poole, E.M., Tamimi, R., Tworoger, S.S., Giovannucci, E., Rosner, B., Ogino, S., 2016. Statistical methods for studying disease subtype heterogeneity. Stat. Med. 35 (5), 782–800. https://doi.org/10.1002/sim.6793.

Willard, V.W., Qaddoumi, I., Chen, S., Zhang, H., Brennan, R., Rodriguez-Galindo, C., Wilson, M.W., Phipps, S., 2014. Developmental and adaptive functioning in children with retinoblastoma: a longitudinal investigation. J. Clin. Oncol. 32 (25), 2788–2793. https://doi.org/10.1200/JCO.2013.53.1996.

Yost, K., Perkins, C., Cohen, R., Morris, C., Wright, W., 2001. Socioeconomic status and breast cancer incidence in California for different race/ethnic groups. Cancer Causes Control 12 (8), 703–711. https://doi.org/10.1023/a:1011240019516.

Yun, J., Li, Y., Xu, C.T., Pan, B.R., 2011. Epidemiology and RB1 gene of retinoblastoma. Int. J. Opthalmol. 4 (1), 103–109. https://doi.org/10.3980/j.issn.2222-3959.2011.01.24.