Published in final edited form as:
J Expo Sci Environ Epidemiol. 2014 September ; 24(5): 497–503. doi:10.1038/jes.2013.75.

An evaluation of metrics for assessing maternal exposure to agricultural pesticides

Joshua L. Warren[1], **Thomas J. Luben**[2], **Alison P. Sanders**[3], **Naomi C. Brownstein**[1], **Amy H. Herring**[1], and **Robert E. Meyer**[4]

[1]Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

[2]National Center for Environmental Assessment, United States Environmental Protection Agency, Research Triangle Park, North Carolina, USA

[3]Department of Environmental Sciences and Engineering, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

[4]Birth Defects Monitoring Program, State Center for Health Statistics, North Carolina Division of Public Health, Raleigh, North Carolina, USA

Abstract

We evaluate the use of three different exposure metrics to estimate maternal agricultural pesticide exposure during pregnancy. Using a geographic information system-based method of pesticide exposure estimation, we combine data on crop density and specific pesticide application amounts/dates to create the three exposure metrics. For illustration purposes, we create each metric for a North Carolina cohort of pregnant women, 2003–2005, and analyze the risk of congenital anomaly development with a focus on metric comparisons. Based on the results, and the need to balance data collection efforts/computational efficiency with accuracy, the metric which estimates total chemical exposure using application dates based on crop-specific earliest planting and latest harvesting information is preferred. Benefits and drawbacks of each metric are discussed and recommendations for extending the analysis to other states are provided.

Keywords

epidemiology; personal exposure; pesticides

Correspondence to: Dr Joshua L. Warren, Department of Biostatistics, University of North Carolina at Chapel Hill, 3101 McGavran-Greenberg, CB#7420, Chapel Hill, NC 27599, USA., Tel.: + 1 919-418-4999., joshuawa@email.unc.edu.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

DISCLAIMER
The views expressed in this paper are those of the authors and do not necessarily reflect the views or policies of the US Environmental Protection Agency.

Supplementary Information accompanies the paper on the Journal of Exposure Science and Environmental Epidemiology website (http://www.nature.com/jes)

INTRODUCTION

Parental pesticide exposure during pregnancy has long been hypothesized to contribute to increased risks of certain congenital anomalies. The process of determining pesticide chemical exposure estimates has been assessed using numerous heterogeneous metrics in previous epidemiological studies of the association. In two California analyses, exposure was defined as residential proximity to known pesticide application sites[1] and as self-reported pesticide use in and around the home.[2] A number of other studies have classified exposure to pesticides through parental occupational history during the pregnancy.[3–9] Surrogate chemical exposure, defined by total crop acreage surrounding the area of interest, has also been used in past analyses.[10,11] Recently, a study investigated how pesticide applications made in close proximity to the residence led to personal exposures within the home in the form of carpet dust respiration.[12] Although several previous studies have been successful in identifying an association between pesticide exposure during the pregnancy and congenital anomalies, these were over limited subpopulations and geographic domains. Our interest is in answering research questions regarding larger-scale geographic and population domains while balancing the need for accuracy/precision with computational efficiency/practicality in estimating individual-level chemical exposures.

In this paper, we contrast and compare the utility of three different geographic information system (GIS)-based metrics for estimating pesticide exposure using a geocoded data set from a cohort of North Carolina (NC) births, 2003–2005. We define pesticide exposure using similar methods originally developed to investigate the association between agricultural pesticide exposure during the pregnancy and the development of hypospadias in eastern Arkansas.[13] Previous studies have implemented similar GIS methods in alternative health outcome settings[14,15] while another confirmed the feasibility of the use of GIS methods in the agricultural chemical setting.[16] Our study is designed to estimate individual-level pesticide exposures using several GIS-based methods that represent tradeoffs between analytical complexity and exposure estimation accuracy. One metric is relatively easy to compute but has the increased potential to misclassify exposures. Another metric is computationally difficult to construct but results in improved classification and explanation of the association of interest. The final metric represents a balance between the others, being computationally tractable and having improved classification properties. Further, a secondary goal is to explore the potential issues associated with creating these exposure metrics in other states.

In the present analysis, agricultural pesticide exposure is estimated based on the spatial location of the maternal residence at delivery and relevant state-level crop information. Using ArcGIS spatial analysis software (ESRI, Redlands, CA, USA), we determine the crop type and amounts (acres) in areas surrounding the home. Based on this information, we estimate maternal pesticide exposure during early pregnancy using the following three metrics: total crop acreage in the area surrounding the residence at delivery, expected chemical exposure based on similar existing methods,[13] and expected chemical exposure based on a modified pesticide application timing technique. Each exposure metric takes into account the dates of the pregnancy, as exposures during the periconceptional period (1 month before conception and 3 months after) are considered to affect the risk of congenital malformations. Each metric estimates individual-level exposure based on aggregated level data, which is necessary to efficiently evaluate the association of interest given the large sample size of the data set. The performance of each metric is compared through an example using the NC cohort while analyzing the risk of developing any birth defect. Recommendations for creating the metrics in different states are discussed.

MATERIALS AND METHODS

Data Description

We obtained crop maps for NC from the National Agricultural Statistics Service (NASS) Cropland Data Layer website.[17] These maps are available for 2002 and 2008–2010 for the state. A crop map for a given year and geographic domain consists of satellite imagery that geographically describes the locations of various crops over the domain for that year. In NC, information on over 70 different crops are collected and reported in the crop maps.

Pesticide chemical application data for NC are obtained from the NASS Pest Management website for 2002–2005.[18] These data include state-wide total amounts of specific chemicals applied in each year to various crops in NC. The available information for each crop includes the name of the applied chemical, the percentage of NC acres of the crop that were treated with the chemical, the number of applications made in the year, the pounds of active ingredient per application, the total pounds of active ingredient applied per treated acre, and the total pounds of active ingredient applied per year in the state. These data are not available for every crop included in the NASS crop maps, but both data sets (NASS chemical applications and NASS crop maps) include information on corn, soybeans, peanuts, cotton, apples, watermelons, and sweet corn, though not necessarily in the same years. Pesticide application data are not available for tobacco during any years of the analysis, and as a result tobacco is not included in the study.

To define the temporal variability of pesticide exposure, we obtained temporally specific crop cycle and pesticide application information for each combination of crop and chemical based on known NC pesticide application dates. These data provide information regarding when a particular chemical is typically applied during the life cycle of a selected crop. A majority of the timing data are found in the online NC crop profiles.[19] Additional timing information is constructed based on the targeted pest(s) for each applied chemical and the life cycle of these pests. Currently, no centralized data set contains this timing information. We also obtained information on typical NC planting and harvesting dates for each crop from the NC crop profiles and also from the NASS.[20]

Chemical half-life data are obtained for each observed pesticide from the USDA.[21] The most reliable estimate of the half-life length of each chemical (days) is used in the analysis to give insight into how long the active ingredient associated with each chemical persists within the application areas.

The analyzed health data set includes birth records on 335,729 singleton live births from the NC State Center for Health Statistics, 2003–2005 linked to data from the NC Birth Defects Monitoring Program (NCBDMP). The data set includes maternal residence at delivery geocoded to a longitude/latitude location for each birth. Variables including infant birth weight, gestational age, gender, and date of birth, as well as maternal race/ethnicity, education, marital status, parity, age, diabetes, and smoking status are obtained from the birth records. Data on congenital anomalies from the NCBDMP for each birth are also provided for a range of neural tube defects, cardiovascular, gastrointestinal, genitourinary, and musculoskeletal defect phenotypes.

Women are excluded from the analysis when missing any of the available demographic covariates of interest (n = 6910 (2.06%)). Also, women with a residence at delivery determined to fall outside of NC are excluded from the analysis (n = 23,829 (7.10%)). Maternal residence at delivery was used as a surrogate for residence during early pregnancy, because information on the latter is not available in the birth files. Infants with a gestational age <20 weeks or >45 weeks are excluded (n = 84 (0.03%)). The final birth cohort used for analyses includes 304,906 births.

Data Preparation

Recall that the NASS crop maps are only available in 2002 and 2008–2010 in NC while our birth cohort data set is available from 2003–2005. We derive crop map estimates for 2003–2005 by extrapolating from the data contained in the available years. We begin by investigating the changes in the acre totals and geographic placement of each NC crop between the available years. For the entire NC cohort, we create a 500 m buffer surrounding each residence at delivery and calculate the individual crop totals within each buffer for each year of the available crop maps. Our goal is to explore the changes in these individual crop totals from year-to-year within the buffers.

To analyze the temporal crop changes, we calculate the percentage of women who had the same crop totals for each year and the mean, median, minimum, and maximum average absolute change in crop totals among all years (among those who had a change). We define the average absolute change in crop totals among all years for woman i as

$\frac{1}{n}\sum\sum_{j<k}|Y_{ij}-Y_{ik}|$ where Y_{ij} is the crop total for year j in buffer i and n represents the number of yearly differences we consider. This quantity is calculated for each woman in the sample. If the crop placements and totals are truly static from year-to-year, this quantity will be zero as $Y_{ij} = Y_{ik}$ for all $j<k$. Once we obtain these measurements for each woman, we calculate the five statistics across all years at first. We then repeat the process while removing a single year from the analysis to test for possible outlier years and the overall sensitivity to a single year. Analyzing these results help us to determine the most sensible way to estimate the individual buffer crop totals for the missing crop map years.

Metric Development

We create three exposure metrics for each woman in the study based on agricultural chemical application dates, yearly applied amounts, and residence at delivery buffer crop totals. These three metrics include:

- Metric 1: Total amount of acres of all crops within a woman’s buffer,

- Metric 2: Total chemical exposure (pounds of active ingredient) based on specific dates of pregnancy and chemical/crop-specific application dates,
- Metric 3: Total chemical exposure (pounds of active ingredient) based on specific dates of pregnancy and chemical application dates based on the planting/harvesting dates of each crop.

We use ArcGIS software to assist in creating exposure Metric 1. ArcGIS allows for the mapping of the geocoded residences at delivery of the birth cohort in NC. We overlay these spatially referenced data with the crop maps from the NASS, creating a map for each year of available crop map data. Once the data sources are combined, we create a 500 m buffer around each woman's residence at delivery. The 500 m buffer is the most common distance used in previous epidemiological studies[12,13,16,22] that investigate the association of interest and represents a reasonable range for the drift effects from agricultural pesticide applications.[16] Figure 1 displays the 2010 NC crop map as well as an example of a 500 m buffer area surrounding a residence at delivery.

As shown in Figure 1, a variety of crops are potentially located within a selected buffer. Using ArcGIS, we are able to calculate the total number of pixels of each crop located within a buffer for the selected year. A single pixel is equivalent to 0.222394 acres for the 2002 and 2010 crop maps and to 0.774922 acres for the 2008–2009 crop maps due to varying pixel sizes. Using these conversions, we then calculate the total number of acres of each recorded NC crop that is grown within 500 m of the residence at delivery in a selected year for each woman in the NC cohort. We sum these acres across all crops within a selected buffer to create Metric 1 for a woman in the analysis such that $M_{1,i}=\sum_{j=1}^{c_i} B_i(j)$ where c_i is the total number of unique crops found within the 500 m buffer for woman i and $B_i(j)$ is the total number of acres of crop j found within buffer i. This process is repeated for each individual buffer in the analysis.

The crop-specific buffer totals used to calculate Metric 1, $B_i(j)$, are also needed to create exposure Metric 2. In order to construct Metric 2, we utilize the relevant pesticide application data from NASS, which informs us which chemicals were applied to each crop in a given year and their yearly applied totals. We need this information for each year and crop in the analysis. Unlike the crop map data, these data are available in 2002–2005.

Next, we combine the pesticide application data with information regarding the specific dates of application for each applied chemical. For a chosen chemical, we use the earliest and the latest possible application dates based on information available in the NC crop profiles or based on crop and pest phenological patterns. We then add the chemical half-life estimate to the latest possible application date to create a probable window of application.

By combining the pesticide application quantity and timing information with the crop buffer totals, we are able to create Metric 2 for each woman in the analysis. For a selected woman, we determine the calendar dates for 1 month before conception through the third month of pregnancy. This period of the pregnancy represents an inclusive window of exposure to pesticides that may be associated with a spectrum of different congenital anomalies. Given the list of crops within a buffer and their respective total acres, we determine the quantities and types of chemicals that were applied to the crops in the state during the woman's year of pregnancy. Next, we analyze the dates of the applications of the chemicals of interest. If these dates within the year overlap with the pregnancy window of interest, we consider the woman as being exposed to that specific chemical. We repeat this process for each chemical/crop combination and then for each woman.

Another important factor in determining Metric 2 for a particular woman is the amount of the crops grown within each buffer. A buffer containing a higher number of crop acres will likely be treated with greater amounts of the chemicals of interest than a buffer with a smaller number of acres. Using the total number of crop acres within a buffer, the percentage of total NC crop acres treated with a certain chemical, along with the total pounds of active ingredients applied per year, we calculate the expected exposure to that chemical for each woman. Metric 2 for woman *i* is then defined as $M_{2,i}=\sum_{j=1}^{c_i}\sum_{k=1}^{n_j} B_i(j)p(j,k)\lambda(j,k)$ where c_i is the total number of unique crops found within the 500 m buffer for woman *i*, n_j is the total number of chemicals applied to crop *j*, $B_i(j)$ is the total number of acres of crop *j* found within buffer *i*, $p(j,k)$ is the proportion of NC acres of crop *j* that were treated with chemical *k*, and $\lambda(j,k)$ is the number of pounds of active ingredient of chemical *k* applied per treated acre of crop *j*. Recall that for a woman whose pregnancy window did not align with the application window of chemical *k* on crop *j*, we set $B_i(j)p(j,k)\lambda(j,k)$ equal to zero.

Metric 3 is calculated by repeating the Metric 2 creation process while replacing the earliest and the latest possible application dates based on crop and pest phenology or specified NC information with those based on the earliest planting and latest harvesting dates of each crop. Table 1 summarizes the information used by each of the three introduced metrics.

Metric 1 acts as a surrogate measure for pesticide chemical exposure as generally we expect a woman with increased total crop acres within 500 m of her residence at delivery to be at risk of higher levels of chemical exposure. Metric 2 incorporates expected chemical exposure based on pregnancy timing and chemical-specific application timing during the year. In contrast, Metric 3 relies on crop planting and harvesting dates alone to determine exposure and represents a computational balance between metrics 1 and 2.

Metric 3 is of interest to see what is gained by considering the more in-depth pesticide timing data utilized in Metric 2, which can be difficult to collect. We want to determine if the extra effort required for Metric 2 affects the results or if the uncertainty associated with these timing data causes the results to be similar to Metric 3. Metric 3 represents an attempt at balancing personal exposure assignment accuracy with the computational feasibility needed when applying a method requiring a large amount of data collection to large geographic and temporal domains.

Statistical Modeling

We explore metric performance by using logistic regression to investigate the association between each exposure metric and risk of any birth defect. Although it is unlikely that pesticide exposure would be causally associated with an increase in all birth defect phenotypes, in this analysis we consider all birth defects simultaneously for illustration of the methodology used for exposure assessment. For each metric, we analyze the crude unadjusted relationship along with the adjusted relationship after controlling for other covariates of interest. These covariates include maternal age, race, education, smoking status, and diabetes status. Variable selection techniques are implemented in order to choose the appropriate covariates in each of the models. Forward, backward, and stepwise methods each resulted in the same choice of covariates for each of the respective models. Linear exposure as well as categories of exposure are considered in separate models. The categories include the following quantiles of exposure: no exposure (serves as the reference group),<0.10, (0.10,0.50), (0.50,0.90), and≥0.90. Akaike's information criterion (AIC) is used to compare models using the various metrics. AIC is a commonly implemented statistical tool used for model selection purposes when there are competing models of interest in an analysis. The AIC analysis helps to determine which metric better explains the association between exposure and birth defect development. Results are presented for the adjusted models due to an improved fit while the unadjusted results are displayed in the Supplementary Materials. The analyses are carried out using SAS/STAT software (SAS Institute, Cary, NC, USA).

RESULTS

Table 2 displays the basic summary information for the births included in the study. The birth defect and non-birth defect groups differed statistically in terms of birth weight, gestational age, maternal age, race, education, parity, smoking, diabetes, and marital status.

The summary information regarding the distribution of the average absolute crop change variable is shown in Tables 3 and 4 for the entire NC cohort. Results suggest that for the considered NC crops, a large proportion of women had the same crop amounts within their buffer for each year. Cotton and peanuts, for example, consistently had over 57% and 90%, respectively, of the sample with the same crop totals across the years. Apples, sweet corn, and watermelons only had data in 2008–2010 (Table 4) but were very consistent through time with each crop having over 95% of the sample with the same crop totals across the years. Removing one year at a time reveals that the crop maps for 2008–2010 are more similar than for 2002, though the maps do not appear substantially different for any of the years. This can be seen in Table 3 once we remove 2002 from the analysis, as the amount of change between the years is slightly closer to zero for the major crops and the percentage of the sample with the same crop totals from year-to-year is increased. Based on the sometimes large difference between the sample means and medians, it is clear that there are a few outlier observations among this cohort of women where the amount of change is relatively large. The median is not affected by these outliers and is a more appropriate estimate of the center of the distribution in this setting. These outliers typically represent residences where the crop was present during each year of the available crop maps. As a result, these women will be correctly classified as exposed in the analysis, though their estimated exposure amounts may be potentially misclassified. Based on Tables 3 and 4, no crops with multiple years of data are removed from the analysis. Table 1 in the Supplementary Materials suggests that for the major crops of interest, the number of harvested acres is relatively constant across the years of interest, providing more evidence that the crop maps for the missing years may be similar to the available years of data.

The extrapolation results suggest that a weighted average of the buffer crop maps for the missing information in years 2003–2005 is appropriate due to the small variability seen in the buffer crop totals across the years. The crop information for the woman with buffer *i* in these missing years becomes $\left(Y_{i,2002}+\frac{Y_{i,2008}+Y_{i,2009}+Y_{i,2010}}{3}\right)/2$, a weighted average of her buffer for the available years. Crops which are accounted for during one crop map year alone (blueberries, squash, cabbage, bell peppers, and tomatoes) are removed from the analysis as we cannot verify that their placement and totals are relatively static over the analysis years. This represents crops that are not heavily planted across the state and therefore does not affect a large number of women in the analysis in terms of chemical exposure.

To explore the consequences of removing these single-year crops from the analysis, we carry out a sensitivity analysis using the single available crop map year of 2010. We assume that the crop map for 2010 is consistent with that of the years 2002–2005 and calculate Metric 1 and Metric 3 exposures for the cohort using these crops alone. We then fit similar statistical models as described in “Statistical Modeling” and analyze the results. The sensitivity analysis results suggest that the relatively small number of planted acres of the excluded single-year crops leads to only a small number of women being exposed to the applied chemicals (<1.3% of the cohort). No statistically significant effects are identified using either of the metrics. The Supplementary Materials displays the estimated exposures for the birth defect and non-birth defect groups (Table 2). The differences between the groups are not statistically significant for either of the metrics.

Table 5 displays the statistical summaries of chemical exposure (acres and pounds of active ingredient) for each exposure metric stratified by births that resulted in any congenital anomaly and births that were free of any defects. On average, Metric 3 gives larger estimates of the chemical exposure experienced by the women when compared with Metric 2 for both the groups. This is due to the use of the less precise windows of exposure, which typically results in more women being identified as exposed during their pregnancy. Each of the presented estimates is statistically significantly different between the birth defect and non-birth defect groups.

For each statistical analysis, we investigate the association between the selected exposure metrics and all birth defects in order to examine the performance of each metric. Figure 2 shows the adjusted odds ratio estimates and 95% confidence intervals for each category of exposure *versus* the unexposed reference group for each metric. The unadjusted categorical exposure results are nearly identical to the adjusted results and can be seen in Figure 1 of the Supplementary Materials. Table 6 displays the adjusted results for each metric for the linear exposure logistic regression models while the unadjusted results are displayed in Table 3 of the Supplementary Materials. Recall that the Metric 1 exposure is measured in acres while metrics 2 and 3 are measured in pounds of active ingredient. As a result, their results are not directly comparable.

As a result of each adjusted model being fit with the same group of women and the exposure metrics alone changing, we are able to compare the resulting model fits through use of AIC. AIC is an indicator of the goodness of fit of a proposed model.[23] We focus on the adjusted categorical exposure results of Figure 2 for the model comparisons as this model is shown to provide a better fit of the data than the linear exposure model in terms of AIC. The AIC values are 60,260.310 (Metric 1), 60,241.640 (Metric 2), and 60,238.496 (Metric 3). It is clear that metrics 2 and 3 are preferred statistically over Metric 1 as differences of >10 indicate that the model with lower AIC provides a better fit. No difference is seen, however, between metrics 2 and 3.

DISCUSSION

The presented results suggest that the introduced metrics can be used to assess associations between large-scale agricultural pesticide exposures and adverse pregnancy health outcomes. In this study, we applied the metric creation methods to a NC cohort of pregnant women and analyzed the risk of developing any congenital anomaly for illustration purposes only. The results for this association in our example may not be fully developed due to the exclusion of a few NC crops (including tobacco) where the necessary data were not fully available. However, the creation, performance, and comparisons of the introduced metrics are valid and remain the major focus of the study.

Figure 2 shows that all three metrics give similar information regarding the association, though it is clear that the odds ratio estimates from Metric 1 are closer to a null relationship than metrics 2 and 3. Overall, the results from the metric analysis did not change drastically between the unadjusted and adjusted models for either the linear or categorical forms of exposure. Metrics 2 and 3 provide very similar odds ratio estimates and potentially suggest a statistically significant effect at categories three (missed by Metric 1) and four. The timing of the chemical applications mainly impacts the total number of women who are identified as exposed and does not drastically affect the results. Based on these findings along with the AIC analysis, we recommend Metric 3 due to its computational benefits.

There are a few issues that are of concern when determining if any of the proposed metric creation methods can be extended to studies in other states. First, the lack of yearly crop map data in a state can be a limiting factor when determining the crop-specific acre amounts within the buffer areas. This affects the construction of all of the introduced metrics. When extending the process to a new state that does not have full yearly coverage of crop maps, it is important to carry out sensitivity analyses, similar to those in “Data Preparation”, to ensure that some weighted average of the available crop maps represents a reasonable estimate for the missing years. Crop rotation patterns could also potentially confuse this process, especially if the rotated crop(s) covers extensive acreage within the state. This was not the case in NC as the most prevalent crops appeared to be reasonably static from year-to-year. These factors may not be as limiting for future studies, however, as the crop map data are currently available nationwide from 2008 to the present.

Creating Metric 2 in other states could potentially be problematic due to the lack of centralized data on chemical application dates. Application dates vary by chemical/crop pairing and also by state. Obtaining this information for a number of different crops, chemicals, and states can therefore be very time and labor intensive. Also, because the data do not come from a central storage location, there is extra variability introduced by combining data from multiple sources. In general, insecticide application dates are likely more variable than herbicide or fungicide application dates as they depend more heavily on pest pressure, which can fluctuate based on climatic conditions. Therefore, Metric 3 may be more appropriate for herbicides and fungicides. Also, pesticide applications made on smaller acreage crops can be more variable from season-to-season and, therefore, harder to estimate using the aggregated yearly state-level data. Obtaining accurate timing information will be the major hurdle in extending this method to health studies in other states.

Metric 3 does not require the collection of this timing data as it relies on the planting and harvesting dates of the relevant crops, which will also vary by state. Given quality crop map data, Metric 1 can be calculated efficiently for multiple states and can give some insight into the exposure/outcome relationship. Metric 2 will require more rigorous computational effort, which may not be necessary to accurately characterize the true relationship between chemical exposure and adverse birth outcomes. Metric 3 represents a balance between metrics 1 and 2 in terms of accuracy and computational efficiency.

The grouping of all birth defects and aggregate-level exposure information, by necessity, may lead to measurement error and likely the underestimation of effect size. Another potential source of measurement error in this study is the use of maternal residence at delivery rather than early pregnancy, which is the relevant period of exposure for birth defects. Although changing addresses during this period is possible, a number of studies have suggested that a majority of women tend to remain at their current address during the entire pregnancy or move only a relatively short distance.[24,25] Such misclassification would tend to bias the odds ratios toward the null in most situations. It seems feasible that each of the proposed metrics can be calculated for women living in multiple locations across the US where quality crop map and chemical application data are available. We recommend the use of Metric 3 due to its similarity to Metric 2, which is more complicated to construct. Future studies should focus on specific birth defect phenotype and chemical combinations of interest using similar metric creation methods for a more complete set of crop map and pesticide application data in the geographic area of interest. Alternate health outcomes such as neuropathies, chronic diseases, and various cancers could also be considered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Andrew Olshan, Professor of Epidemiology and Department Chair at UNC Chapel Hill, Kristy J. Michie, Supervising Public Health Epidemiologist at the Monterey County Health Department, and Leon S. Warren Jr., Agricultural Research Associate in the North Carolina State University Department of Crop Science for providing helpful input regarding the metric creation process and general pesticide/crop timing information. This research was supported in part by grants from the National Institute of Environmental Health Sciences (T32ES007018, P30ES010126).

NIH-PA Author Manuscript

NIH-PA Author Manuscript

References

1. Bell EM, Hertz-Picciotto I, Beaumont JJ. A case-control study of pesticides and fetal death due to congenital anomalies. Epidemiology. 2001; 12:148–156. [PubMed: 11246574]
2. Shaw GM, Wasserman CR, O'Malley CD, Nelson V, Jackson RJ. Maternal pesticide exposure from multiple sources and selected congenital anomalies. Epidemiology. 1999; 10:60–66. [PubMed: 9888281]
3. Blatter BM, Roeleveld N, Zielhuis GA, Gabreels FJM, Verbeek ALM. Maternal occupational exposure during pregnancy and the risk of spina bifida. Occup Environ Med. 1996; 53:80–86. [PubMed: 8777455]
4. Garry VF, Schreinemachers D, Harkins ME, Griffith J. Pesticide appliers, biocides, and birth defects in rural Minnesota. Environ Health Perspect. 1996; 104:394–399. [PubMed: 8732949]
5. Garry VF, Harkins ME, Erickson LL, Long-Simpson LK, Holland SE, Burroughs BL. Birth defects, season of conception, and sex of children born to pesticide applicators living in the Red River Valley of Minnesota, USA. Environ Health Perspect. 2002; 110:441–449. [PubMed: 12060842]
6. Kristensen P, Irgens LM, Andersen A, Bye AS, Sundheim L. Birth defects among offspring of Norwegian farmers, 1967–1991. Epidemiology. 1997; 8:537–544. [PubMed: 9270956]
7. Regidor E, Ronda E, Garcia AM, Dominguez V. Paternal exposure to agricultural pesticides and cause specific fetal death. Occup Environ Med. 2004; 61:334–339. [PubMed: 15031391]
8. Rocheleau CM, Romitti PA, Sanderson WT, Sun L, Lawson CC, Waters MA, et al. Maternal occupational pesticide exposure and risk of hypospadias in the National Birth Defects Prevention Study. Birth Defects Res A Clin Mol Teratol. 2011; 91:927–936. [PubMed: 21954192]
9. Weidner IS, Moller H, Jensen TK, Skakkebaek NE. Cryptorchidism and hypospadias in sons of gardeners and farmers. Environ Health Perspect. 1998; 106:793–796. [PubMed: 9831539]
10. Nelson CJ, Holson JF, Green HG, Gaylor D. Retrospective study of the relationship between agricultural use of 2,4,5-T and cleft palate occurrence in Arkansas. Teratology. 1979; 19:377–383. [PubMed: 473090]
11. Schreinemachers DM. Birth malformations and other adverse perinatal outcomes in four U.S. wheat-producing states. Environ Health Perspect. 2003; 111:1259–1264. [PubMed: 12842783]
12. Gunier RB, Ward MH, Airola M, Bell EM, Colt J, Nishioka M, et al. Determinants of agricultural pesticide concentrations in carpet dust. Environ Health Perspect. 2011; 119:970–976. [PubMed: 21330232]
13. Meyer KJ, Reif JS, Rao Veeramachaneni DN, Luben TJ, Mosley BS, Nuckols JR. Agricultural pesticide use and hypospadias in eastern Arkansas. Environ Health Perspect. 2006; 114:1589–1595. [PubMed: 17035148]
14. Brody JG, Vorhees DJ, Melly SJ, Swedis SR, Drivas PJ, Rudel RA. Using GIS and historical records to reconstruct residential exposure to large-scale pesticide application. J Expo Anal Environ Epidemiol. 2002; 12:64–80. [PubMed: 11859434]
15. Royster MO, Hilborn ED, Barr D, Carty CL, Rhoney S, Walsh D. A pilot study of global positioning system/geographical information system measurement of residential proximity to agricultural fields and urinary organophosphate meta-bolite concentrations in toddlers. J Expo Anal Environ Epidemiol. 2002; 12:433–440. [PubMed: 12415492]
16. Ward MH, Nuckols JR, Weigel SJ, Maxwell SK, Cantor KP, Miller RS. Identifying populations potentially exposed to agricultural pesticides using remote sensing and a geographic information system. Environ Health Perspect. 2000; 108:5–12. [PubMed: 10622770]
17. CropScape—Cropland Data Layer [Internet]. 2012. [cited 2 October 2012]. Available from nassgeodata.gmu.edu/CropScape/
18. NASS Pest Management [Internet]. 2012. [cited 2 October 2012]. Available from http://www.pestmanagement.info/nass/index.html
19. North Carolina Pest Management Information Program (NCPMIP)—Crop Profiles [Internet]. 2012. [cited 2 October 2012]. Available from http://ipm.ncsu.edu/ncpmip/cropprofiles.htm
20. North Carolina Crops—Usual Planting & Harvesting Dates [Internet]. 2012. [cited 2 October 2012]. Available from http://www.ncagr.gov/stats/crops/Dates.pdf

21. United States Department of Agriculture (USDA). Agricultural Research Service—Pesticide Properties Database [Internet]. 2012. [cited 2 October 2012]. Available from http://www.ars.usda.gov/Services/docs.htm?docid=14199
22. Xiang H, Nuckols JR, Stallones L. A geographic information assessment of birth weight and crop production patterns around mother's residence. Environ Res. 2000; 82:160–167. [PubMed: 10662530]
23. Akaike, H. Information Theory and an Extension of the Maximum Likelihood Principle. In: Petrov, BN.; Czaki, F., editors. 2nd International Symposium on Information Theory. Akademiai Kiado; Budapest, Hungary: 1973. p. 267-281.
24. Nuckols, JR.; Langlois, P.; Lynberg, ML.; Luben, T. Linking geographic water utility data with study participant residences from the National Birth Defects Prevention Study. American Water Works Association Research Foundation; Denver, CO, USA: 2004.
25. Chen L, Bell EM, Caton AR, Druschel CM, Lin S. Residential mobility during pregnancy and the potential for ambient air pollution exposure misclassification. Environ Res. 2010; 110:162–168. [PubMed: 19963212]

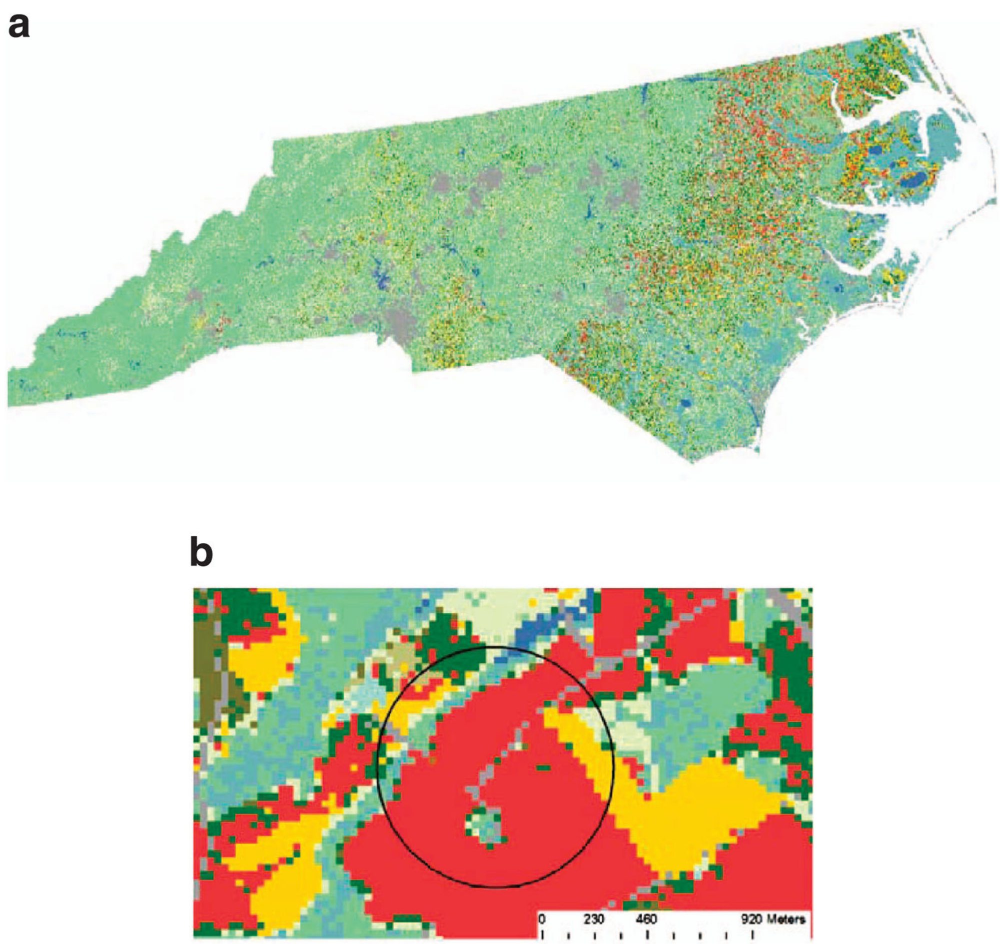

Figure 1.
2010 NC crop map plot and example buffer region for a selected residence at delivery. Major NC crops key: Red (Cotton), Yellow (Corn), and Green (Soybeans).

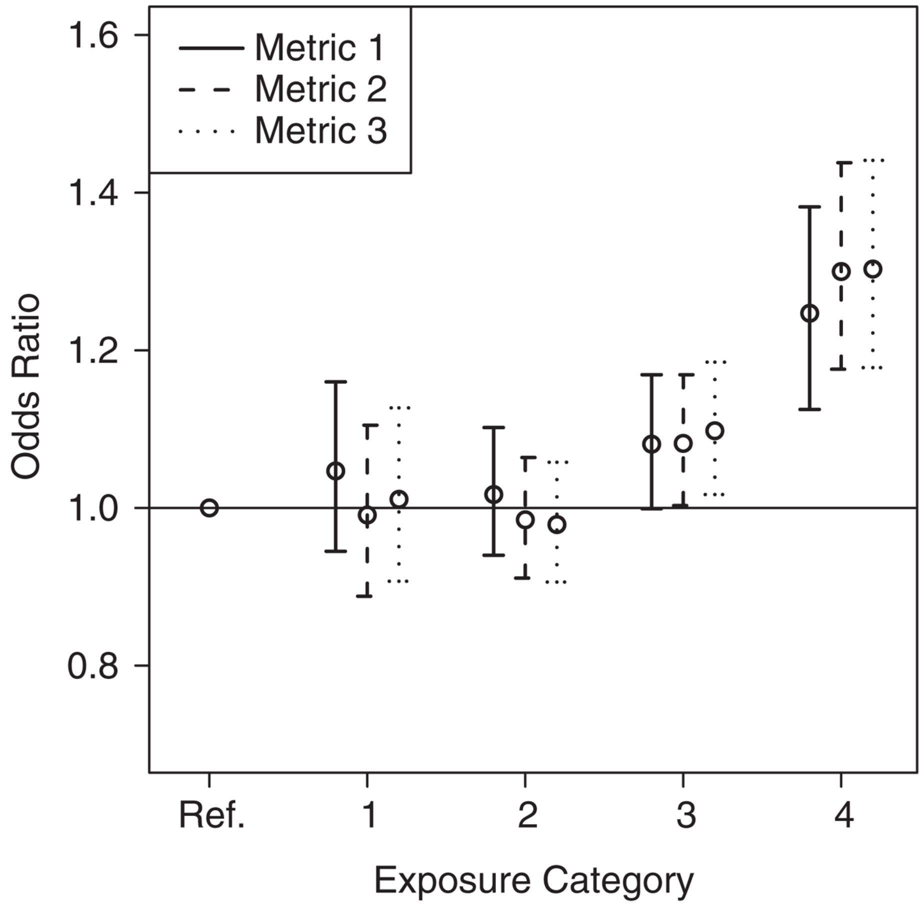

Figure 2.

Adjusted odds ratio estimates and 95% confidence intervals for various levels of categorical exposure (Ref: No exposure, 1:<10%, 2: (10%, 50%), 3: (50%, 90%), 4:≥90%). The odds of developing any birth defect is being modeled, and results for each exposure metric are displayed. Results should only be used to compare the performance of each metric due to the exclusion of a few NC crops of interest.

Table 1

Summary of the information used to create each considered pesticide exposure metric.

	Metric 1	Metric 2	Metric 3
Buffer crop acreage	X	X	X
Applied chemical quantities		X	X
Crop planting/harvesting dates		X	X
Specified chemical application dates		X	
Crop/pest phenology information		X	

Note: Metric 2 only uses planting/harvesting crop dates when more detailed application date information is unavailable.

Table 2

Summary information for the births included in the study by congenital anomaly status.

Characteristic	**Birth defects (*n* = 6358)**	**No birth defects (*n* = 298,548)**	***P*-value**
Mean birth weight in grams	3,106.69 (798.23)	3,334.40 (557.75)	<**0.0001**
Mean gestational age in weeks	38.09 (3.42)	39.09 (2.33)	<**0.0001**
Maternal age (%)			**0.0322**
<20	12.25	11.34	0.0231
20–24	25.51	26.41	0.1088
25–29	26.22	26.98	0.1751
≥30	36.02	35.27	0.2189
Maternal race/ethnicity (%)			**0.0320**
Black/non-Hispanic	22.98	21.87	0.0339
Hispanic	13.37	13.91	0.2175
Other	3.48	3.98	0.0418
White/non-Hispanic	60.18	60.24	0.9134
Maternal education (%)			<**0.0001**
<High school	24.10	22.19	0.0003
High school	30.04	28.74	0.0229
>High school	45.86	49.08	<0.0001
Previous live births (%)			**0.0019**
None	41.55	41.22	0.5900
One	31.83	33.71	0.0017
>One	26.61	25.07	0.0051
Smoked during pregnancy (%)	13.59	12.42	**0.0050**
Diabetes (%)	4.45	2.75	<**0.0001**
Married (%)	61.64	63.98	**0.0001**

SDs are presented in parentheses for continuous variables. *P*-values were obtained through two-sample *t*-tests for continuous variables and chi-square tests for categorical variables. Individual category comparisons are considered when the overall chi-square test (bold *P*-value) is significant at the 0.05 level.

Table 3

Summary information for the average absolute crop change (acres) within a woman's buffer region for all combinations of years and NC crops available in 2002, 2008–2010.

Crop	% No change	Average absolute change (acres)			
		Mean	Median	Min.	Max.
All years:					
Corn	24.9	15.14	4.17	0.50	413.83
Cotton	57.7	23.59	5.00	0.50	418.67
Peanuts	90.6	7.27	1.50	0.50	291.17
Soybeans	22.9	19.28	6.00	0.50	421.83
2002, 2009–2010:					
Corn	26.6	18.48	4.67	0.67	541.33
Cotton	58.0	29.12	6.67	0.67	508.67
Peanuts	90.9	9.31	2.00	0.67	382.67
Soybeans	23.5	21.58	7.33	0.67	490.67
2002, 2008, 2009:					
Corn	30.5	15.43	4.00	0.67	378.00
Cotton	59.5	29.11	7.33	0.67	513.33
Peanuts	92.6	8.93	2.00	0.67	294.00
Soybeans	26.4	17.55	6.67	0.67	430.00
2002, 2008, 2010:					
Corn	25.8	17.24	4.67	0.67	508.00
Cotton	58.0	29.14	6.67	0.67	513.33
Peanuts	91.4	9.77	2.00	0.67	382.00
Soybeans	23.8	22.95	7.33	0.67	490.67
2008–2010:					
Corn	35.6	13.18	3.33	0.67	541.33
Cotton	78.5	17.93	2.67	0.67	466.67
Peanuts	92.7	6.59	1.33	0.67	382.67
Soybeans	40.6	21.29	4.00	0.67	483.33

Apples, sweet corn, and watermelons are not included in the table as the crop map data only included 2008–2010 for these crops.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 4

Summary information for the average absolute crop change variable for all combinations of years and NC crops available in 2008–2010.

Crop	% No change	Average absolute change (acres)			
		Mean	Median	Min.	Max.
2008–2010:					
Apples	95.2	2.14	1.03	0.07	40.81
Sweet Corn	97.0	2.58	0.67	0.67	112.67
Watermelons	98.1	2.05	0.67	0.67	48.67

Table 5

Metric summaries for the included births by congenital anomaly status.

	Birth defects		No birth defects	
	Mean (SD)	**Range**	**Mean (SD)**	**Range**
Metric 1 (acres)	11.80 (23.29)	(0, 170.25)	10.28 (21.40)	(0, 209.95)
Metric 2 (lbs. a.i.)	14.46 (44.33)	(0, 684.34)	12.71 (61.50)	(0, 6194.67)
Metric 3 (lbs. a.i.)	16.22 (46.86)	(0, 684.80)	14.41 (64.16)	(0, 6204.21)

Metric 1 is given in acres while metrics 2 and 3 are shown in pounds of active ingredient (lbs. a.i.).

Table 6

Results from each exposure metric using a linear exposure logistic regression model to analyze the odds of developing any birth defect.

	Odds ratio	(95% CI)
Metric 1	1.061	(1.037, 1.086)
Metric 2	1.016	(0.999, 1.033)
Metric 3	1.016	(0.999, 1.034)

Adjusted results are displayed. Results are based on the standardized exposure for each metric. Results should only be used to compare the performance of each metric due to the exclusion of a few NC crops of interest.