Using Public Datasets to Evaluate Atrazine Intensity and Birth Defects

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Maturing national data collection initiatives have created new possibilities for chemical risk analysis. This study demonstrates the potential for public datasets in this field, combining a population-level live birth dataset (~29 million records) and national pesticide use volume estimates (~3000 counties) over seven years (2006-2012) to examine whether mothers living in areas with high atrazine use experience higher than average birth defect rates. Controlling for a variety of socioeconomic factors and the intense application of four other common pesticides, the data show four birth defects previously associated with atrazine (gastroschisis/omphalocele, anencephaly, spina bifida/myelomeningocele, and hypospadias) appearing 28% to 60% more often in birth records from U.S. counties with the highest intensity atrazine application – a relationship that persists under a variety of sensitivities. These results are subject to several important qualifications related to the datasets used, and efforts should be made to identify and implement data collection improvements to assist researchers and policymakers. Nonetheless, the results of this data-oriented approach are consistent with prior studies using other methods and

may provide a useful starting point for future large-scale assessment of chemical exposures on human health.

INTRODUCTION

Atrazine is the second-most heavily applied pesticide in the United States.[1] It is used primarily on corn and soybeans, to kill broadleaf weeds that otherwise compete with the crop for nutrients. The most recent available data indicate about 60 million pounds (30 million kg) of atrazine applied in the contiguous U.S. per year, across over 100 million acres of crop land.

Since the early 2000s, research has accumulated suggesting that atrazine disrupts developmental processes in vertebrate species, particularly in frogs but also in other animals and humans.[2–6] This effect has been observed at exposure levels below current regulatory limits.[4] In 2003, the European Union banned atrazine, while the U.S. approved its continued use.[7] Since that time, investigation has continued into a potential relationship between atrazine and birth defects in humans, although the causal claim has remained disputed. A recent review concluded that the claims "about a causal link between [atrazine] and adverse pregnancy outcomes are not warranted."[8] The United States Environmental Protection Agency has recently agreed, proposing to conclude that "the epidemiology evidence for an association between atrazine exposure and risk of birth defects [is] weak."[9] These conclusions are not consistent with those of many of the studies reviewed.[10–15]

The statistical power of prior studies has been limited by sample size. Very few exceed n = 1,000, and the largest examined 210,723 birth records.[12] In the general population, the birth defects under investigation occur at rates of only one per several thousand. Larger datasets provide the opportunity to examine spatial relationships and social and demographic variables potentially excluded from smaller studies.[16] This may by particularly useful where agricultural chemicals are in heavy use in some areas and not in others. Combining a nationwide birth record dataset with a nationwide pesticide application dataset provides a sample size large enough to support statistical analysis of the distribution of relatively rare birth outcomes and pesticide application across the United States.

MATERIALS AND METHODS

Data. The U.S. National Center for Health Statistics' (NCHS) National Vital Statistics System maintains the U.S. Natality dataset, which compiles U.S. live birth records. U.S. birth certificates are formatted according to national NCHS specifications last updated in 2003.[17] County-coded birth records are available by request to NCHS, subject to confidentiality restrictions. This study began with all live birth records in the U.S. Natality dataset between January 1, 2006 and December 31, 2012 (n = 28,919,346).

The United States Geological Survey's (USGS) Pesticide National Synthesis Project (PNSP) dataset provides annual estimates (kg/y) of pesticide use in approximately 3,000 counties in the contiguous U.S. Briefly, USGS combined survey data on pesticide use at the Crop Reporting District level with federal data on annual crop-acres farmed per county to generate county-level pesticide application estimates.[18–20] This data is publicly available online (https://water.usgs.gov/nawqa/pnsp/usage/maps/).

Identifying Births with Mothers from Counties with High Atrazine Use. To avoid over-reliance on the PNSP absolute estimates, the PNSP data were transformed from cardinal sorting (by absolute estimated kg/county applied) to ordinal sorting (percentile mean annual estimated kg / county land area). Counties in 60-75, 75-90, and 90-100th percentile atrazine intensity were categorized as Level 1, Level 2, or Level 3 intensity counties, respectively. Figure 1 presents a map of Level 1, 2, and 3 atrazine counties. For example, during the period 2006 to 2012, an average of 25 kg atrazine per square mile were applied each year in Clay County, Arkansas – placing it at Level 2. Any birth records from that county were tagged as "level 2 atrazine" birth records. This was repeated for all birth records.

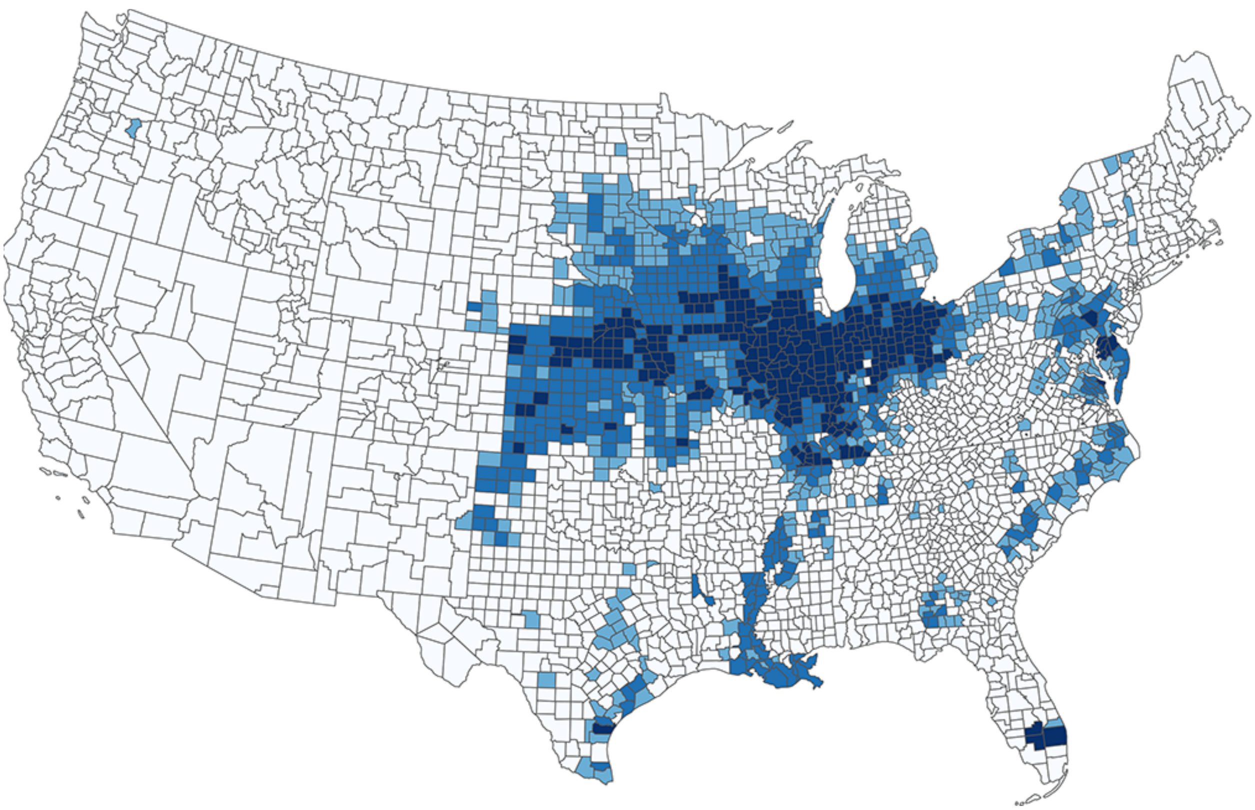

Figure 1. High-Intensity Atrazine Counties 2006-2012, Levels 1, 2, and 3 (lightest to darkest).

The PNSP dataset required cleaning prior to use because it does not include every U.S. county for every pesticide. The missing counties were addressed as follows:

- The atrazine dataset included only a few California counties. As explained in Baker and Stone,[20] California maintains its own application records, and California application data was imported into the PNSP after the rest of the dataset was complete. In contrast to other states, where zero-application counties are included as nulls, this resulted in the PNSP dataset including only those California counties with greater than 10 kg/y pesticide application. Data in the USGS dataset from California were compared to its California DPR source files to verify that application amounts in USGS files were consistent with DPR files (they were). All missing California counties were then added to the PNSP dataset, with null atrazine application amounts. Sensitivity to the California data was tested by dropping California and rerunning the primary analysis.

- Approximately 40 Virginia cities have separate county codes which are not reflected in the PNSP data for any pesticide. Each of these cities is a "Virginia independent city" that is surrounded by or adjacent to another county. Each Virginia independent city was coded with the atrazine level of the county that surrounds or is adjacent to it. Independent cities on the Virginia Peninsula were matched to York County. Sensitivity to the Virginia data was tested by dropping Virginia and rerunning the primary analysis.
- The atrazine dataset did not include application volume data for the following major U.S. metropolitan areas: the New York City area; Washington, D.C.; Boston, MA; Philadelphia, PA; New Orleans, LA; and St. Louis, MO. Atrazine application volume was marked as "0" in all urban counties with published SDWA Drinking Water Quality Reports between 2006 and 2012 indicating that drinking water did not contain atrazine and assuming low exposure probability via other pathways. In the St. Louis and New Orleans metropolitan areas, where atrazine has been detected in drinking water during the study period, atrazine intensity was set to Level 2. Sensitivity to the metropolitan data was tested by running the primary analysis a) after dropping New Orleans and St. Louis and b) after dropping all non-reported metro counties.

- The PNSP atrazine database was missing data from an additional fifteen rural counties, with a total population of approximately 90,000. These counties were dropped from the analysis.

Similar adjustments were made to the control pesticides (discussed below), as necessary. Figures 2 through 5 show Level 1, 2, and 3 counties for 2,4-D, chlorpyrifos, glyphosate, and metolachlor-s.

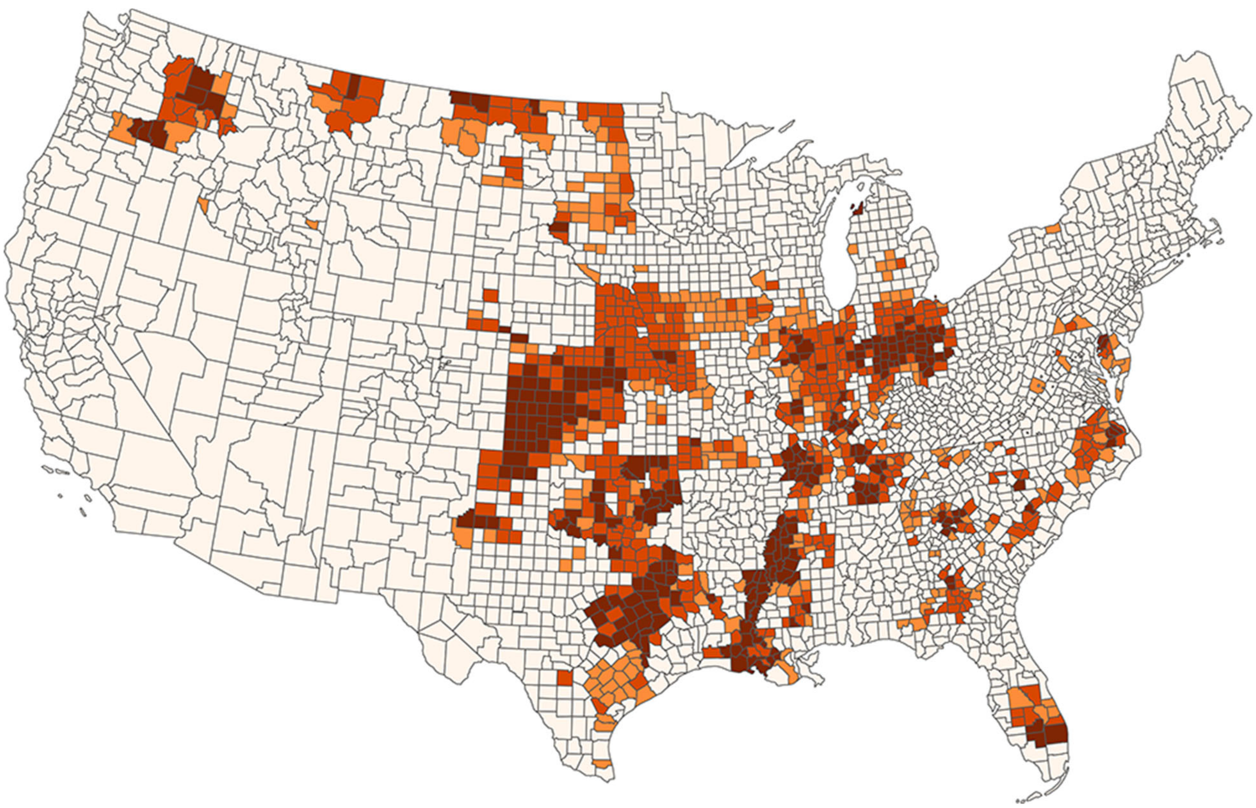

Figure 2. High-Intensity 2,4-D Counties 2006-2012, Levels 1, 2, and 3 (lightest to darkest)

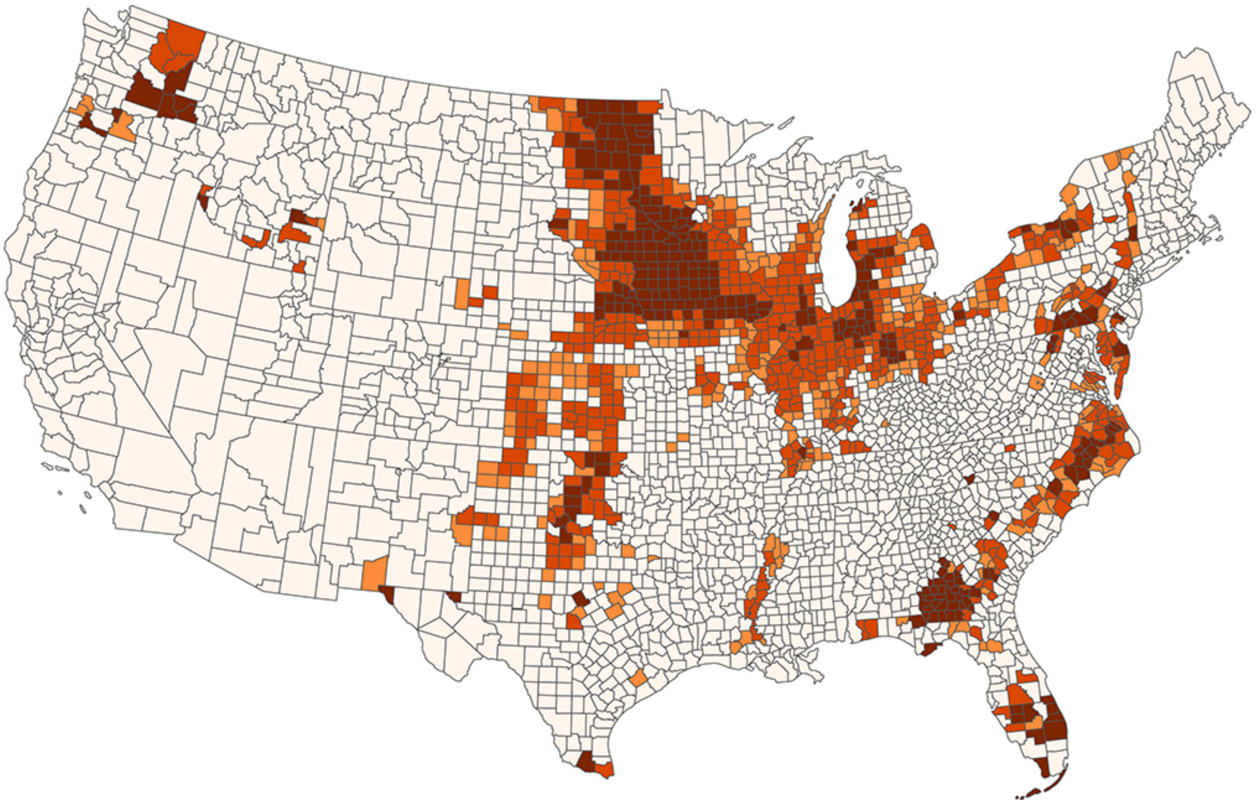

Figure 3. High-Intensity Chlorpyrifos Counties 2006-2012, Levels 1, 2, and 3 (lightest to darkest)

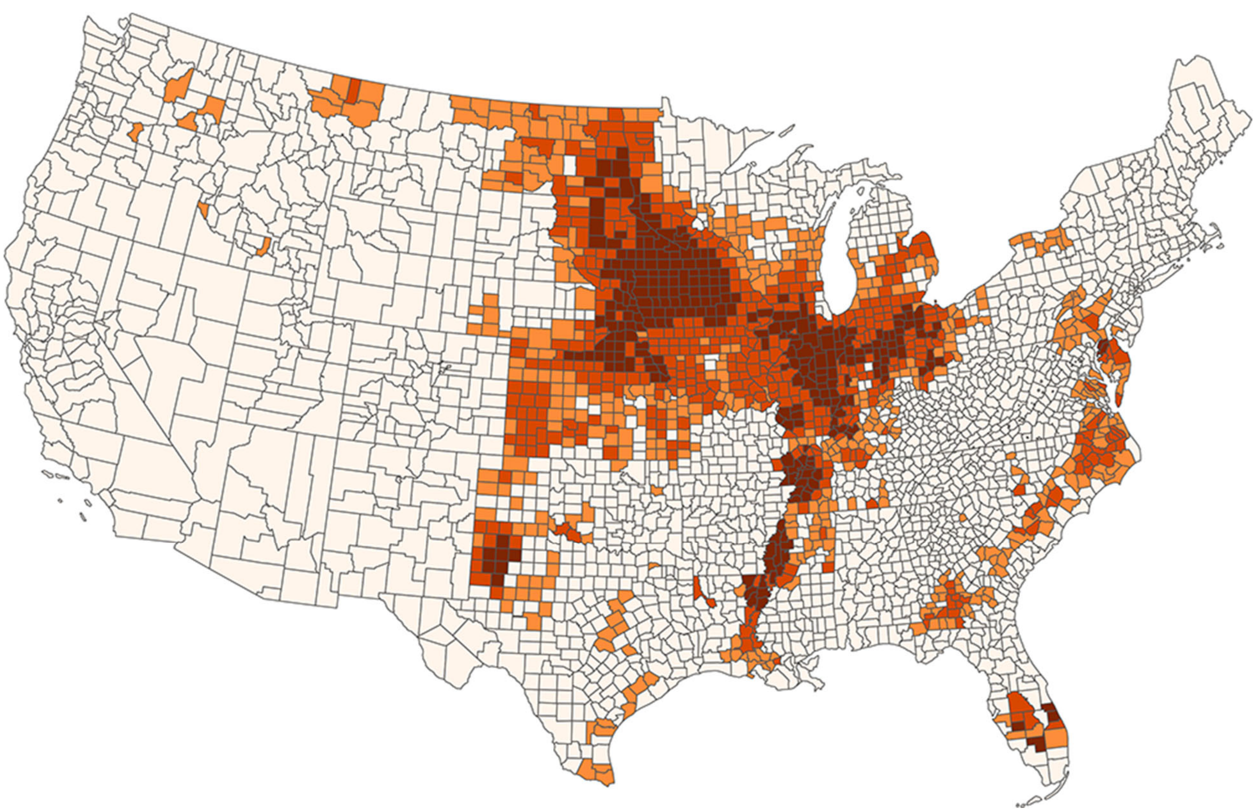

Figure 4. High-Intensity Glyphosate Counties 2006-2012, Levels 1, 2, and 3 (lightest to darkest)

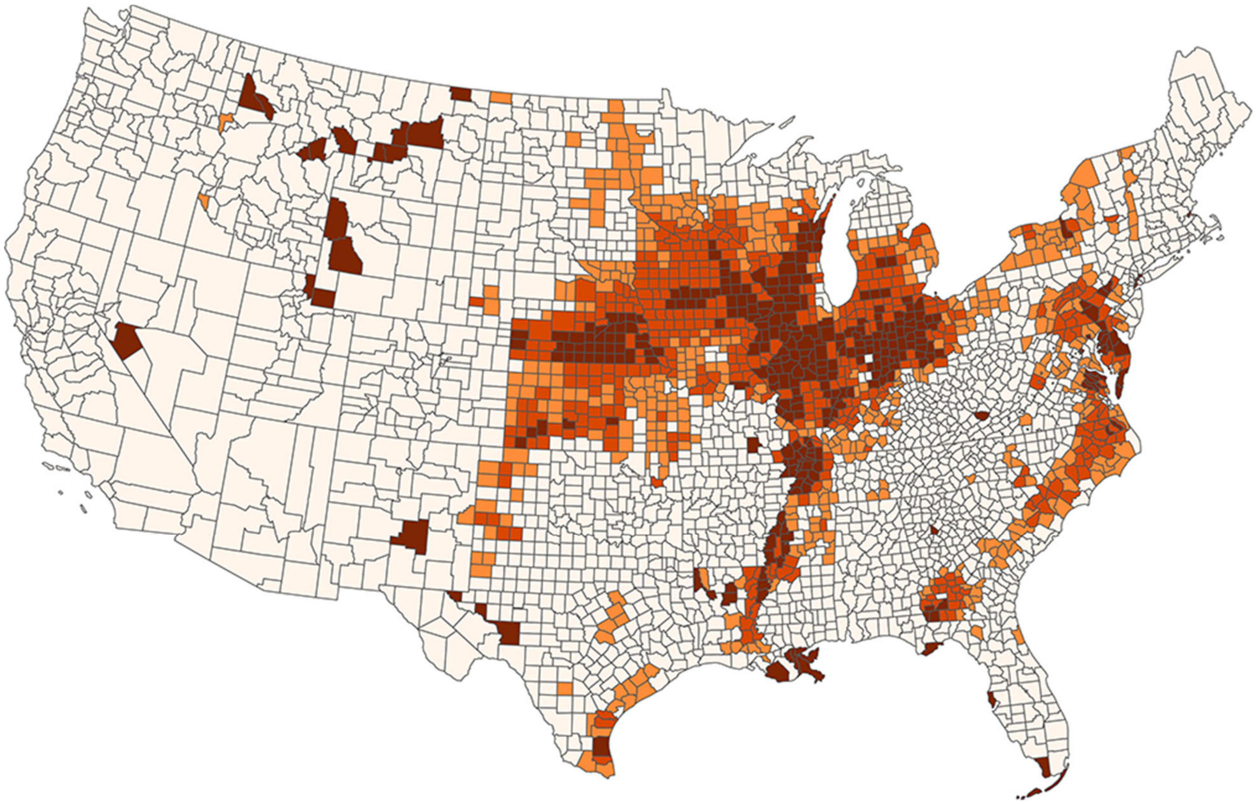

Figure 5. High-Intensity Metolachlor-S Counties 2006-2012, Levels 1, 2, and 3 (lightest to darkest)

Identifying Birth Defects. The birth records were coded for reporting of the following birth defects: gastroschisis/omphalocele, anencephaly, spina bifida/myelomeningocele, and hypospadias. This required some adjustment, as birth defect reporting standards changed during the study period. Although the current standard was finalized in 2003, it was phased in across states. In 2006 and 2007, almost 15 percent of U.S. birth records were taken under the older standard. By 2012, the number had fallen to about 5 percent. Between 2006 and 2012, about 8.5 million live births were reported under the older standard. To compensate for this, the gastroschisis and omphalocele reports under the 2003 standard were combined, to match the 1989 standard. Under this treatment, the dataset included 10,806 recorded cases of gastroschisis/omphalocele (1 in 2,650), 3,279 cases of anencephaly (1 in 8,735), 4,770 cases of spina bifida/myelomeningocele (1 in 6,002), and 10,733 cases of hypospadias (1 in 1,366 male births).

Tagging Birth Records with County Codes and Control Variables. Five-digit FIPS codes were generated for all remaining birth records. Each birth record was then tagged with the county-level pesticide information generated in the high-use county identification process described above. To isolate the potential effect of the "high atrazine" variable, the birth records were tagged with a variety of control variables: mother's race (non-Hispanic white, black, Hispanic (all), Asian (all), Native American); mother's education level (revised standard); mother's age below 25 (dummy variable); mother's tobacco use (dummy variable, revised standard); county poverty level above 20% (dummy variable); and birth year.

Finally, birth records were tagged with county-level application intensity quartile statistics for four other pesticides: 2,4-D, glyphosate, chlorpyrifos, and metolachlor-s. These pesticides were chosen because they are among the top ten most applied pesticides by volume in the U.S. and are well covered in the USGS NSPS dataset. Carbofuran and simazine were considered but not used, given limitations of the NSPS dataset for these pesticides.

Statistical Analysis. With the 28,643,141 remaining records, a series of logistic regressions (Stata 13: logistic) were performed using birth defect variables as the explained variables, and atrazine intensity and the control variables as the explanatory variables. That is, the reported prevalence of birth defects in U.S. counties with the highest (90th percentile) amounts of atrazine applied between 2006 and 2012 were compared to the reported prevalence of the same defects in other U.S. counties during the same period, with controls for mother's age, mother's race, mother's smoking, high poverty level, and Level 3 intensity of 2,4-D, chlorpyrifos, glyphosate, and metolachlor-s application. In order to assess the impact of level assignment decisions documented above, the same logistic regressions were run on the dataset with California, Virginia, New Orleans and St. Louis, and all non-reporting-for-atrazine metro counties dropped. The primary analysis (without sensitivities) was repeated with atrazine and control variables at Level 2 (75-90th percentiles) and Level 1 (60-75th percentile).

Findings (excluding non-pesticide controls) for the Level 3, 2, and 1 analyses are reported in Table 1, below, as odds ratio (OR) with a 95% confidence interval. See Supplemental Information for Stata .do files and complete outputs.

RESULTS AND DISCUSSION

Birth records from Level 3 atrazine intensity counties were more likely to report gastroschisis/omphalocele (1.28 [1.16, 1.41]), anencephaly (1.39 [1.16, 1.68]), spina bifida (1.60 [1.39, 1.85]), and hypospadias (1.42 [1.28, 1.56]). The results were not substantially different under sensitivities.

<table>
<tr><th></th><th colspan="2">Level 1</th><th colspan="2">Level 2</th><th colspan="2">Level 3</th></tr>
<tr><td>Gastroschisis & Omphalocele</td><td>O.R. (C.I. 95%)</td><td>P>|z|</td><td>O.R. (C.I. 95%)</td><td>P>|z|</td><td>O.R. (C.I. 95%)</td><td>P>|z|</td></tr>
<tr><td>Atrazine</td><td>1.00 (0.93, 1.08)</td><td>0.950</td><td>1.05 (0.97, 1.13)</td><td>0.254</td><td>1.28 (1.16, 1.41)</td><td>0.000</td></tr>
<tr><td>2,4-D</td><td>1.11 (1.04, 1.19)</td><td>0.001</td><td>0.98 (0.91, 1.05)</td><td>0.569</td><td>1.02 (0.93, 1.12)</td><td>0.671</td></tr>
<tr><td>Chlorpyrifos</td><td>1.09 (1.02, 1.16)</td><td>0.007</td><td>1.21 (1.14, 1.30)</td><td>0.000</td><td>1.02 (0.95, 1.09)</td><td>0.678</td></tr>
<tr><td>Glyphosate</td><td>1.08 (1.01, 1.16)</td><td>0.019</td><td>0.95 (0.88, 1.02)</td><td>0.170</td><td>1.06 (0.95, 1.19)</td><td>0.313</td></tr>
<tr><td>Metolachlor-S</td><td>0.95 (0.89, 1.03)</td><td>0.200</td><td>1.12 (1.03, 1.22)</td><td>0.005</td><td>1.10 (1.02, 1.19)</td><td>0.018</td></tr>
<tr><td>Anencephaly</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Atrazine</td><td>0.92 (0.80, 1.06)</td><td>0.252</td><td>1.15 (0.99, 1.33)</td><td>0.067</td><td>1.39 (1.15, 1.68)</td><td>0.001</td></tr>
</table>

2,4-D	1.13 (1.00, 1.29)	0.050	1.24 (1.09, 1.41)	0.001	1.39 (1.18, 1.64)	0.000
Chlorpyrifos	1.20 (1.07, 1.34)	0.002	1.07 (0.94, 1.22)	0.317	1.03 (0.90, 1.17)	0.677
Glyphosate	1.20 (1.07, 1.36)	0.003	1.01 (0.88, 1.16)	0.895	1.30 (1.06, 1.60)	0.012
Metolachlor-S	0.98 (0.85, 1.12)	0.747	1.24 (1.07, 1.44)	0.005	0.85 (0.73, 0.99)	0.033
Spina Bifida						
Atrazine	0.98 (0.88, 1.10)	0.764	1.27 (1.14, 1.43)	0.000	1.60 (1.39, 1.85)	0.000
2,4-D	1.22 (1.10, 1.34)	0.000	1.23 (1.11, 1.36)	0.000	1.07 (0.93, 1.23)	0.355
Chlorpyrifos	1.07 (0.98, 1.18)	0.139	1.47 (1.33, 1.61)	0.000	0.89 (0.80, 0.99)	0.038
Glyphosate	1.11 (1.00, 1.23)	0.041	0.96 (0.86, 1.08)	0.513	1.36 (1.16, 1.60)	0.000
Metolachlor-S	1.06 (0.95, 1.18)	0.271	1.08 (0.96, 1.21)	0.206	0.95 (0.85, 1.07)	0.428
Hypospadias[1]						
Atrazine	1.16 (1.08, 1.24)	0.000	1.01 (0.94, 1.08)	0.833	1.42 (1.29, 1.56)	0.000
2,4-D	1.19 (1.12, 1.27)	0.000	0.97 (0.91, 1.04)	0.456	0.84 (0.76, 0.93)	0.001
Chlorpyrifos	1.15 (1.09, 1.22)	0.000	1.14 (1.07, 1.21)	0.000	0.86 (0.80, 0.92)	0.000
Glyphosate	0.91 (0.86, 0.97)	0.000	0.95 (0.88, 1.02)	0.156	1.36 (1.23, 1.51)	0.000
Metolachlor-S	0.96 (0.90, 1.03)	0.231	1.31 (1.22, 1.41)	0.000	0.83 (0.77, 0.90)	0.000

Table 1: Selected Results from Statistical Analysis (C.I. 95%)

For atrazine, coefficients decreased in Level 2 counties, and (except for hypospadias) decreased again in Level 1 counties. However, some control pesticides exhibited a different pattern: coefficients increased from Level 3 to Level 2 (e.g., gastroschisis and 2,4-D intensity), or from Level 2 to Level 1 (e.g., anencephaly and chlorpyrifos or glyphosate intensity). As with many prior studies, the data are suggestive but present challenges to inferring causation between atrazine exposure and birth defect prevalence.

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[1] Male births only, n=12,834,982.

A causal inference would assume that records of birth defects in the U.S. Natality dataset are reasonably accurate, both in the sense of reporting defects that did occur and not reporting defects that did not occur, or that – even if it the dataset is not complete – that the reports represent a spatially consistent sample of birth defects that did occur. However, underreporting of birth defects on birth records has been documented, with racial and socioeconomic biases.[21,22] This is potentially visible in the Natality dataset, which shows significantly lower prevalence (reporting) of birth defects among children of black mothers and in higher-poverty counties. Because poverty and racial demographics are not geographically homogenous, this may bias results in the present study. In fact, top-percentile atrazine counties are significantly more non-Hispanic white and higher poverty than the average county. The study sought to address this by including racial and economic control variables in the regression, but it is not currently known to what degree any reporting bias may have influenced the results.

Furthermore, the Natality dataset appears to underreport spina bifida and hypospadias. The dataset prevalence of gastroschisis/omphalocele and anencephaly appear to be consistent with reliable analyses.[23-27] However, the literature reports rates of spina bifida/myelomeningocele twice as high as that in the dataset,[25] and ten times as high for hypospadias.[26–29] In other words, the Natality dataset could be missing half the spina bifida cases, and ninety percent of the hypospadias, in the live birth population. To the extent that this underreporting is not spatially homogenous, this could bias the present analysis. The analysis did not control for this, and it is not currently known to what degree this reporting bias may have influenced the results for hypospadias and spina bifida.

A causal inference from this analysis would also assume that a mother's recorded residence in a high-intensity atrazine county is a sufficient proxy for gestational exposure. This may be reasonable: atrazine is known to transport through air, water, and soil after application;[30,31] and commercial atrazine products are known to enter the body through inhalation, oral ingestion, or dermal contact.[32,33] Therefore, all else equal, an expecting mother's likelihood of exposure to atrazine should increase in counties where atrazine is applied outdoors in relatively high volumes. Consistent with this assumption, a variety of atrazine exposure assessment criteria have been used, including proxies based on surface water concentrations,[13] proximity to agriculture,[34] nearby crop acreages and pesticide volumes,[10] and self-reported exposure.[35] Still, the more general the exposure proxy, the less likely it will be possible to confirm in individual cases that mothers of children who were recorded as resident in counties with high atrazine use were, in fact, exposed to atrazine during their child's gestation period (or that mothers resident in other counties were not). On the other hand, at scales beyond a few hundred, it is not feasible to test urine for exposure biomarkers.[11] This study attempted to address this by controlling for a variety of traditional factors associated with birth defects, as well as the high-intensity application of other commercial pesticides – which occur in agricultural areas that are in many ways similar to those using atrazine. Nonetheless, in-county residence reporting is not residence in fact, and residence in fact does not necessarily mean exposure, and it is not currently known whether this biases the results.

Finally, a causal inference would assume that the pesticide controls chosen for this analysis are sufficient to elucidate the potential relationships and interactions between exposure to atrazine and other pesticides. This is not likely to be the case, as only four other chemicals could be used, and some of these exhibited non-linear relationships between application intensity and birth defect prevalence. Although no part of the analysis resulted in significant reduction to the atrazine coefficients, it is still possible that some interaction or other factor associated with atrazine, but not atrazine itself, could be behind the observed relationship.

The analysis could be extended with improved data, additional controls, and further statistical investigation. Incorporation of still-birth records could provide further cases and controls. Adding crop coverage and crop type information could provide useful controls. Revisions to the NSPS datasets could allow for additional pesticides as controls, and improvements to birth defect reporting could increase the reliability of the results. Time-series analysis could be performed, in combination with difference-in-differences statistical analysis, focusing on areas that increased or decreased crop production, pesticide usage, or both.

“Big data” are not often collected with environmental and human health research in mind, and are not typically standardized or linkable without researcher effort.[36] Nonetheless data analysis is an increasingly important component of much environmental science.[37] While it is possible to argue that 29 million birth records do not qualify as “big,” and certainly no sophisticated machine learning techniques were necessary to develop initial insights, the present analysis demonstrates the potential value of the birth record datasets in combination with environmental datasets, and the need for chemical risk assessment experts to attend to the improvement of both the nation’s birth record data collection and environmental and chemical release inventories. Using relatively simple statistical techniques, the combination of two existing datasets has revealed a previously unobserved, highly significant increase in birth defects in counties selected only for high intensity atrazine use. This approach suggests new directions for work on large-scale chemical risk and human health assessment.

ASSOCIATED CONTENT

orford_atrazine.master.do, containing model and statistical analysis (Stata file)

orford_20xxallpests.xlsx, containing all pesticide data used (Excel file)

orford_results.txt, containing Stata output of statistical analysis (text file)

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