



# Livestock and poultry density and childhood cancer incidence in nine states in the USA



Benjamin J. Booth<sup>a,b</sup>, Rena R. Jones<sup>a</sup>, Mary E. Turyk<sup>b</sup>, Sally Freels<sup>b</sup>, Deven M. Patel<sup>a</sup>,  
Leslie T. Stayner<sup>b,1</sup>, Mary H. Ward<sup>a,\*,1</sup>

<sup>a</sup> Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, 9609 Medical Center Dr., Room 6E138, Rockville, MD 20850, USA

<sup>b</sup> Division of Epidemiology and Biostatistics, School of Public Health, University of Illinois at Chicago, Chicago, IL, USA

## ARTICLE INFO

### Keywords:

Childhood cancer  
Livestock  
Poultry  
Farm animals  
Agricultural exposures  
Environmental epidemiology

## ABSTRACT

**Background:** Parental occupational and childhood exposures to farm animals have been positively associated with childhood brain tumors, whereas associations with childhood leukemia are equivocal. The developing immune system may be influenced by allergen, virus, or other exposures from animal sources, which may contribute to childhood cancer incidence.

**Methods:** Incident cancers (acute lymphoblastic leukemia [ALL], acute myeloid leukemia [AML], central nervous system [CNS], peripheral nervous system [PNS]) for children aged 0–4 diagnosed between 2003 and 2008 were obtained from nine National Cancer Institute Surveillance, Epidemiology and End Results (SEER) registries and were linked to U.S. Census of Agriculture data from 2002 and 2007 by county of diagnosis. Animal densities (animal units [AU]/km<sup>2</sup>; one animal unit is 1000 pounds of animal weight) were estimated for hogs, cattle, chickens (layers and broilers, separately), equine (horses, ponies, mules, burros, donkeys), goats, sheep, turkeys, and total animals. Animal density was examined in models as both continuous (AU per km<sup>2</sup>) and categorical variables (quartiles). Animal operation densities (per km<sup>2</sup>) by size of operation (cattle, hogs, chickens, sheep) were modeled continuously. Rate ratios and 95% confidence intervals were estimated using Poisson regression.

**Results:** We found positive associations between AML and broiler chicken densities (RR<sub>per 10 AU/km<sup>2</sup></sub> = 1.14, 95% CI = 1.02–1.26). ALL rates increased with densities of hog operations (RR<sub>per operation/100 km<sup>2</sup></sub> = 1.06, 95% CI = 1.02–1.11). PNS cancer rates were inversely associated with layer chicken density (RR<sub>per log of AU/km<sup>2</sup></sub> = 0.94, 95% CI = 0.89–0.99). No association was found between any cancer type and densities of cattle, equine, or goats.

**Conclusions:** Although limited by the ecologic study design, some of our findings are novel and should be examined in epidemiological studies with individual level data.

## 1. Introduction

Epidemiologic studies of childhood cancer provide some evidence that living on a farm or in agricultural areas is associated with an increased risk of childhood cancer. In Korea, residence in counties with high agricultural intensity was positively associated with increased childhood leukemia mortality rates (Cha et al., 2014). In the United States, the percentage of the county land use in agricultural crops was positively associated with incidence of childhood leukemia, central nervous system (CNS) cancers, and peripheral nervous system (PNS) cancers (Carozza et al., 2008). A case-control study using data pooled from seven countries across three continents (Australia, North America,

and Europe) reported that living on a farm during the first six months of life increased the odds of developing childhood brain tumors (CBT) (Efird et al., 2003). Furthermore, two case-control studies found positive associations between living on a farm during childhood, contact with farm animals, and CBT (Efird et al., 2003; Gold et al., 1979).

Hypothesized mechanisms for animal exposures and childhood cancer include exposures to viruses and immune response linked to allergies. Animal viruses, such as avian sarcoma virus, oncornaviruses, papovaviruses, and adenoviruses can cause brain tumors in animals (Copeland et al., 1975; Swenberg, 1977) and positive associations between *Toxoplasma gondii* and CNS tumors have been reported in case-control studies of human adults (Ryan et al., 1993; Schuman et al.,

\* Corresponding author.

E-mail address: [wardm@mail.nih.gov](mailto:wardm@mail.nih.gov) (M.H. Ward).

<sup>1</sup> Co-senior authors.

1967). Allergy rates are lower among children with early life exposure to animals (Campo et al., 2006; Ownby et al., 2002) and who live on farms (Riedler et al., 2001; Stein et al., 2016). Lower prevalence of allergic disease among children living on farms or in agricultural areas may be a mechanism for increased risk of CBT and childhood leukemia, because allergy and atopic disease are associated with decreased risk of these cancers (Harding et al., 2008; Roncarolo and Infante-Rivard, 2012; Linabery et al., 2010; Nanni et al., 1996; Schuz et al., 2003; t' Mannelte et al., 2012).

Previous research on animal exposure and childhood cancer has largely employed case-control studies, although registry-based cohorts have also been used to examine associations with parental occupational exposure to animals. Many of these studies did not evaluate relationships separately for specific animal types, which is important because exposures to chemical and biological agents may vary by animal species and animal management practices (Spellman and Whiting, 2007). Most studies of childhood leukemia found no associations with parental or childhood exposure to animals (Keegan et al., 2012; Kristensen et al., 1996; McKinney et al., 2003; Meinert et al., 1996; Rudant et al., 2010; van Steensel-Moll et al., 1985); whereas most studies of CBTs found positive associations with parental or childhood exposure to animals (Christensen et al., 2012; Efird et al., 2003; Holly et al., 1998; Keegan et al., 2013; Kristensen et al., 1996).

Ecologic studies in the United States have evaluated relationships between county-level incidence rates of childhood cancers and the density of specific crop types as a proxy for potential agricultural pesticide exposure (Booth et al., 2015; Carozza et al., 2008). However, densities of animals and animal operations have not previously been studied in relation to childhood cancer. We used county-level data on densities of animals and animal operations to assess relationships with incidence rates of total childhood leukemia, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), CNS cancers, and PNS cancers among children less than five years old, accounting for crop density. Several of the animal types that we examined in our study had not been previously evaluated in relation to childhood cancer.

## 2. Methods

### 2.1. Cancer incidence and population data

We obtained cancer incidence data by gender and race (white, black, and other) at the county level for children under the age of five from the Surveillance, Epidemiology, and End Results (SEER) program using SEER\*Stat software version 8.1.5 (SEER, 2014). We included nine states with complete case ascertainment from 2003 through 2008 (California, Connecticut, Georgia, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, and Utah). Site codes from the International Classification of Childhood Cancer, third edition (ICCC-3) were used to categorize childhood cancers into total leukemias (ICCC-3 code: 011–015), ALL (011), AML (012), CNS and miscellaneous neoplasms (031–036), and neuroblastomas and other PNS cancers (041–042) (Steliarova-Foucher et al., 2005). Inter-censal estimates of county populations by age, race, and sex were obtained from the U.S. Census Bureau and were used as denominators for estimating cancer incidence rates (U.S. Census Bureau, 2010). County-level incidence rates were computed based on residence at the time of cancer diagnosis and county-level population data. Counties with populations greater than 300,000 ( $N = 48$  counties) had few animal operations. We excluded these counties due to their low animal counts and concerns about residual confounding due to urban factors that may be associated with childhood cancer incidence (e.g., specific air pollutants) and that may vary across the study states. After exclusions, data from 541 counties were included in the analysis.

### 2.2. Animal and operation densities

County-level data on animal inventories and number of animal operations were obtained from the 2002 and 2007 U.S. Department of Agriculture (USDA) National Agricultural Statistics Service (NASS) Census of Agriculture (USDA, 2002, 2007). Inclusion in the Census of Agriculture required that a farm or operation sell or produce at least \$1000 in agricultural products. To characterize the time period preceding or overlapping case diagnosis (2003–2008) we averaged the data from the 2002 and 2007 censuses. Counts of animals and operations were available for total cattle (including calves), hogs, chickens (broilers and layers, separately), sheep, goats, turkeys, and equine (horses and ponies; mules, burros, and donkeys). Additionally, the number of operations by size (number of animals per operation) was available for cattle ( $< 500$ ,  $\geq 500$ ), layer chickens (1–399, 400–99,999,  $\geq 100,000$ ), hogs ( $< 1000$ ,  $\geq 1000$ ), and sheep (1–99, 100–999,  $\geq 1000$ ). To avoid potential identification of individual operations, the USDA suppressed the number of animals in a county when there were fewer than three operations in a county or when there was an operation that was very large in size compared to other operations in a county (USDA, 2002). However, data were suppressed only for the number of animals, not the number of animal operations.

For counties with missing animal numbers, we imputed five complete datasets for each state in each census period using truncated linear regression. For cattle, hogs, sheep, and layer chickens we used the information on the number of operations by size to impute missing counts within the operation size range. For the other animal types, we used the total number of animal operations of that type to impute suppressed animal counts. We excluded all counties in Iowa, New Jersey, and Utah from our analysis of turkey density because over 45% of the counties had missing data in 2002, 2007, or both years. Further, we did not include turkeys in our calculation of total animal density.

We converted animal counts to animal units (AUs) using the EPA definition, which defines one AU as 1000 pounds based on the average animal weights (Environmental Protection Agency (EPA), 2001). One AU equals one cow, 2.5 hogs, 100 chickens (broilers or layers), 0.5 horses, 10 sheep, 10 goats, one mule, and 55 turkeys. Total land area in  $\text{km}^2$  for each county was obtained from the U.S. Census Bureau, 2013 Tiger/LineFile (U.S. Census Bureau, 2013). We computed densities of each animal type and animal operation by dividing the average of the 2002 and 2007 AUs and number of operations by the land area of each county ( $\text{AU}/\text{km}^2$  and  $\text{operation}/\text{km}^2$ , respectively).

### 2.3. Covariate data

We evaluated factors that have been associated with incidence of one or more childhood cancers and were available for our study counties including population density, urbanicity, population mobility, socioeconomic status, and agricultural crop density. County-level estimates of median household income, educational attainment (percent with at least a bachelor's degree), percent of population with a change of residence within the last five years (from within county, within state, within country, or another country), and percent of residents employed in agriculture (farming, fishing, and forestry) were obtained from the 2005–2009 American Community Survey (U.S. Census Bureau, 2009). Population density was computed by dividing the total population in each county by the total land area. Urbanicity of a county was characterized using the 2003 rural-urban continuum codes created by the USDA (USDA, 2003). The rural-urban continuum categorizes counties into nine levels based on population size, metropolitan designation, and adjacency to metropolitan areas. We also evaluated the proportion of workers in non-metropolitan counties that commute to adjacent metropolitan areas (USDA, 2003).

Data on total harvested acres of cropland by type of crop for each county were obtained from the 2002 and 2007 USDA NASS Census of Agriculture (USDA, 2002, 2007). Estimates of crop acreage were

available for all states for barley, corn, hay, oats, sorghum, soybeans, and wheat, and were averaged from the two censuses. The percentage of county acreage comprising total cropland and the percentages of specific crop types were created by dividing the harvested crop acres by the county land area.

## 2.4. Statistical analysis

Poisson regression models were used to generate incidence rate ratios (RR) and 95% confidence intervals (95% CI) for total leukemia, ALL (82% of total leukemias), AML, CNS, and PNS tumors. Results for total leukemia were similar to those for ALL and are not presented. We summarized results from models of the five imputed datasets using PROC MIANALYZE in SAS (SAS Institute Inc., Cary, NC, USA). Animal density for each animal type was modeled both in quartiles and as continuous variables (AU/km<sup>2</sup>; rescaled based on their specific distributions) as a means of evaluating the pattern of incidence with increasing density. We tested for trends across quartiles by modeling the median of each quartile as a continuous variable. The density of animal operations was modeled only as a continuous variable due to the more limited range in the distributions of these variables. After visual inspection of the relationships, we used cubic splines to evaluate potential non-linear relationships.

Animal operations and their respective animal densities were moderately to highly correlated: cattle ( $\rho = 0.82$ ), hogs (0.70), broiler chickens (0.69), layer chickens (0.43), goats (0.88), sheep (0.83), horses (0.98), mules (0.91), and turkeys (0.76). We modeled density of operations by categories of size for animals for which this information was available, including cattle, hogs, sheep, and layer chickens. Animal operation counts by size of the operation were not available for broiler chickens, horses/ponies, and mules/burros/donkeys; because associations with cancer incidence were similar to those for animal densities results are not presented. Analyses of turkey operations were limited by small numbers of counties with data and a narrow distribution of densities and are not presented.

With the exception of state, population density, and percent of the population with a bachelor's degree, the aforementioned covariates were not significant ( $p \leq 0.2$ ) in stepwise regression models and were not included in final models. Final models were therefore adjusted for state, race (white, black, other), sex, population density, and percent of the population with a bachelor's degree or higher. We conducted sensitivity analyses to evaluate the influence of including counties in Iowa, New Jersey, and Utah with turkey counts in our analysis of turkey and total animal density. To do this, we used the turkey numbers from the census years in which they were available (2002 or 2007) and excluded counties with suppressed turkey counts in both years. We found the estimates to be nearly identical to our results presented in the tables, which excluded these counties.

All analyses were performed using SAS Version 9.3. Spline analyses were created using Stata Statistical Software, Version 13.0 (StataCorp, College Station, TX, USA).

## 3. Results

Our analysis included 541 counties with < 300,000 population in nine states with a combined average annual population of over 1.2 million children under the age of five (Table 1). From 2003 to 2008, 718 incident leukemia cases (591 ALL and 93 AML), and 389 CNS and 256 PNS cancers were identified. State-level crude incidence rates of leukemia ranged from 50.1 to 98.3 cases per 100,000 children, while rates of CNS cancers ranged from 16.4 to 38.4 cases per 100,000 children and PNS cancers ranged from 12.5 to 36.9 cases per 100,000 children.

Median animal densities varied across the SEER areas (Table 2). Turkeys had the lowest median density across all states (0.002 AU per 10 km<sup>2</sup>), while cattle density was the highest (96.3 AU per 10 km<sup>2</sup>). The

median densities of goats, mules, and sheep were less than 0.4 AU per 10 km<sup>2</sup> across all states. The highest densities of cattle (217.2 AU/10 km<sup>2</sup>), hogs (346.4 AU/10 km<sup>2</sup>), and sheep (1.2 AU/10 km<sup>2</sup>) were in Iowa, which also had the highest median density of total animals (588.0 AU/10 km<sup>2</sup>). New Mexico had the lowest median total animal density (37.3/10 km<sup>2</sup>) and the lowest densities for each animal type except for sheep, which were lowest in Louisiana. Georgia had the highest densities of broiler (68.9 AU/10 km<sup>2</sup>) and layer chickens (6.8 AU/10 km<sup>2</sup>).

We found no evidence of an exposure-response relationship for any cancer and density of cattle, hogs, goats, horses, mules, turkeys or total animals (Table 3). We found a positive association between AML and densities of broiler chickens ( $RR_{\text{per } 10 \text{ AU/km}^2} = 1.14$ , 95% CI = 1.02–1.26) and total chickens ( $RR_{\text{per } 10 \text{ AU/km}^2} = 1.11$ , 95% CI = 1.01–1.22). We observed an inverse association between the log of layer chicken density and PNS cancers ( $RR_{\text{per } 1 \text{ unit change in log AU/km}^2} = 0.94$ , 95% CI = 0.89–0.99). The fourth quartile of sheep density was associated with significantly increased risk of ALL ( $RR_{Q4} = 1.68$ , 95% CI = 1.18–2.41). However, cubic spline models revealed a nonlinear relationship. Rate ratios for ALL increased linearly and plateaued at about 1 sheep per km<sup>2</sup> (~81st percentile of sheep density) (not shown).

The median operation densities were highest for cattle (14.6 operations per 100 km<sup>2</sup>) with similar distributions of animal densities by operation size (Table 4). In contrast, animal densities of hogs, layer chickens, and sheep were higher in counties with higher operation densities.

We found no association between the operation densities for cattle and sheep and incidence of any childhood cancer, overall or by operation size (Table 5). We found positive associations between density of hog operations and ALL ( $RR_{\text{per operation per } 100 \text{ km}^2} = 1.06$ , 95% CI = 1.02–1.11). When we modeled hog operation density by size category, RRs for ALL increased with the density of operations with < 1000 hogs but not with the density of larger operations, which were less common. Layer chicken operation density was inversely associated with PNS cancer for the middle operation size category (400 to 99,999 layers).

## 4. Discussion

In this analysis of childhood cancer incidence in nine states, we found significant positive associations between the density of chickens and incidence of AML. We also observed a significant positive association between density of hog operations and ALL. This association was present for operations with < 1000 hogs but not larger operations, which had lower densities. PNS tumor incidence was inversely associated with layer chicken density and with density of medium size operations, but not smaller and larger operations (< 400, > 100,000, respectively). We observed no associations with animal densities or operations for CNS tumors. Our results did not change after adjusting for crop density, the proportion of the county employed in agriculture, percent of population with a change of residence in the last five years, and demographic factors.

To our knowledge, no prior ecologic studies have evaluated measures of animal production, such as animal and operation densities, and childhood leukemia or CBT incidence or mortality in the United States. Case-control and cohort studies of childhood leukemia and exposure to animals were exclusively conducted in Europe and primarily focused on parental occupational exposure; most found no associations (Keegan et al., 2012; Kristensen et al., 1996; McKinney et al., 2003; Meinert et al., 1996; Rudant et al., 2010; van Steensel-Moll et al., 1985). Additionally, most of these studies did not evaluate exposure to particular animal species. A registry-based cohort study in Norway (Kristensen et al., 1996) found no association between parental occupations in animal husbandry and childhood ALL or AML. Similarly, case-control studies in the Netherlands (van Steensel-Moll et al., 1985) and the United Kingdom (UK) (McKinney et al., 2003) found no association between maternal or paternal occupational exposure to animals and

**Table 1**

Population at risk, number of cases, and childhood cancer rates<sup>a</sup> for children 0–4 years of age from nine Surveillance, Epidemiology and End Results states, 2003–2008, excluding counties with populations > 300,000.

State	Number of counties	Population <sup>b</sup>	Total Leukemia		ALL		AML		CNS		PNS	
			Cases	rate	Cases	rate	Cases	rate	Cases	rate	Cases	rate
California	36	161,566	113	69.9	90	55.7	20	12.4	49	30.3	35	21.7
Connecticut	5	36,624	28	76.5	25	68.3	2	5.5	6	16.4	8	21.8
Georgia	155	338,537	170	50.2	138	40.8	20	5.9	106	31.3	68	20.1
Iowa	98	121,423	72	59.3	60	49.4	11	9.1	46	37.9	21	17.3
Kentucky	119	170,393	115	67.5	94	55.2	16	9.4	67	39.3	41	24.1
Louisiana	61	174,827	82	46.9	63	36.0	12	6.9	46	26.3	37	21.2
New Jersey	8	56,949	56	98.3	50	87.8	3	5.3	20	35.1	21	36.9
New Mexico	32	71,788	36	50.1	30	41.8	4	5.6	19	26.5	9	12.5
Utah	27	78,087	46	58.9	41	52.5	5	6.4	30	38.4	16	20.5
Total	541	1210,194	718	59.3	591	48.8	93	7.7	389	32.1	256	21.2

<sup>a</sup> Crude rates per 100,000 children. ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CNS = central nervous system; PNS = peripheral nervous system.

<sup>b</sup> Average annual population at risk, children 0–4 years of age.

childhood leukemia or ALL. Two other case-control studies reported no relationship between childhood leukemia and paternal occupational animal exposure (Keegan et al., 2012) or with parental occupation in cattle breeding (Meinert et al., 1996). A case-control study in France (Rudant et al., 2010) found inverse associations between the child's contact with farm animals at least once per week before the age of one and ALL (OR = 0.6, 95% CI = 0.5–0.8) and AML (OR = 0.4, 95% CI = 0.2–1.0). They also reported inverse associations between exposure before the age of one to cows (OR = 0.3, 95% CI = 0.2–0.7), sheep (OR = 0.4, 95% CI = 0.2–0.9), and poultry (OR = 0.6, 95% CI = 0.4–0.9) and ALL; whereas, no association was found for contact with horses or pigs. Thus, the positive associations we observed between animal and operation densities and leukemia incidence rates differ from results of analytic studies of childhood leukemia that evaluated parental occupational or early childhood exposure to animals.

A few studies of adult leukemia incidence or mortality have evaluated county-level animal counts and report associations that are

generally consistent with our findings. A case-control study of leukemia mortality among Nebraska farmers found that county chicken and hog inventories were positively associated with unspecified acute leukemia mortality (Blair and Thomas, 1979). An ecologic study in Iowa found statistically significant positive rank correlations between incidence of ALL in men and county-level densities of cows, pigs, and chickens, but no association with turkey densities or with animal densities and leukemia rates among women (Donham et al., 1980). Another ecologic study in Iowa found positive associations between unspecified lymphatic leukemia mortality (not including chronic lymphocytic leukemia) in men and the number of layer chickens and milk cows in the county (Burmeister et al., 1982). In contrast, a study in the contiguous 48 U.S. states found no association between county-level counts of cattle, swine, or chickens and adult leukemia mortality rates (Blair et al., 1980).

Case-control and cohort studies of animal exposure in relation to adult leukemia have mixed findings. A case-control study in New

**Table 2**

Median (25th percentile, 75th percentile) county animal densities<sup>a</sup> (average of 2002 and 2007) for nine Surveillance, Epidemiology and End Results states, excluding counties with populations > 300,000.

Animal type	Total (541 counties)	California (36 counties)	Connecticut (5 counties)	Georgia (155 counties)	Iowa (98 counties)
Cattle	96.26 (41.71, 187.2)	52.13 (21.48, 93.59)	62.06 (46.41, 95.59)	78.14 (42.01, 114.16)	217.91 (148.46, 315.37)
Chickens – Broilers	1.63 (0.00, 49.85)	0.08 (0.00, 1.45)	0.51 (0.06, 1.33)	68.95 (4.78, 212.15)	0.25 (0.03, 2.12)
Chickens – Layers	0.09 (0.02, 6.69)	0.03 (0.01, 0.09)	0.42 (0.25, 0.44)	6.85 (0.02, 19.98)	0.28 (0.06, 13.74)
Chickens – Broilers and Layers	8.23 (0.08, 62.73)	0.18 (0.03, 1.92)	0.97 (0.45, 1.96)	81.18 (20.78, 235.32)	3.62 (0.21, 15.42)
Goats	0.32 (0.12, 0.68)	0.28 (0.06, 0.71)	0.30 (0.29, 0.35)	0.47 (0.31, 0.73)	0.16 (0.01, 0.33)
Hogs	2.36 (0.27, 30.75)	0.18 (0.06, 0.45)	1.17 (0.98, 1.50)	4.30 (0.62, 19.28)	346.43 (155.65, 602.12)
Horses and Ponies	9.76 (5.12, 18.34)	6.56 (2.92, 11.40)	19.38 (17.42, 20.06)	8.34 (5.12, 15.64)	9.42 (6.80, 12.84)
Mules, Burros, and Donkeys	0.28 (0.11, 0.56)	0.13 (0.07, 0.23)	0.23 (0.17, 0.31)	0.39 (0.19, 0.65)	0.22 (0.12, 0.32)
Sheep	0.18 (0.05, 0.74)	0.86 (0.24, 1.64)	0.55 (0.35, 0.72)	0.05 (0.01, 0.11)	1.18 (0.69, 1.97)
Turkeys <sup>b</sup>	0.00 (0.00, 0.01)	0.20 (0.00, 8.03)	0.03 (0.03, 0.03)	0.00 (0.00, 0.00)	–
Total Animal Units <sup>a,c</sup>	195.49 (74.21, 467.02)	70.19 (31.23, 112.90)	86.95 (66.04, 115.89)	177.32 (95.07, 372.25)	588.00 (405.25, 865.29)
Animal type	Kentucky (119 counties)	Louisiana (61 parishes)	New Jersey (8 counties)	New Mexico (32 counties)	Utah (27 counties)
Cattle	179.41 (93.74, 393.29)	57.43 (34.63, 116.12)	38.25 (6.41, 69.58)	34.67 (17.42, 60.08)	38.10 (20.42, 78.38)
Chickens – Broilers	22.25 (0.04, 690.32)	2.17 (0.00, 22.12)	0.06 (0.03, 0.15)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Chickens – Layers	0.12 (0.06, 0.61)	0.04 (0.02, 0.56)	0.20 (0.14, 0.48)	0.01 (0.00, 0.01)	0.01 (0.00, 0.02)
Chickens – Broilers and Layers	25.40 (0.27, 74.07)	2.57 (0.05, 24.03)	0.25 (0.17, 0.63)	0.01 (0.00, 0.01)	0.01 (0.00, 0.02)
Goats	0.77 (0.46, 1.17)	0.15 (0.07, 0.23)	0.79 (0.24, 1.05)	0.05 (0.02, 0.07)	0.05 (0.01, 0.09)
Hogs	6.14 (0.64, 21.09)	0.31 (0.16, 0.61)	2.49 (1.34, 6.27)	0.02 (0.02, 0.04)	0.21 (0.10, 0.85)
Horses and Ponies	25.26 (12.78, 41.36)	7.30 (4.32, 12.92)	33.34 (11.92, 43.28)	2.64 (1.92, 4.24)	5.28 (2.34, 11.12)
Mules, Burros, and Donkeys	0.72 (0.40, 1.17)	0.24 (0.09, 0.39)	0.45 (0.19, 0.90)	0.03 (0.02, 0.06)	0.05 (0.02, 0.11)
Sheep	0.22 (0.09, 0.61)	0.03 (0.01, 0.09)	1.14 (0.17, 1.71)	0.16 (0.07, 0.45)	1.00 (0.33, 2.66)
Turkeys <sup>b</sup>	0.00 (0.00, 0.01)	0.00 (0.00, 0.00)	–	0.00 (0.00, 0.00)	–
Total Animal Units <sup>a,c</sup>	324.22 (159.45, 551.75)	103.42 (44.12, 176.88)	88.80 (24.73, 128.36)	37.29 (22.34, 63.71)	44.56 (25.64, 91.94)

<sup>a</sup> Defined as animal units per 10 square kilometers. Animal units based on EPA definition of 1000 pounds of animal weight per animal unit.

<sup>b</sup> IA, NJ and UT not included in total due to suppression > 45% in at least one census period.

<sup>c</sup> Total animal units do not include Turkeys.



**Table 3**

Rate ratios (RR) and 95% confidence intervals (CI) for childhood cancers (0–4 years of age, 2003–2008) associated with animal densities in nine Surveillance, Epidemiology and End Results states, excluding counties with populations > 300,000.

Animal type	Animals units per 10 km <sup>2</sup>	RR (95% CI)			
		ALL	AML	CNS	PNS
Cattle	41.7–96.3	1.10 (0.88, 1.37)	0.85 (0.46, 1.59)	0.90 (0.68, 1.20)	1.00 (0.71, 1.41)
	96.3–187.2	0.92 (0.71, 1.19)	0.90 (0.46, 1.75)	0.92 (0.68, 1.24)	1.09 (0.76, 1.58)
	187.2–1381.8	1.19 (0.91, 1.56)	1.44 (0.75, 2.78)	0.96 (0.69, 1.34)	0.89 (0.58, 1.36)
	p-trend	0.2324	0.1420	0.9642	0.5800
	Continuous <sup>a</sup>	1.02 (0.98, 1.07)	1.03 (0.92, 1.16)	1.02 (0.97, 1.08)	0.97 (0.89, 1.05)
Hogs	0.28–2.36	1.02 (0.79, 1.33)	1.05 (0.58, 1.90)	1.04 (0.76, 1.43)	0.87 (0.62, 1.24)
	2.36–30.76	1.14 (0.84, 1.56)	1.05 (0.48, 2.31)	0.95 (0.66, 1.37)	0.77 (0.49, 1.21)
	30.76–2391.8	1.09 (0.69, 1.71)	0.55 (0.11, 2.82)	1.12 (0.66, 1.92)	0.89 (0.43, 1.85)
	p-trend	0.9352	0.4343	0.6125	0.9250
	Continuous <sup>a</sup>	1.03 (0.97, 1.09)	0.99 (0.83, 1.18)	1.05 (0.99, 1.11)	0.95 (0.83, 1.09)
Chickens (Broilers)	0.005–1.63	0.90 (0.66, 1.21)	0.81 (0.38, 1.72)	0.99 (0.68, 1.46)	0.88 (0.55, 1.40)
	1.63–49.86	0.99 (0.74, 1.32)	0.83 (0.40, 1.73)	0.88 (0.62, 1.26)	0.78 (0.52, 1.16)
	49.86–2286.0	0.86 (0.62, 1.19)	1.05 (0.44, 2.52)	0.92 (0.63, 1.33)	0.77 (0.49, 1.20)
	p-trend	0.4051	0.7203	0.8028	0.4539
	Continuous <sup>a</sup>	1.00 (0.94, 1.05)	<b>1.14 (1.02, 1.26)</b>	0.96 (0.89, 1.04)	0.94 (0.85, 1.03)
Chickens (Layers)	0.02–0.09	1.18 (0.89, 1.55)	0.92 (0.44, 1.89)	1.04 (0.75, 1.45)	1.02 (0.69, 1.51)
	0.09–6.69	1.05 (0.77, 1.45)	1.07 (0.50, 2.28)	1.22 (0.86, 1.75)	0.87 (0.56, 1.34)
	6.69–238.45	1.12 (0.81, 1.55)	1.15 (0.53, 2.52)	0.93 (0.62, 1.37)	0.67 (0.42, 1.07)
	p-trend	0.8495	0.5978	0.3481	0.0647
	Continuous <sup>a,b</sup>	1.01 (0.79, 1.29)	0.99 (0.57, 1.74)	0.99 (0.72, 1.34)	<b>0.94 (0.89, 0.99)</b>
Chickens (Broilers and Layers)	0.08–8.23	1.04 (0.78, 1.38)	1.03 (0.52, 2.02)	1.11 (0.78, 1.57)	0.98 (0.67, 1.45)
	8.23–62.73	1.09 (0.78, 1.51)	1.22 (0.55, 2.68)	0.99 (0.70, 1.41)	0.82 (0.52, 1.28)
	62.73–2524.4	0.87 (0.63, 1.20)	0.99 (0.45, 2.17)	1.10 (0.77, 1.59)	0.74 (0.48, 1.16)
	p-trend	0.1894	0.8602	0.6787	0.2360
	Continuous <sup>a</sup>	1.00 (0.95, 1.05)	<b>1.11 (1.01, 1.22)</b>	0.97 (0.91, 1.04)	0.94 (0.86, 1.03)
Goats	0.12–0.32	1.09 (0.81, 1.47)	0.59 (0.28, 1.24)	0.99 (0.70, 1.42)	1.28 (0.80, 2.05)
	0.32–0.68	1.03 (0.74, 1.44)	0.88 (0.40, 1.93)	1.01 (0.70, 1.47)	1.01 (0.61, 1.70)
	0.68–3.97	1.09 (0.77, 1.54)	1.03 (0.45, 2.37)	0.80 (0.53, 1.22)	1.35 (0.80, 2.29)
	p-trend	0.8295	0.2477	0.1572	0.4014
	Continuous <sup>c</sup>	1.07 (0.88, 1.31)	1.22 (0.75, 1.99)	0.95 (0.73, 1.23)	0.89 (0.64, 1.23)
Sheep	0.05–0.18	1.12 (0.84, 1.50)	1.17 (0.53, 2.60)	1.10 (0.79, 1.53)	0.95 (0.62, 1.44)
	0.18–0.74	1.17 (0.85, 1.61)	1.31 (0.59, 2.92)	1.07 (0.74, 1.55)	1.20 (0.78, 1.87)
	0.74–14.15	<b>1.68 (1.18, 2.41)</b>	1.32 (0.53, 3.30)	0.96 (0.62, 1.47)	1.05 (0.62, 1.78)
	p-trend	<b>0.0010</b>	0.7259	0.5021	0.8671
	Continuous <sup>d,e</sup>	1.21 (0.72, 2.02)	0.91 (0.26, 3.16)	0.69 (0.32, 1.51)	0.95 (0.39, 2.29)
Horses and Ponies	12.8–25.1	0.92 (0.68, 1.25)	0.62 (0.26, 1.45)	0.82 (0.57, 1.18)	0.80 (0.50, 1.28)
	25.1–41.1	1.04 (0.78, 1.39)	0.86 (0.42, 1.77)	1.01 (0.71, 1.42)	1.04 (0.68, 1.59)
	41.1–368.4	1.23 (0.91, 1.66)	1.20 (0.55, 2.59)	1.08 (0.75, 1.54)	1.07 (0.69, 1.67)
	p-trend	0.0589	0.2704	0.3667	0.5049
	Continuous <sup>a</sup>	1.14 (0.92, 1.42)	1.24 (0.87, 1.78)	1.13 (0.88, 1.46)	0.76 (0.48, 1.19)
Mules, Burros, and Donkeys	0.1–0.3	0.95 (0.71, 1.28)	0.62 (0.30, 1.28)	0.95 (0.65, 1.37)	0.72 (0.47, 1.11)
	0.3–0.6	1.22 (0.93, 1.61)	0.71 (0.36, 1.40)	1.11 (0.78, 1.58)	1.27 (0.86, 1.88)
	0.6–2.4	1.13 (0.82, 1.54)	0.89 (0.39, 2.04)	1.12 (0.77, 1.63)	1.15 (0.74, 1.79)
	p-trend	0.3419	0.9506	0.4147	0.2194
	Continuous <sup>c</sup>	1.24 (0.98, 1.57)	1.24 (0.63, 2.44)	1.08 (0.80, 1.45)	1.18 (0.82, 1.70)
Turkeys <sup>f</sup>	0.0004–0.002	1.07 (0.76, 1.52)	1.30 (0.51, 3.32)	0.88 (0.61, 1.27)	1.44 (0.83, 2.48)
	0.002–0.005	1.24 (0.85, 1.80)	1.74 (0.69, 4.38)	0.71 (0.47, 1.05)	1.46 (0.85, 2.48)
	0.005–53.07	1.09 (0.76, 1.55)	1.59 (0.63, 3.99)	0.77 (0.53, 1.12)	1.56 (0.92, 2.63)
	p-trend	0.8954	0.4677	0.3105	0.2782
	Continuous <sup>d</sup>	1.01 (0.89, 1.14)	1.08 (0.82, 1.43)	1.06 (0.90, 1.25)	0.98 (0.80, 1.19)
Total Animals <sup>g</sup>	74.2–195.5	1.12 (0.88, 1.43)	0.59 (0.31, 1.15)	1.03 (0.76, 1.38)	1.26 (0.88, 1.81)
	195.5–467.0	0.98 (0.73, 1.31)	0.88 (0.45, 1.73)	1.13 (0.81, 1.58)	1.24 (0.82, 1.86)
	467.0–3565.5	1.08 (0.80, 1.45)	1.17 (0.58, 2.34)	1.04 (0.73, 1.48)	0.93 (0.58, 1.47)
	p-trend	0.7753	0.2657	0.9556	0.3668
	Continuous <sup>a</sup>	1.01 (0.99, 1.04)	1.04 (0.99, 1.10)	1.01 (0.98, 1.04)	0.96 (0.92, 1.01)

All models were restricted to counties with < 300,000 people and adjusted for state, race, sex, population density, and percent of population with at least a bachelor's degree. One animal unit is equal to 1000 lbs. Average animal weights to calculate animal units are based on EPA definition. ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CNS=central nervous system; PNS=peripheral nervous system.

<sup>a</sup> RR per 10 animal units per km<sup>2</sup>.

<sup>b</sup> PNS model - RR per 1 unit change in the log of animal units per km<sup>2</sup>.

<sup>c</sup> RR per 0.1 animal units per km<sup>2</sup>.

<sup>d</sup> RR per 1 animal unit per km<sup>2</sup>.

<sup>e</sup> Cubic spline model indicates non-linear association for ALL.

<sup>f</sup> Models exclude IA, NJ, and UT due to high proportion of suppression.

<sup>g</sup> Animal totals in animal units – Turkeys excluded due to high suppression in IA, NJ, and UT.

Zealand found an increase in hematological cancer mortality in adults who grew up on a poultry farm (t Mannetje et al., 2012). A case-control study in Canada found no association between occupational exposure to poultry, horses, or pigs and leukemia in adults (Fritsch et al., 2002). A

cohort study of male farmers in Iowa and North Carolina found no association between farmers engaged in poultry or beef production and leukemia incidence (Beane Freeman et al., 2012). It is unknown whether the findings for adult leukemia and county-level animal counts and

**Table 4**

Median (25th percentile, 75th percentile) operation densities by operation size<sup>a</sup> (average of 2002 and 2007), for 541 counties in nine Surveillance, Epidemiology and End Results states, excluding counties with populations > 300,000.

Animal type	Operation size (number of animals)	Counties with > 0 operations	Operation density per 100 km <sup>2</sup> (all counties)
Cattle	< 500	541	14.1 (6.2, 26.5)
	500 +	427	0.20 (0.0, 0.4)
	Total	541	14.6 (6.7, 27.1)
Hogs	< 1000	534	0.8 (0.3, 1.7)
	1000 +	182	0.0 (0.0, 0.1)
	Total	534	0.9 (0.3, 1.9)
Chickens (Broilers)	Total	479	0.3 (0.1, 0.7)
Chickens (layers)	1 to 399	536	1.3 (0.6, 2.4)
	400 to 99,999	194	0.0 (0.0, 0.1)
	100,000 +	66	0.0 (0.0, 0.0)
	Total	536	1.3 (0.7, 2.4)
Goats	Total	529	1.7 (0.7, 3.4)
Sheep	1 to 99	511	0.7 (0.2, 1.7)
	100 to 999	237	0.0 (0.0, 0.1)
	1000 +	65	0.0 (0.0, 0.0)
	Total	511	0.7 (0.2, 1.8)
Horses and Ponies	Total	541	7.3 (4.3, 14)
Mules/Burros/ Donkeys	Total	529	0.8 (0.4, 1.8)
Turkeys	Total	453	0.2 (0.0, 0.3)

<sup>a</sup> Operation size categories were only available for cattle, hogs, layer chickens, and sheep.

occupational exposures are relevant for leukemia risk among children, who are less likely to have direct contact with farm animals.

Exposure to animals has been studied more extensively as a risk factor for CBT than for childhood leukemia, and most studies found positive associations between parental exposure to one or more types of animals and CNS tumors in children. A registry-based case-control study in the UK (Keegan et al., 2013) found a positive association between paternal occupational exposure to animals and childhood CNS tumors (OR = 1.40, 95% CI = 1.01–1.96). A population based case-control study in the United States (Holly et al., 1998) found elevated odds ratios for CBT among children whose mothers lived or worked on a farm with horses (OR = 2.2, 95% CI = 1.0–4.8) and pigs during

pregnancy (OR = 3.8, 95% CI = 1.2–12.0). A pooled analysis of population based case-control studies (Efird et al., 2003), including the aforementioned study, found positive associations between CBT and exposure during childhood to pigs (OR = 1.7, 95% CI = 1.0–3.0) and horses (OR = 1.6, 95% CI = 1.0–2.4). This study also found positive associations between CBT and maternal exposure during pregnancy to horses (OR = 1.8, 95% CI = 1.0–3.1), pigs (OR = 2.3, 95% CI = 1.1–4.9), and poultry (OR = 1.5, 95% CI = 1.0–2.2). A registry-based cohort study in Norway (Kristensen et al., 1996) found increased risk of CBT in the offspring if either parent worked in pig farming (RR = 1.6, 95% CI = 1.2–2.2). In contrast, a population based case-control study of CBT in Denmark, Norway, Sweden, and Switzerland (Christensen et al., 2012) found no association with maternal animal exposures during pregnancy, but inverse associations with the child's exposure to sheep and goats (OR = 0.48, 95% CI = 0.24–0.97) and birds (including chickens, turkeys, ducks, and other birds) (OR = 0.61, 95% CI = 0.39–0.94) during the first 3 years of life. Early childhood exposure to horses/ponies/donkeys, pigs, or cows were not associated with CBT. We did not identify any studies that examined exposure to animals in relation to PNS cancers.

The lack of consistency between the findings from our ecological study and those from epidemiologic studies with individual-based exposure assessment may be due to differences in the study designs, including the age of the study populations (most studies included children up to age 15 and sometimes adult offspring). Furthermore, a major limitation of this analysis is that county-level animal densities are not likely to be a good surrogate for parental occupational or children's direct exposure to animals. The median percent of the population in our study area employed in agriculture during the period of 2005–2009 was 1.2% (interquartile range [IQR]: 0.5–2.5%), comparable to the national prevalence of farming occupations in 2007 (1%) (33). For counties in the top quartile of total animal density, the median percent employed in agriculture was only slightly higher (median = 1.8%, IQR: 0.9–2.7%). Therefore, parental occupational exposure to farm animals and children's direct exposure via living on a farm was relatively rare even in counties with high animal production.

Spearman correlations between animal and operation densities were generally high for all animal types (i.e.,  $\rho > 0.63$ ) except for layer chickens; however, these metrics may characterize different aspects of animal exposure. Operation density may be a better indicator of the potential for environmental exposures due to residential proximity to

**Table 5**

Rate ratios (RR) and 95% confidence intervals (CI) for childhood cancers (0–4 years of age, 2003–2008) associated with density of animal operations by size in nine Surveillance, Epidemiology and End Results states, excluding counties with populations > 300,000.

Animal type	Operation size (number of animals) <sup>a</sup>	RR (95% CI)			
		ALL	AML	CNS	PNS
Cattle <sup>b</sup>	< 500	1.02 (0.97, 1.08)	1.03 (0.89, 1.20)	1.00 (0.93, 1.07)	1.02 (0.93, 1.10)
	500 +	1.06 (0.35, 3.23)	0.59 (0.03, 10.48)	1.32 (0.34, 5.17)	0.24 (0.03, 2.02)
	Total	1.02 (0.97, 1.08)	1.02 (0.89, 1.18)	1.00 (0.94, 1.07)	1.00 (0.92, 1.09)
Hogs <sup>c</sup>	< 1000	<b>1.11 (1.02, 1.21)</b>	1.09 (0.88, 1.35)	0.97 (0.86, 1.09)	1.14 (0.99, 1.31)
	1000 +	1.00 (0.90, 1.12)	0.82 (0.52, 1.29)	1.08 (0.95, 1.23)	0.87 (0.68, 1.11)
	Total	<b>1.06 (1.02, 1.11)</b>	1.00 (0.87, 1.15)	1.02 (0.96, 1.08)	1.03 (0.96, 1.12)
Chickens (layers) <sup>c</sup>	1 to 399	1.03 (0.99, 1.08)	0.91 (0.79, 1.05)	0.96 (0.90, 1.03)	1.05 (0.98, 1.12)
	400 to 99,999	1.07 (0.90, 1.28)	1.18 (0.76, 1.83)	0.90 (0.67, 1.20)	<b>0.62 (0.39, 0.99)</b>
	100,000 +	0.83 (0.16, 4.18)	6.48 (0.17, 251.05)	1.01 (0.11, 9.70)	5.71 (0.37, 88.27)
	Total	1.04 (0.99, 1.08)	0.96 (0.85, 1.09)	0.96 (0.90, 1.02)	1.02 (0.96, 1.09)
Sheep <sup>d</sup>	1 to 99	1.00 (0.99, 1.01)	0.99 (0.98, 1.01)	0.99 (0.99, 1.01)	1.00 (0.99, 1.01)
	100 to 999	0.96 (0.89, 1.03)	0.99 (0.85, 1.15)	1.03 (0.94, 1.12)	0.97 (0.86, 1.10)
	1000 +	0.99 (0.68, 1.44)	0.66 (0.23, 1.88)	0.60 (0.35, 1.04)	0.63 (0.30, 1.33)
	Total <sup>c</sup>	1.03 (0.99, 1.08)	0.96 (0.83, 1.12)	0.98 (0.91, 1.04)	1.04 (0.98, 1.11)

All models were restricted to counties with < 300,000 people and adjusted for state, race, sex, population density, and percent of population with at least a bachelor's degree. ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CNS = central nervous system; PNS = peripheral nervous system.

<sup>a</sup> Density of operations was modeled continuously and models for operation sizes other than total are mutually adjusted for each other.

<sup>b</sup> RR per operation per 10 km<sup>2</sup>.

<sup>c</sup> RR per operation per 100 km<sup>2</sup>.

<sup>d</sup> RR per operation per 1000 km<sup>2</sup>.

an operation than animal density, especially for animals like cattle, hogs, and chickens, which are commonly raised in large concentrated animal feeding operations.

Children may have environmental exposures to bioaerosols from animal operations, which can occur without direct animal contact. Particulate matter (PM) collected downwind from cattle feeding yards has been shown to contain antibiotics, bacteria, and antibiotic resistant genes (McEachran et al., 2015). Further, PM less than 10  $\mu\text{m}$  in diameter ( $\text{PM}_{10}$ ) has been measured as far as 3.5 km downwind of these facilities (Hiranuma et al., 2011), suggesting that animal operations may serve as exposure sources for neighboring communities. A case-control study of methicillin-resistant *Staphylococcus aureus* (MRSA) in Pennsylvania (Casey et al., 2013) found a significant positive association between MRSA and density of swine livestock operations around homes, but no association with dairy/veal livestock operation density. Likewise, a case-control study of livestock associated methicillin-resistant *Staphylococcus aureus* in community members with typeable strains of MRSA in the Netherlands (Feingold et al., 2012) found significant positive associations with densities of pig and cattle regardless of whether participants had direct contact with livestock.

There are several possible mechanisms for childhood cancer development in relation to early life exposure to animals. Exposure to animals in early childhood has been associated with decreased development of allergies (Campo et al., 2006; Ownby et al., 2002) and allergies have been inversely associated with leukemia risk in children and adults (Linabery et al., 2010; Nanni et al., 1996; Schuz et al., 2003; t' Mannetje et al., 2012). Additionally, maternal infections during pregnancy or early life infections in children have been positively associated with childhood leukemia in some studies (Maia Rda and Wunsch Filho, 2013). Studies have shown that infection with viruses found in animals, such as avian sarcoma virus (Copeland et al., 1975), oncornaviruses, papovaviruses, and adenoviruses (Swenberg, 1977) can lead to the development of brain tumors in animals. Furthermore, case-control studies have found positive associations between the protozoan *Toxoplasma gondii*, a common infection in animals (Hill and Dubey, 2013), and CNS tumors (Ryan et al., 1993; Schuman et al., 1967). Atopic disease, which is inversely associated with farm and animal exposure (Riedler et al., 2000, 2001; Von Ehrenstein et al., 2000), has been explored as a possible etiologic factor for CBT. Two case-control studies have yielded inverse associations (Harding et al., 2008; Roncarolo and Infante-Rivard, 2012) between atopic disease and CBT; whereas, one case-control study found no associations (Shu et al., 2014).

County-level animal density may be a proxy for other agricultural exposures not accounted for in our analyses. For instance, farm animal density may be related to other farm-based exposures such as pesticides, grain dust, engine exhaust, and solvents (Coble et al., 2002). We attempted to account for the impact of other farm-based exposures by examining potential confounders such as the proportion of the population employed in agriculture, crop density for major agricultural crops, and several census-based demographic variables, but these did not change our findings for animal and operation densities. Besides the ecologic design, another limitation of our analysis was that we used county of residence at time of diagnosis to assign exposure, as we had no information about residence at birth for children in our study. However, we attempted to mitigate this source of exposure misclassification by limiting our analyses to children under the age of five. Furthermore, we evaluated multiple associations with animal and operation densities and some of our findings may be due to chance. Our analysis was subject to the modifiable area unit problem and our results might be different if our analyses were conducted at smaller geographic scales. Strengths of our study were that we examined animal density in relation to over 700 incident cases of childhood leukemia and over 600 combined CNS and PNS cancer cases and were able to evaluate animal densities by animal type. Further, the states included in our study provided a wide range of exposure to livestock and poultry density.

Further, we adjusted our analyses for county-level population density and education and we evaluated urbanicity, population migration, income, and agricultural crop densities as potential confounders.

## 5. Conclusions

Using data from nine U.S. states, we found positive associations between the density of chickens and county-level rates of AML and between the density of hog operations and ALL rates. PNS cancers were inversely associated with chicken density. We found no associations between densities of cattle, equine, and turkeys and county incidence rates of ALL, AML, CNS, or PNS cancers. Case-control and prospective cohort studies that assess species-specific animal exposures for both children and parents and account for other agricultural exposures and potential confounding factors will be informative.

## Competing interests

The authors declare that they have no competing interests.

## Funding sources

This research was partially supported by the intramural research program of the National Cancer Institute (Project Z01 CP01012522).

## References

- Beane Freeman, L.E., De Roos, A.J., Koutros, S., Blair, A., Ward, M.H., Alavanja, M., et al., 2012. Poultry and livestock exposure and cancer risk among farmers in the agricultural health study. *Cancer Causes Control* 23, 663–670.
- Blair, A., Thomas, T.L., 1979. Leukemia among Nebraska farmers: a death certificate study. *Am. J. Epidemiol.* 110, 264–273.
- Blair, A., Fraumeni Jr., J.F., Mason, T.J., 1980. Geographic patterns of leukemia in the United States. *J. Chronic Dis.* 33, 251–260.
- Booth, B.J., Ward, M.H., Turyk, M.E., Stayner, L.T., 2015. Agricultural crop density and risk of childhood cancer in the midwestern United States: an ecologic study. *Environ. Health* 14, 82.
- Burmeister, L.F., Van Lier, S.F., Isacson, P., 1982. Leukemia and farm practices in Iowa. *Am. J. Epidemiol.* 115, 720–728.
- Campo, P., Kalra, H.K., Levin, L., Reponen, T., Olds, R., Lummus, Z.L., et al., 2006. Influence of dog ownership and high endotoxin on wheezing and atopy during infancy. *J. Allergy Clin. Immunol.* 118, 1271–1278.
- Carozza, S.E., Li, B., Elgethun, K., Whitworth, R., 2008. Risk of childhood cancers associated with residence in agriculturally intense areas in the United States. *Environ. Health Perspect.* 116, 559–565.
- Casey, J.A., Curriero, F.C., Cosgrove, S.E., Nachman, K.E., Schwartz, B.S., 2013. High-density livestock operations, crop field application of manure, and risk of community-associated methicillin-resistant *Staphylococcus aureus* infection in Pennsylvania. *JAMA Int. Med.* 173, 1980–1990.
- Cha, E.S., Hwang S-s, Lee, W.J., 2014. Childhood leukemia mortality and farming exposure in South Korea: a national population-based birth cohort study. *Cancer Epidemiol.* 38, 401–407.
- Christensen, J.S., Mortensen, L.H., Roosli, M., Feychting, M., Tynes, T., Andersen, T.V., et al., 2012. Brain tumors in children and adolescents and exposure to animals and farm life: a multicenter case-control study (cefalo). *Cancer Causes Control* 23, 1463–1473.
- Coble, J., Hoppin, J.A., Engel, L., Elci, O.C., Dosemeci, M., Lynch, C.F., et al., 2002. Prevalence of exposure to solvents, metals, grain dust, and other hazards among farmers in the agricultural health study. *J. Expo. Anal. Environ. Epidemiol.* 12, 418–426.
- Copeland, D.D., Vogel, F.S., Bigner, D.D., 1975. The induction of intracranial neoplasms by the inoculation of avian sarcoma virus in perinatal and adult rats. *J. Neuropathol. Exp. Neurol.* 34, 340–358.
- Donham, K.J., Berg, J.W., Sawin, R.S., 1980. Epidemiologic relationships of the bovine population and human leukemia in Iowa. *Am. J. Epidemiol.* 112, 80–92.
- Efrid, J.T., Holly, E.A., Preston-Martin, S., Mueller, B.A., Lubin, F., Filippini, G., et al., 2003. Farm-related exposures and childhood brain tumours in seven countries: results from the search international brain tumour study. *Paediatr. Perinat. Epidemiol.* 17, 201–211.
- Environmental Protection Agency (EPA), 2001. National pollutant discharge elimination system permit regulation and effluent limitations guidelines and standards for concentrated animal feeding operations. *Fed. Regist.* 66, 2960–3145.
- Feingold, B.J., Silbergeld, E.K., Curriero, F.C., van Cleef, B.A., Heck, M.E., Kluytmans, J.A., 2012. Livestock density as risk factor for livestock-associated methicillin-resistant *Staphylococcus aureus*, the Netherlands. *Emerg. Infect. Dis.* 18, 1841–1849.
- Fritsch, L., Johnson, K.C., Kliever, E.V., Fry, R., Canadian Cancer Registries Epidemiology Research Group, 2002. Animal-related occupations and the risk of

- leukemia, myeloma, and non-Hodgkin's lymphoma in Canada. *Cancer Causes Control* 13, 563–571.
- Gold, E., Gordis, L., Tonascia, J., Szklo, M., 1979. Risk factors for brain tumors in children. *Am. J. Epidemiol.* 109, 309–319.
- Harding, N.J., Birch, J.M., Hepworth, S.J., McKinney, P.A., 2008. Atopic dysfunction and risk of central nervous system tumours in children. *Eur. J. Cancer* 44, 92–99.
- Hill, D.E., Dubey, J.P., 2013. *Toxoplasma gondii* prevalence in farm animals in the United States. *Int. J. Parasitol.* 43, 107–113.
- Hiranuma, N., Brooks, S.D., Gramann, J., Auvermann, B.W., 2011. High concentrations of coarse particles emitted from a cattle feeding operation. *Atmos. Chem. Phys.* 11, 8809–8823.
- Holly, E.A., Bracci, P.M., Mueller, B.A., Preston-Martin, S., 1998. Farm and animal exposures and pediatric brain tumors: results from the United States West Coast childhood brain tumor study. *Cancer Epidemiol. Biomark. Prev.* 7, 797–802.
- Keegan, T.J., Bunch, K.J., Vincent, T.J., King, J.C., O'Neill, K.A., Kendall, G.M., et al., 2012. Case-control study of paternal occupation and childhood leukaemia in Great Britain, 1962–2006. *Br. J. Cancer* 107, 1652–1659.
- Keegan, T.J., Bunch, K.J., Vincent, T.J., King, J.C., O'Neill, K.A., Kendall, G.M., et al., 2013. Case-control study of paternal occupation and social class with risk of childhood central nervous system tumours in Great Britain, 1962–2006. *Br. J. Cancer* 108, 1907–1914.
- Kristensen, P., Andersen, A., Irgens, L.M., Bye, A.S., Sundheim, L., 1996. Cancer in offspring of parents engaged in agricultural activities in Norway: incidence and risk factors in the farm environment. *Int. J. Cancer* 65, 39–50.
- Linabery, A.M., Jurek, A.M., Duval, S., Ross, J.A., 2010. The association between atopy and childhood/adolescent leukemia: a meta-analysis. *Am. J. Epidemiol.* 171, 749–764.
- Maia Rda, R., Wunsch Filho, V., 2013. Infection and childhood leukemia: review of evidence. *Rev. Saude Publica* 47, 1172–1185.
- McEachran, A.D., Blackwell, B.R., Hanson, J.D., Wooten, K.J., Mayer, G.D., Cox, S.B., et al., 2015. Antibiotics, bacteria, and antibiotic resistance genes: aerial transport from cattle feed yards via particulate matter. *Environ. Health Perspect.* 123, 337–343.
- McKinney, P.A., Fear, N.T., Stockton, D., U.K. Childhood Cancer Study Investigators, 2003. Parental occupation at periconception: findings from the United Kingdom childhood cancer study. *Occup. Environ. Med.* 60, 901–909.
- Meinert, R., Kaatsch, P., Kaletsch, U., Krummenauer, F., Miesner, A., Michaelis, J., 1996. Childhood leukaemia and exposure to pesticides: results of a case-control study in northern Germany. *Eur. J. Cancer* 32A, 1943–1948.
- Nanni, O., Amadori, D., Lugaes, C., Falcini, F., Scarpi, E., Saragoni, A., et al., 1996. Chronic lymphocytic leukaemias and non-Hodgkin's lymphomas by histological type in farming-animal breeding workers: a population case-control study based on a priori exposure matrices. *Occup. Environ. Med.* 53, 652–657.
- Ownby, D.R., Johnson, C.C., Peterson, E.L., 2002. Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6–7 years of age. *JAMA* 288, 963–972.
- Surveillance Epidemiology and End Results (SEER) Program, 2014. SEER\*Stat statistical software. Available: <<http://seer.cancer.gov/seerstat/>> (Accessed 30 July 2014).
- Riedler, J., Eder, W., Oberfeld, G., Schreuer, M., 2000. Austrian children living on a farm have less hay fever, asthma and allergic sensitization. *Clin. Exp. Allergy* 30, 194–200.
- Riedler, J., Braun-Fahrlander, C., Eder, W., Schreuer, M., Waser, M., Maisch, S., et al., 2001. Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. *Lancet* 358, 1129–1133.
- Roncarolo, F., Infante-Rivard, C., 2012. Asthma and risk of brain cancer in children. *Cancer Causes Control* 23, 617–623.
- Rudant, J., Orsi, L., Menegaux, F., Petit, A., Baruchel, A., Bertrand, Y., et al., 2010. Childhood acute leukemia, early common infections, and allergy: the ESCALE study. *Am. J. Epidemiol.* 172, 1015–1027.
- Ryan, P., Hurley, S.F., Johnson, A.M., Salzberg, M., Lee, M.W., North, J.B., et al., 1993. Tumours of the brain and presence of antibodies to *Toxoplasma gondii*. *Int. J. Epidemiol.* 22, 412–419.
- Schuman, L.M., Choi, N.W., Gullen, W.H., 1967. Relationship of central nervous system neoplasms to *Toxoplasma gondii* infection. *Am. J. Public Health Nations Health* 57, 848–856.
- Schuz, J., Morgan, G., Bohler, E., Kaatsch, P., Michaelis, J., 2003. Atopic disease and childhood acute lymphoblastic leukemia. *Int. J. Cancer* 105, 255–260.
- Shu, X., Prochazka, M., Lannering, B., Schuz, J., Roosli, M., Tynes, T., et al., 2014. Atopic conditions and brain tumor risk in children and adolescents—an international case-control study (cefalo). *Ann. Oncol.* 25, 902–908.
- Spellman, F.R., Whiting, N.E., 2007. Environmental Management of Concentrated Animal Feeding Operations (CAFOS). CRC Press, 219–254.
- Stein, M.M., Hrusch, C.L., Gozdz, J., Igartua, C., Pivniouk, V., Murray, S.E., et al., 2016. Innate immunity and asthma risk in Amish and Hutterite farm children. *N. Engl. J. Med.* 375, 411–421.
- Steliarova-Foucher, E., Stiller, C., Lacour, B., Kaatsch, P., 2005. International classification of childhood cancer, third edition. *Cancer* 103, 1457–1467.
- Swenberg, J.A., 1977. Chemical- and Virus-induced Brain Tumors. 46. National Cancer Institute Monographs, 3–10.
- t' Mannetje, A., Eng, A., Pearce, N., 2012. Farming, growing up on a farm, and haematological cancer mortality. *Occup. Environ. Med.* 69, 126–132.
- U.S. Census Bureau, 2009. 2005–2009 American community survey 5-year estimates. Available: <<http://factfinder.census.gov/faces/nav/jsf/pages/searchresults.xhtml?refresh=t>> (Accessed 2 October 2015).
- U.S. Census Bureau, 2010. Intercensal estimates of the resident population by five-year age groups, sex, race, and hispanic origin for counties: April 1, 2000 to July 1, 2010. Available: <<http://www.census.gov/popest/data/intercensal/county/CO-EST00INT-alldata.html>> (Accessed 30 July 2014).
- U.S. Census Bureau, 2013. 2013 tiger/line shapefiles. Available: <<https://www.census.gov/cgi-bin/geo/shapefiles2013/main>> (Accessed 30 July 2014).
- USDA, 2002. The 2002 census of agriculture volume 1: Geographic area series. Washington, DC.
- USDA, 2003. Rural-urban continuum codes. Available: <<http://www.ers.usda.gov/data-products/rural-urban-continuum-codes.aspx>> (Accessed 12 October 2015).
- USDA, 2007. The 2007 census of agriculture volume 1: Geographic area series. Washington, DC.
- van Steensel-Moll, H.A., Valkenburg, H.A., van Zanen, G.E., 1985. Childhood leukemia and parental occupation. A register-based case-control study. *Am. J. Epidemiol.* 121, 216–224.
- Von Ehrenstein, O.S., Von Mutius, E., Illi, S., Baumann, L., Bohm, O., von Kries, R., 2000. Reduced risk of hay fever and asthma among children of farmers. *Clin. Exp. Allergy* 30, 187–193.