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Authors

Lombardi, Christina
Thompson, Shiraya
Ritz, Beate
et al.

Publication Date

2021-03-31

Peer reviewed

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Christina Lombardi[a*], Shiraya Thompson[b*], Beate Ritz[b], Myles Cockburn[c], Julia E. Heck[b,d,e]

[a]Department of Cancer Prevention and Control, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, 700 N. San Vicente Blvd., Pacific Design Center, G599, West Hollywood, CA 90069, USA

[b]Department of Epidemiology, Fielding School of Public Health, University of California, 650 Charles E. Young Dr. S, Box 951772, Los Angeles, CA, 90095-1772, USA

[c]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, 2001, N. Soto Street, Suite 318-A, Los Angeles, CA, USA

[d]Jonsson Comprehensive Cancer Center, University of California, Box 951781, Los Angeles, CA 90095-1781, USA

[e]College of Health and Public Service, University of North Texas, 1155 Union Circle #311340, Denton, TX 76203-5017, USA

* Shared first authors

Corresponding Author:

Julia E. Heck, PhD

Postal Address: 1155 Union Circle #311340, Denton, TX 76203-5017

Email Address: julia.heck@unt.edu

RESIDENTIAL PROXIMITY TO PESTICIDE APPLICATION AS A RISK FACTOR FOR CHILDHOOD CENTRAL NERVOUS SYSTEM TUMORS

Christina Lombardi, Shiraya Thompson, Beate Ritz, Myles Cockburn, and Julia E. Heck

Abstract

Background: Pesticide exposures have been examined previously as risk factors for childhood brain cancers, but few studies were able to assess risk from specific agents.

Objective: To evaluate risks for childhood central nervous system tumors associated with residential proximity to agricultural pesticide applications.

Methods: Using the California Cancer Registry, we identified cancer cases less than 6 years of age and frequency matched them by year of birth to 20 cancer-free controls identified from birth certificates. We restricted analyses to mothers living in rural areas and births occurring between 1998 and 2011, resulting in 667 cases of childhood central nervous system tumors and 123,158 controls. Possible carcinogens were selected per the Environmental Protection Agency's (US. EPA) classifications, and prenatal exposure was assessed according to pesticides reported by the California Department of Pesticide Regulation's (CDPR) Pesticide Use Reporting (PUR) system as being applied within 4000m of the maternal residence at birth. We computed odds ratios for individual pesticide associations using unconditional logistic and hierarchical regression models.

Results: We observed elevated risks in the hierarchical models for diffuse astrocytoma with exposure to bromacil (OR: 2.12, 95% CI: 1.13-3.97), thiophanate-methyl (OR: 1.64, 95% CI: 1.02-2.66), triforine (OR: 2.38, 95% CI: 1.44-3.92), and kresoxim methyl (OR: 2.09, 95% CI: 1.03-4.21); elevated risks for medulloblastoma with exposure to chlorothalonil (OR: 1.78, 95% CI: 1.15-2.76), propiconazole (OR: 1.60, 95% CI: 1.02, 2.53), dimethoate (OR: 1.60, 95% CI: 1.06, 2.43), and linuron (OR: 2.52, 95% CI: 1.25, 5.11); and elevated risk for ependymoma with exposure to thiophanate-methyl (OR: 1.72, 95% CI: 1.10-2.68).

Conclusion: Our study suggests that exposure to certain pesticides through residential proximity to agricultural applications during pregnancy may increase the risk of childhood central nervous system tumors.

Keywords: Childhood cancers, central nervous system, pesticides, ambient exposure, pregnancy

Introduction

Brain tumors are the most common solid tumors found in children, and the leading cause of childhood deaths from cancer. Survivors of childhood brain tumors are likely to suffer neurocognitive deficits that may result in reduced cognitive functioning, academic achievement, attention, psychomotor and visual-spatial skills, verbal memory, and language abilities (Robinson et al. 2010; Ullrich and Embry 2012). The most common subtypes of brain tumors in children under 15 years of age are pilocytic astrocytoma (17.7%), glioma malignant, NOS (14.5%), and embryonal tumors (12.7%) (Ostrom et al. 2020). These tumor types peak at different ages in children, suggesting distinct etiologies or sensitive periods of exposure. A small percentage (~5%) of brain tumors can be attributed to family history or genetic syndromes including neurofibromatosis, Li-Fraumeni syndrome, basal cell nevus (Gorlin's) syndrome, Turcot syndrome, and ataxia telangiectasia (Baldwin and Preston-Martin 2004). Among risk factors that have been considered to date, ionizing radiation is the only one considered an established risk factor.

Pesticides have been investigated as possible risk factors for childhood cancer since medical case studies were published in the 1970s (Infante and Newton 1975; Reeves et al. 1981). The EPA has classified over one hundred pesticides as possible or probable carcinogens based on toxicological and epidemiological data (EPA 2012a), and many are neurotoxicants (Baldwin et al. 2004). Pesticides have been found in cord blood, indicating placental transfer of these toxins to the developing fetus (Baldwin and Preston-Martin 2004). As some childhood cancers are initiated in utero, this gives some biological plausibility to the hypothesis that prenatal pesticide

exposure may increase childhood brain cancer risk (Infante-Rivard and Weichenthal 2007; Jurewicz and Hanke 2006).

Several case-control studies (Infante-Rivard and Weichenthal 2007; Bunin et al 1994; Cordier et al. 1994; Davis et al 1993; Pogoda and Preston-Martin. 1997; Wilkins 3rd and Koutras 1988) and two cohort studies (Feychting et al. 2001; Kristensen et al. 1996) have found increased risks for childhood brain tumors with parental pesticide exposure (Vinson et al. 2011; Van Maele-Fabry et al. 2013). However, the majority of studies have focused on parental occupational exposure, relying mainly on job title or industry, which are often poor proxies of pesticide exposure (Van Maele-Fabry et al. 2013). Other studies have found elevated risks of brain tumors with parental home and garden pesticide use and professional pest control treatments at home (Infante-Rivard and Weichenthal 2007; Greenop et al. 2013; Shim et al. 2009); but, most of these studies relied on exposure information retrospectively obtained from maternal questionnaires or interviews, which may be subject to recall errors and bias (Jurewicz and Hanke 2006). Additionally, the majority of studies have employed designs that grouped all pesticides together instead of reporting on specific pesticides (Infante-Rivard and Weichenthal 2007). A number of meta-analyses have suggested that pesticide exposure during the prenatal period increases the risk of childhood gliomas (Van Maele-Fabry et al. 2017; Kunkle et al. 2014; Chen et al. 2015). One focused on parental occupational exposure, including parental employment in farming or agriculture, and reported increased odds of 30% (summary odds ratio (SOR): 1.30; 95% CI: 1.11, 1.53) for case-control studies and 53% for cohort studies (SOR: 1.53; 95% CI: 1.20, 1.95) (Van Maele-Fabry et al. 2013). Another meta-analysis combined occupational and residential pesticide exposure, and observed increased odds for paternal exposure to any pesticide before or after birth (SOR=1.49; 95% CI 1.23, 1.79 and SOR=1.66;

95% CI: 1.11, 2.49, respectively) (Vinson et al. 2011). They also estimated a weak increase in risk for maternal prenatal exposure to pesticides.

Another major source of pesticide exposure is from residential proximity to pesticide application in agricultural communities. The EPA estimates that an excess of 1.1 billion pounds of pesticides were used in the U.S. in both 2011 and 2012 (EPA 2017). Pesticides have been shown to drift several hundred meters from treatment sites (Lee et al. 2002).

However, few studies have examined the relationship between agricultural pesticide exposure and childhood brain tumors, and they have reported mixed results (Kristensen et al. 1996; Reynolds et al. 2002, 2005).

Although some studies have found elevated risks specifically for high-grade gliomas (Greenop et al. 2013) and astrocytomas (Shim et al. 2009; van Wijngaarden et al. 2003), there have been only a small number of studies adequately powered to investigate childhood brain tumor subtypes. In 1990, California became the first state to require reporting of all agricultural pesticide use. California's pesticide reporting system is among the most detailed in the United States—collecting information on each pesticide's active ingredient, poundage applied, the crop and acreage of the field, the application method, and the date and location of the application at a resolution of 1 square mile, which we have further refined to a smaller geographical scale: our validated exposure model combines this detailed pesticide use reporting data with land use data from the California Department of Water Resources, to pinpoint the location of the pesticide application within each 1 square mile land parcel for more accurate exposure assessment (Rull and Ritz 2003). Using this fine grained exposure model, we conducted a population-based case-control study in order to evaluate associations between specific pesticide exposures occurring during pregnancy and central nervous system tumor subtypes in young children in California.

Methods

Study population

Cancer cases in children ages 0 to 5 years were drawn from California Cancer Registry records for 1988-2013 and matched to their birth certificates using name, date of birth, and social security number when available. We achieved 89% matching success (n=13,674); most of the remaining 11% were likely born out of state (Urayama et al., 2009). Twenty controls per case were randomly selected from birth certificate data and frequency matched on birth year to all childhood cancer cases during the study period (n=270,941) to ensure the distribution of year of birth would be the same for cases and controls. We excluded controls who died before age six (n=1215) as they did not have the opportunity to become cases, as well as subjects with unknown sex (n=3), gestational age less than 20 weeks (n=680), or birth weight less than 500-g (n=131). We also excluded birth addresses outside of California (n=488); we do not have exposure information for these locations, since most states do not require pesticide use reporting. Methods for the Environmental Health Tracking and Childhood Cancer Study are detailed elsewhere (Heck et al. 2012, 2013a, 2013b). We limited analyses to the time period when full residential addresses were available on the electronic dataset of birth certificates (1998-2011). Pesticide applications for house fumigations are reported at the county level only, therefore we restricted the present study to those mothers living during pregnancy within 4000m of an agricultural field to which at least one pesticide was applied. Our final study population consisted of 387 cases of all astrocytoma (combined), 119 cases of diffuse astrocytoma, 256 cases of pilocytic astrocytoma, 123 cases of ependymoma, 157 cases of medulloblastoma, and 123,158 controls.

Pesticide exposures

As described in detail previously, pesticide exposures were assessed with the GIS-based Residential Ambient Pesticide Estimation System (GRAPES), which uses California Land Use data from the California Department of Water Resources and pesticide use data reported to the California Department of Pesticide Regulation to locate the precise area within the square mile Public Land Survey System grid where pesticide applications occurred (Goldberg et al., 2008). Using date of last menstrual period, date of birth, and home address from the birth certificate, we assessed ever pesticide exposure within a 4000-mbuffer of maternal residence during pregnancy, based on approaches taken by previous studies (Cockburn et al., 2011; Costello et al., 2009; Marusek et al., 2006) and community-based air monitoring of pesticides by CA EPA (Wofford et al., 2014). For our analyses, we preselected 132 pesticides that have been classified by the EPA as possibly or probably carcinogenic (EPA 2012a). These were then grouped by chemical class (organochlorines, organophosphates, triazines, etc.) based on the Pesticide Action Network (PAN) database (Kegley et al. 2011). Of these, we report results for 77 pesticides for which at least 10 cases were exposed during the study period.

Statistical methods

Given the large number of pesticides, we employed the analytic strategy suggested by Momoli (Momoli et al., 2010). Unconditional logistic regression was used to estimate odds ratios and 95% confidence intervals for pesticides and cancer in single models for the 77 pesticides. We adjusted for child's birth year (matching factor), mother's age (<25, 25-34, 35+ years), race/ethnicity (Non-Hispanic White, Hispanic any race, Black, Asian/Pacific Islander/Other), and neighborhood socioeconomic status (SES) (quintiles). Neighborhood SES was calculated from

California Census data based on an algorithm developed by Yost et al. from census data in California using principal components analysis (Yost et al., 2001). This index was created from seven census indicator variables of SES at the block-group level (education index, median household income, percent living 200% below poverty level, percent blue-collar workers, percent older than 16 years in workforce without job, median rent, and median house value). Maternal age, race/ethnicity, and SES have been associated with brain tumors in children and may be associated with pesticide exposure (Chow et al., 2010; Johnson et al., 2009). We also tested the following confounders in models for astrocytoma and pesticide class: payment method for prenatal care, mother's education, father's education, child's sex, father's race/ethnicity, father's age, mother born in U.S., rural/urban residence, birth weight, gestational age, parity, region of California, and season of birth. As none of these variables changed our estimates by 10% or more, our final models did not include them.

To account for pesticide co-exposures and multiple comparisons, we utilized multiple-pesticide models co-adjusted for exposure to all other selected pesticides using semi-Bayesian hierarchical regression, with T^2 set to 0.5 (Greenland, 1992, 1994). We ran this model under two separate assumptions. The first assumed that estimated effects are drawn from separate distributions according to pesticide class (2,6 dinitroanilines, amides, anilides, azoles, chloroacetanilides, dicarboximides, halogenated organics, n-methyl carbamates, organochlorines, organophosphates, pyrethroids, substituted benzenes, triazines, and ureas). The second assumed that estimated effects are drawn from separate distributions of highly correlated pesticide applications. For this second assumption, we conducted factor analysis to assess which pesticide exposures were most correlated among controls and created grouping variables for the hierarchical logistic regression model based on factor loadings. This correlation structure is

shown in Fig 1. Both assumptions yielded similar results, therefore, we present results from the hierarchical regression model using the pesticide class distribution assumption. The assumption that all pesticides belonging to a particular class have a similar effect on childhood central nervous system tumors is likely not valid; however, we employed this hierarchical modeling (HLM) approach as to adjust for other carcinogenic pesticide exposures while mitigating error due to multiple comparisons.

All analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC). This study was approved by 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.

Results

Fig. 1 shows four main clusters of positively correlated pesticides, along with several other pesticides that were correlated; for example, maneb was highly correlated with paraquat dichloride, propanil with molinate, and chlorothalonil with mancozeb, among others—reflecting frequent co-application of these pesticides in agriculture.

Characteristics of cases and controls are shown in Table 1. For all subtypes, mothers were more likely to be Hispanic or White non-Hispanic than any other race. Mothers of astrocytoma cases were more likely to be White non-Hispanic. Children with medulloblastoma were more often male.

ORs for individual pesticides, shown by CNS tumor subtype, are presented in Supplementary Tables 1-5. In Table 2, we present these results only for the pesticides for which we observed elevated odds in single or multiple-pesticide models (HLM) by each CNS tumor

subtype. For all astrocytoma (combined), we observed elevated odds with exposure to several pesticides in the single-pesticide models; however, in hierarchical regression models estimated effects were slightly attenuated, leaving only bromacil exposure with a consistently strong association with astrocytoma.

For diffuse astrocytoma, we observed increased odds with exposure to bromacil, thiophanate-methyl, triforine, and kresoxim-methyl in the hierarchical regression model. Several of the listed pesticides resulted in elevated odds for pilocytic astrocytoma in the single-pesticide models, though for none of them the odds remained elevated in the hierarchical regression model.

Regarding medulloblastoma, we observed increased odds with exposure to chlorothalonil, propiconazole, dimethoate, and linuron. Lastly, in the hierarchical model for ependymoma we estimated elevated odds for thiophanate-methyl.

Discussion

In our population-based study of agricultural pesticide exposures and childhood central nervous system tumors, the analysis of individual pesticides showed a number of positive associations with specific tumor subtypes. To the best of our knowledge, this is the first publication with this level of detail for both pesticide type and brain tumor subtype. When comparing results from single-pesticide and multiple-pesticide models, the following pesticide associations were found to be consistently elevated: chlorthalonil, bromacil, thiophanate-methyl, triforine, kresoxim-methyl, propiconazole, dimethoate, and linuron.

Most previous studies examining residential pesticide exposure in relation to childhood brain tumors have assessed exposure by grouping pesticides together according to type

(insecticides, fungicides, herbicides, etc.) or class (organophosphate, organochlorine, urea, etc.). Many of these studies may have been affected by exposure misclassification owing to possibly erroneous parental recall of pesticide exposures. There have been few studies with designs similar to ours. A previous ecological study, which used California Pesticide Use Report data to estimate agricultural pesticide density by census block group, did not find associations for agricultural pesticide use and risk of childhood gliomas or other childhood cancers (Reynolds et al. 2002). More specifically, the authors found no association between chlorothalonil exposure and risk of childhood gliomas, which differs from our finding for chlorothalonil showing elevated risks for all astrocytoma, diffuse astrocytoma, and medulloblastoma. A later study by the same authors calculated pounds of pesticides applied within a half-mile radius of a mother's residential address to assess the relationship between prenatal agricultural pesticide exposure and cancer in young children, and also did not find associations with childhood nervous system tumors (Reynolds et al. 2005). Nondifferential exposure misclassification and inadequate power to analyze brain tumor subtypes may account for the differences in findings between the previous and our current study. A simulation found that pesticide exposures based on the Pesticide Use Report data as used in the previous studies may trade sensitivity for specificity, which can result in substantial attenuation of effect estimates (Rull and Ritz 2003). Our study combined PUR and land-use data which might have resulted in more accurately locating pesticide applications near homes.

Of the pesticides we identified as being associated with increased risk for cancer, data on neurocarcinogenicity is limited. Chlorothalonil has been the subject of an IARC Monograph as a tumor-causing chemical in rodents (IARC 1999), but previous studies in humans have reported weak associations between chlorothalonil exposure and cancer (Reynolds et al. 2002; Mozzachio

et al. 2008). Though we were not able to find previous studies on the carcinogenicity of bromacil, triforine, or thiophanate-methyl in humans, developmental toxicity studies for these pesticides observed increased skeletal malformations (EPA 1996, 2012b) and decreased numbers of fetuses in rats and rabbits (EPA 2004; CalEPA 1999). Skull malformations are frequently consistent with neural anomalies, as the brain and skeleton share genetic signaling networks (Richtsmeier and Flaherty 2013).

Carbendazim, the primary metabolite of thiophanate-methyl, is associated with central nervous system malformations in rats, including domed head, exencephaly, and bulged eyes (EPA 2004). A study in African catfish found that antioxidant enzyme levels in the brain declined with duration of exposure to carbendazim, while levels of oxidative stress biomarkers increased, indicating that carbendazim induces oxidative stress in the brain as well as adverse effects on the development of the central nervous system (Ezeoyili et al. 2019).

Kresoxim-methyl, a strobilurin class fungicide, was found to be a neurotoxic compound, inducing neuron death (Reguerio et al. 2015) and altering neural transcription (Pearson et al. 2016). Kresoxim-methyl was associated with acute lymphoblastic lymphoma in childhood in a previous study (Park et al. 2020); however, the present study appears to be the first to find a link between kresoxim-methyl and childhood CNS tumors.

Propiconazole is classified as a possible human carcinogen on the basis of elevated hepatocellular carcinoma in male mice following chronic exposure (EPA 2006b). The pesticide has also been found to induce oxidative stress in zebrafish (Valadas et al. 2019), as well as glial cell proliferation and neuron death in the aquatic species *channa punctata* Bloch (Tabassum et al. 2016). Research on the effect of propiconazole exposure in humans is sparse.

Dimethoate has been found to increase the production of inflammatory molecules in neonatal astrocyte cells in male rats (Astiz et al. 2014). Chronic inhalation of dimethoate, as with other organophosphorus pesticides, has also been shown to inhibit brain acetylcholinesterase in rats, which corresponded to generation of free radicals and oxidative stress (EPA 2006a; Farag et al. 2006; Sharma et al. 2005).

Lastly, the herbicide linuron is a substituted urea class pesticide that is banned in Europe due to its potentially high risk for toxicity in mammals (EFSA 2016). Previous studies in non-target species have identified this pesticide as cytotoxic (Scassellati-Sforzolini 1997), teratogenic (Khera et al. 1978), and possibly carcinogenic. A study examining the effects of linuron on the central nervous system reported that it boosted neuroinflammation in mice (Wheeler et al. 2019).

Pests and weeds frequently develop resistance to chemicals; therefore, new pesticides are constantly being developed and marketed and existing ones reformulated. In our data, we have observed regular and rapid changes in the use of specific pesticides over time. In terms of annual pounds of pesticides applied nationally throughout the study period, bromacil and linuron usage have exhibited a steady decline, and triforine use rapidly decreased until 2002. Thiophanate-methyl and propiconazole have steadily increased, while kresoxim-methyl, chlorothalonil and dimethoate applications have remained fairly constant aside from brief dips and spikes in usage (USGS 2020).

Aerial spray drift following pesticide applications can result in pesticide movement and subsequent exposure to individuals living near sprayed fields (Richter et al. 1986). Past studies have examined this drift via air monitoring methods and biomarkers. Elevated pesticide levels have been detected in samples from nearby residential communities (Weppner et al. 2006;

Richards et al. 2001), and chemical concentrations in the air above trace levels were measured up to 8 km away from the spray site (Wofford et al. 2014).

Pesticides may increase the risk of childhood CNS tumors through parental germ line mutations during the preconception period, or somatic mutations from prenatal or childhood exposure (Jurewicz and Hanke 2006; Vinson et al 2011). Our study focuses on exposures occurring during pregnancy, however, the most relevant time period for exposure has yet to be identified and may vary according to CNS tumor subtype.

A study of children enrolled in the West Coast Childhood Brain Tumor Study reported interactions between children's genotypes for pesticide metabolism genes (*PON1* and *FMO1*) and insecticide treatment in the home and their risk of brain tumors (Searles Nielsen et al. 2010), suggesting that genetic factors involved in the metabolism of pesticides may be important modifiers of the estimated effects. We did not have genetic data available for this study for mothers or children. Another limitation of our study is that we did not have access to information regarding pesticide exposures from occupational, home and garden use, or dietary exposures. The proportion of rural residents working in agriculture, specifically, is obscure; however, depending on how rural is defined, 6-10% of California's rural population is employed in 'agriculture, forestry, fishing, hunting, mining industries'(USDA 2007). Our ability to assess exposure across residential history was also limited, since we had only one residential address available for each mother. However, in one of our own previous analyses, results did not differ substantially in a sensitivity analysis when we had full residential histories available (Ling et al 2019).

Our study included a large number of cases, which is a strength that allowed for the examination of associations for several central nervous system tumor subtypes. Additionally, our

pesticide exposure model provided spatially fine-grained information on individual pesticides applications, allowing for objective exposure assessment not subject to recall errors.

In conclusion, this study is the first, to our knowledge, to estimate effects for a large number of specific pesticides in relation to CNS tumor subtypes. Our results suggest that exposure to specific pesticides may best explain the results of previous studies that reported relationships between broader pesticide types and central nervous system tumors. Policy interventions to reduce pesticide exposure in individuals residing near agricultural fields should be considered to protect the health of children. Reductions in exposure can be achieved by restriction of application methods such as aerial spraying and air blast that lead to increased drift, and more optimally by implementation of Integrated Pest Management systems that decrease reliance on pesticides (Hertz-Picciotto et al 2018).

Acknowledgments

This study was supported by grants from the US National Institutes of Health (R21ES019986, R21ES018960). Ms. Thompson was supported by the Alex's Lemonade Stand Foundation Pediatric Oncology Student Training grant. The funders had no role in the study design, data collection and analysis, decision to publish nor preparation of the manuscript.

References

Astiz M, Acaz-Fonseca E, Garcia-Segura LM. Sex differences and effects of estrogenic compounds on the expression of inflammatory molecules by astrocytes exposed to the insecticide dimethoate. *Neurotox Res*. 2014;25(3):271-285. doi:10.1007/s12640-013-9417-0

Baldwin RT, Preston-Martin S. Epidemiology of brain tumors in childhood--a review. *Toxicol Appl Pharmacol*. 2004;199(2):118-131. doi:10.1016/j.taap.2003.12.029

Bunin GR, Buckley JD, Boesel CP, Rorke LB, Meadows AT. Risk factors for astrocytic glioma and primitive neuroectodermal tumor of the brain in young children: a report from the Children's Cancer Group. *Cancer Epidemiol Biomarkers Prev*. 1994;3(3):197-204.

CalEPA (California Environmental Protection Agency), Office of Environmental Health Hazard Assessment. Chemicals meeting the criteria for listing as developmental and reproductive toxicants (DARTs) via the authoritative bodies mechanism: 5 chemicals identified by U.S. EPA. 1999. https://oehha.ca.gov/proposition-65/crnr/chemicals-meeting-critieria-listing-developmental-and-reproductive-toxicants. Accessed August 31, 2020.

Chen M, Chang CH, Tao L, Lu C. Residential Exposure to Pesticide During Childhood and Childhood Cancers: A Meta-Analysis. *Pediatrics*. 2015;136(4):719-729. doi:10.1542/peds.2015-0006

Chow EJ, Puumala SE, Mueller BA, et al. Childhood cancer in relation to parental race and ethnicity: a 5-state pooled analysis. *Cancer*. 2010;116(12):3045-3053. doi:10.1002/cncr.25099

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

Cordier S, Iglesias MJ, Le Goaster C, Guyot MM, Mandereau L, Hemon D. Incidence and risk factors for childhood brain tumors in the Ile de France. *Int J Cancer* 1994;59:776- 82.

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

Davis JR, Brownson RC, Garcia R, Bentz BJ, Turner A. Family pesticide use and childhood brain cancer. *Arch Environ Contam Toxicol*. 1993;24(1):87-92. doi:10.1007/BF01061094

EFSA (European Food Safety Authority) (2016). Peer review of the pesticide risk assessment of the active substance linuron. EFSA J. 14, 4518.

EPA (United States Environmental Protection Agency). Bromacil. Prevention, Pesticides, and Toxic Substances; 1996. https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/fs_PC-012301_1-Aug-96.pdf. Accessed July 31, 2020.

EPA. Thiophanate-methyl. Prevention, Pesticides, and Toxic Substances; 2004. https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-102001_1-Nov-04.pdf. Accessed July 31, 2020.

EPA. Interim Reregistration Eligibility Decision (IRED) for Dimethoate. Prevention, Pesticides, and Toxic Substances; 2006. https://archive.epa.gov/pesticides/reregistration/web/pdf/revised_dimethoate_ired.pdf. Accessed August 5, 2020.

EPA. Reregistration Eligibility Decision (RED) for Propiconazole. Prevention, Pesticides, and Toxic Substances; 2006. https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-122101_18-Jul-06.pdf. Accessed August 3, 2020.

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

EPA. Chlorothalonil Human Health Scoping Document for Registration Review. 2012. https://www.regulations.gov/document?D=EPA-HQ-OPP-2011-0840----2. Accessed August 19, 2020.

EPA. 2008-2012 Market Estimates. EPA Biological and Economic Analysis Division; 2017.

Ezeoyili IC, Mgbenka BO, Atama CI, Ngwu GI, Madu JC, Nwani CD. Changes in Brain Acetylcholinesterase and Oxidative Stress Biomarkers in African Catfish Exposed to Carbendazim. *J Aquat Anim Health*. 2019;31(4):371-379. doi:10.1002/aah.10089

Farag AT, Karkour TA, El Okazy A. Developmental toxicity of orally administered technical dimethoate in rats. *Birth Defects Res B Dev Reprod Toxicol*. 2006;77(1):40-46. doi:10.1002/bdrb.20066

Feychting M, Plato N, Nise G, Ahlbom A. Paternal occupational exposures and childhood cancer. *Environ Health Perspect*. 2001;109(2):193-196. doi:10.1289/ehp.01109193

Goldberg DW, Wilson JP, Knoblock CA, Ritz B, Cockburn MG. An effective and efficient approach for manually improving geocoded data. *Int J Health Geogr*. 2008;7:60. doi:10.1186/1476-072X-7-60

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, 219-230. Doi:10.1002/sim.4780110208.

Greenland, S, 1994. Hierarchical regression for epidemiologic analyses of multiple exposures. Environ Health Perspect 102 (suppl 8), 33-39. Doi:10.1289/ehp.94102s833.

Greenop KR, Peters S, Bailey HD, et al. Exposure to pesticides and the risk of childhood brain tumors [published correction appears in Cancer Causes Control. 2014 Sep;25(9):1239-40]. *Cancer Causes Control*. 2013;24(7):1269-1278. doi:10.1007/s10552-013-0205-1

Heck JE, Lombardi CA, Cockburn M, Meyers TJ, Wilhelm M, Ritz B. Epidemiology of rhabdoid tumors of early childhood. *Pediatr Blood Cancer*. 2013;60(1):77-81. doi:10.1002/pbc.24141

Heck JE, Lombardi CA, Meyers TJ, Cockburn M, Wilhelm M, Ritz B. Perinatal characteristics and retinoblastoma. *Cancer Causes Control*. 2012;23(9):1567-1575. doi:10.1007/s10552-012-0034-7

Heck JE, Meyers TJ, Lombardi C, et al. Case-control study of birth characteristics and the risk of hepatoblastoma. *Cancer Epidemiol*. 2013;37(4):390-395. doi:10.1016/j.canep.2013.03.004

Hertz-Picciotto I, Sass JB, Engel S, Bennett DH, Bradman A, Eskenazi B, et al. Organophosphate exposures during pregnancy and child neurodevelopment: Recommendations for essential policy reforms. *PLoS Med*. 2018;15(10): e1002671. https://doi.org/10.1371/journal.pmed.1002671

IARC (International Agency for Research on Cancer). IARC monographs on the evaluation of carcinogenic risks to humans, Volume 73. Some Chemicals that Cause Tumours of the Kidney or Urinary Bladder in Rodents and Some Other Substances. IARC. 1999. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono73.pdf. Accessed March 4, 2021.

Infante PF, Newton WA Jr. Letter: Prenatal chlordane exposure and neuroblastoma. *N Engl J Med*. 1975;293(6):308. doi:10.1056/nejm197508072930625

Infante-Rivard C, Weichenthal S. Pesticides and childhood cancer: an update of Zahm and Ward's 1998 review. *J Toxicol Environ Health B Crit Rev*. 2007;10(1-2):81-99. doi:10.1080/10937400601034589

Johnson KJ, Carozza SE, Chow EJ, et al. Parental age and risk of childhood cancer: a pooled analysis. *Epidemiology*. 2009;20(4):475-483. doi:10.1097/EDE.0b013e3181a5a332

Jurewicz J, Hanke W. Exposure to pesticides and childhood cancer risk: has there been any progress in epidemiological studies. *Int J Occup Med Environ Health*. 2006;19:152-69.

Kegley SE, Hill BR, Orme S, Choi AH. PAN Pesticide Database. Pesticide Action Network, North America. 2011.

Khera KS, Whalen C, Trivett G. Teratogenicity studies on linuron, malathion, and methoxychlor in rats. *Toxicol Appl Pharmacol.* 1978;45(2):435-444. doi:10.1016/0041-008x(78)90107-2

Kristensen P, Andersen A, Irgens LM, Bye AS, Sundheim L. Cancer in offspring of parents engaged in agricultural activities in Norway: incidence and risk factors in the farm environment. *Int J Cancer*. 1996;65(1):39-50. doi:10.1002/(SICI)1097-0215(19960103)65:1<39::AID-IJC8>3.0.CO;2-2.

Kunkle B, Bae S, Singh KP, Roy D. Increased risk of Childhood Brain Tumors among children whose parents had farm-related pesticide exposures during pregnancy. *JP J Biostat*. 2014;11(2):89-101.

Lee S, McLaughlin R, Harnly M, Gunier R, Kreutzer R. Community exposures to airborne agricultural pesticides in California: ranking of inhalation risks. *Environ Health Perspect*. 2002;110(12):1175-1184. doi:10.1289/ehp.021101175

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

Marusek JC, Cockburn MG, Mills PK, Ritz BR. Control selection and pesticide exposure assessment via GIS in prostate cancer studies. *Am J Prev Med*. 2006;30(2 Suppl):S109-S116. doi:10.1016/j.amepre.2005.09.002

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.

Mozzachio AM, Rusiecki JA, Hoppin JA, et al. Chlorothalonil exposure and cancer incidence among pesticide applicator participants in the agricultural health study. *Environ Res*. 2008;108(3):400-403. doi:10.1016/j.envres.2008.07.018

Ostrom QT, Patil N, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2013-2017. *Neuro Oncol.* 2020;22(12 Suppl 2):iv1-iv96. doi: 10.1093/neuonc/noaa200. PMID: 33123732; PMCID: PMC7596247.

Park AS, Ritz B, Yu F, Cockburn M, Heck JE. Prenatal pesticide exposure and childhood leukemia - A California statewide case-control study. *Int J Hyg Environ Health*. 2020;226:113486. doi:10.1016/j.ijheh.2020.113486

Pearson BL, Simon JM, McCoy ES, Salazar G, Fragola G, Zylka MJ. Identification of chemicals that mimic transcriptional changes associated with autism, brain aging and neurodegeneration. *Nat Commun*. 2016;7:11173. Published 2016 Mar 31. doi:10.1038/ncomms11173

Pogoda JM, Preston-Martin S. Household pesticides and risk of pediatric brain tumors. *Environ Health Perspect*. 1997;105(11):1214-1220. doi:10.1289/ehp.971051214

Reeves JD, Driggers DA, Kiley VA. Household insecticide associated aplastic anaemia and acute leukaemia in children. *Lancet*. 1981;2(8241):300-301. doi:10.1016/s0140-6736(81)90540-7

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

Reynolds P, Von Behren J, Gunier RB, Goldberg DE, Hertz A, Harnly ME. Childhood cancer and agricultural pesticide use: an ecologic study in California. *Environ Health Perspect*. 2002;110(3):319-324. doi:10.1289/ehp.02110319

Reynolds P, Von Behren J, Gunier RB, Goldberg DE, Harnly M, Hertz A. Agricultural pesticide use and childhood cancer in California. *Epidemiology*. 2005;16:93-100.

Richards S, McClure G, Lavy T, et al. Propanil (3,4-Dichloropropionanilide) Particulate Concentrations Within and Near the Residences of Families Living Adjacent to Aerially Sprayed Rice Fields. *Arch Environ Contam Toxicol*. 2001; 41:112-116.

Richter ED, Rosenvald Z, Kaspi L, et al. Sequential cholinesterase tests and symptoms for monitoring organophosphate absorption in field workers and in persons exposed to pesticide spray drift. *Toxicol Lett*. 1986;33:25-35

Richtsmeier JT, Flaherty K. Hand in glove: brain and skull in development and dysmorphogenesis. *Acta Neuropathol*. 2013;125(4):469-489. doi:10.1007/s00401-013-1104-y

Robinson KE, Kuttesch JF, Champion JE, et al. A quantitative meta-analysis of neurocognitive sequelae in survivors of pediatric brain tumors. *Pediatr Blood Cancer*. 2010;55(3):525-531. doi:10.1002/pbc.22568

Rull RP, Ritz B. Historical pesticide exposure in California using pesticide use reports and land-use surveys: an assessment of misclassification error and bias. *Environ Health Perspect*. 2003;111(13):1582-1589. doi:10.1289/ehp.6118

Scassellati-Sforzolini G, Pasquini R, Moretti M, et al. In vivo studies on genotoxicity of pure and commercial linuron. *Mutat Res*. 1997;390(3):207-221. doi: 10.1016/s1383-5718(97)00012-0

Searles Nielsen S, McKean-Cowdin R, Farin FM, Holly EA, Preston-Martin S, Mueller BA. Childhood brain tumors, residential insecticide exposure, and pesticide metabolism genes. *Environ Health Perspect.* 2010;118:144-9.

Sharma Y, Bashir S, Irshad M, Gupta SD, Dogra TD. Effects of acute dimethoate administration on antioxidant status of liver and brain of experimental rats. *Toxicology.* 2005;206(1):49-57. doi:10.1016/j.tox.2004.06.062

Shim YK, Mlynarek SP, van Wijngaarden E. Parental exposure to pesticides and childhood brain cancer: U.S. Atlantic coast childhood brain cancer study. *Environ Health Perspect.* 2009;117:1002-6.

Tabassum H, Khan JU, Salman MY, Raisuddin S, & Parvez S. Propiconazole induced toxicological alterations in brain of freshwater fish Channa punctata Bloch. *Ecol Indic.* 2016;62, 242-248.

Ullrich NJ, Embry L. Neurocognitive dysfunction in survivors of childhood brain tumors. *Semin Pediatr Neurol*. 2012;19(1):35-42. doi:10.1016/j.spen.2012.02.014

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

USDA (U.S. Department of Agriculture) Economic Research Service. California-Rural Definitions: State-Level Maps. 2007. https://www.ers.usda.gov/webdocs/DataFiles/53180/25559_CA.pdf?v=300.1. Accessed March 4, 2021.

USGS (U.S. Geological Survey) Pesticide National Synthesis Project. Estimated Annual Agricultural Pesticide Use. 2020. https://water.usgs.gov/nawqa/pnsp/usage/maps/compound_listing.php. Accessed March 6, 2021.

Valadas J, Mocelin R, Sachett A, et al. Propiconazole induces abnormal behavior and oxidative stress in zebrafish. *Environ Sci Pollut Res Int*. 2019;26(27):27808-27815. doi:10.1007/s11356-019-05977-3

Van Maele-Fabry G, Hoet P, Lison D. Parental occupational exposure to pesticides as risk factor for brain tumors in children and young adults: a systematic review and meta-analysis. *Environ Int*. 2013;56:19-31. doi:10.1016/j.envint.2013.02.011

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

van Wijngaarden E, Stewart PA, Olshan AF, Savitz DA, Bunin GR. Parental occupational exposure to pesticides and childhood brain cancer. *Am J Epidemiol.* 2003;157:989-97.

Vinson F, Merhi M, Baldi I, Raynal H, Gamet-Payrastre L. Exposure to pesticides and risk of childhood cancer: a meta-analysis of recent epidemiological studies. *Occup Environ Med*. 2011;68(9):694-702. doi:10.1136/oemed-2011-100082

Weppner S, Elgethun K, Lu C, et al. The Washington aerial spray drift study: Children's exposure to methamidophos in an agricultural community following fixed-wing aircraft applications. *J Expo Sci Environ Epidemiol*. 2006;16:387-396.

Wheeler MA, Jaronen M, Covacu R, et al. Environmental Control of Astrocyte Pathogenic Activities in CNS Inflammation. *Cell*. 2019;176(3):581-596.e18. doi:10.1016/j.cell.2018.12.012

Wilkins JR 3rd, Koutras RA. Paternal occupation and brain cancer in offspring: a mortality-based case-control study. *Am J Ind Med*. 1988;14(3):299-318. doi:10.1002/ajim.4700140308

Wofford P, Segawa R, Schreider J, et al. Community air monitoring for pesticides. Part 3: using health-based screening levels to evaluate results collected for a year. *Environ Monit Assess.* 2014;186:1355-1370.

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