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THE ASSOCIATION OF ATRAZINE AND NON-HODGKIN LYMPHOMA IN KENTUCKY

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ABSTRACT OF CAPSTONE

Justine F. Maxwell

The College of Public Health

University of Kentucky

2016

THE ASSOCIATION OF ATRAZINE AND NON-HODGKIN LYMPHOMA IN KENTUCKY

ABSTRACT OF CAPSTONE

A Capstone project submitted in partial fulfillment of the
requirements for the degree of Doctor of Public Health in the
College of Public Health
at the University of Kentucky
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ABSTRACT OF CAPSTONE

THE ASSOCIATION OF ATRZINE AND NON-HODGKIN LYMPHOMA IN KENTUCKY

Atrazine, one of the most widely used agricultural pesticides, largely sprayed on corn. throughout the Midwest.[34] The Environmental Protection Agency (EPA) has estimated 76.4 million pounds are applied annually where its usage on corn accounts for approximately 86% of total United States (US) domestic usage (in pounds).[35] Approximately 75% of the field corn acreage grown in the U.S. is treated with atrazine.[35] Once atrazine enters into waterways, it can persist having a half-life greater than 200 days in surface waters.[34] In Kentucky, atrazine is the most heavily applied in heavy corn-producing locations, which are mostly in western regions of the state.[8] Although some research has suggested a possible link between atrazine exposure and cancers, including breast, thyroid, and ovarian cancers, few studies have focused on the association of atrazine exposure and non-Hodgkin's lymphoma (NHL). [17,21,38] Even fewer of these studies have assessed atrazine exposure using water sampling data. The purpose of this study was to conduct a descriptive exposure analysis and to evaluate the association between atrazine exposure metrics and NHL in Kentucky. Among the four metrics used to assess atrazine exposure, acres of corn planted, mean concentration level, number of samples above the maximum contaminant level, and percent above the Limit of Detection (LOD), the study found no evidence to support an association between atrazine and NHL. Study findings support the majority of previous research, therefore, strengthening the notion of no association between NHL and atrazine.

KEYWORDS: Atrazine, NHL , Mean Concentraion Level, Acres of Corn, Percent of Samples above LOD, MCL, Mean Concentration Level

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Date June 8, 2016

THE ASSOCIATION OF ATRZINE AND NON-HODGKIN LYMPHOMA IN KENTUCKY

By
Justine F. Maxwell
2016

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THE ASSOCIATION OF ATRZINE AND NON-HODGKIN LYMPHOMA IN KENTUCKY

Justine F. Maxwell

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CHAPTER 1

INTRODUCTION

Background

Atrazine, one of the most widely used agricultural pesticides, is largely used on corn, sorghum, and sugarcane throughout the Midwest. Pesticides are chemical substances used to control various types of pests, and include insecticides, herbicides, and fungicides. As a selective herbicide registered first in 1958, atrazine has been used primarily before and after planting to control broadleaf and grassy weeds.[35] It can be sprayed prior to crops starting to grow or after they have emerged from the soil.[34] The Environmental Protection Agency (EPA) has estimated 76.4 million pounds are applied annually where its usage on corn accounts for approximately 86% of total United States (US) domestic usage (in pounds), followed by sorghum at 10% and sugarcane at 3%. Approximately 75% of the field corn acreage grown in the U.S. is treated with atrazine.[35] After assessing atrazine drinking water monitoring data, the EPA, under the Safe Drinking Water Act, set a maximum contaminant level (MCL) for atrazine at 0.003 mg/L.[4] The MCL is the highest level of a contaminant that is allowed in drinking water; it is a legally enforceable standard applied to public water systems. The MCL was set to prevent potential health effects from atrazine exposure, including cardiovascular system or reproductive health problems when exposed to atrazine over long periods of time.

Although most often used as an agricultural herbicide in the US, it has also been used on residential lawns.[35] However, only persons who are licensed as certified herbicide users are permitted to purchase or use atrazine.[34] Once it is applied to crops, atrazine can remain in the soil from days to months and in some cases years. Its half-life is estimated to range from weeks to several months.[34] It can also migrate from upper soil surfaces to deeper soil layers and enter the groundwater.[34] Although atrazine can be broken down in the soil or taken up by plants, rainwater can also wash atrazine away from the soil causing it to enter waterways such as streams, lakes, and rivers.[34] Atrazine entering into waterways persists longer compared to atrazine remaining in soil due to its slow breakdown in groundwater and waterways.[34] Atrazine detected in surface waters can have a half-life greater than 200 days.[34] Due to its ability to persist in soils and move through water combined with its volume of usage, atrazine is the most commonly detected pesticide in surface waters. Concentrations in surface soils vary with season and usage patterns. Atrazine is most often applied during the spring season where concentrations in ground and surface waters peak immediately before and after the planting seasons.[35] Rural populations are at an elevated risk of exposure to these chemicals via drinking water.[7] This is important in Kentucky, as the US Department of Agriculture reports that approximately 44% of the state's population lives in rural areas.[39] Atrazine is most heavily applied in heavy corn-producing locations, which are mostly in western regions of Kentucky.[8] In 2007, atrazine was applied to 70% of corn planted, which again made it the most commonly applied agricultural herbicide.[5]

Groundwater data analyzed for atrazine in Kentucky regions collected from 1990 until 2005 from the Kentucky Groundwater Data Repository detected atrazine at 91 sites including 75 springs and 15 wells.[37] Ten of the sites reported samples greater than the MCL of 0.0003 mg/L. The US Geological Survey (USGS) has several monitoring projects in Kentucky that identified atrazine in water samples over 2-year periods.[8] Atrazine and simazine were identified most frequently in surface and spring water samples in the western Kentucky counties of Breckinridge and Meade counties from

2004 to 2005, with 24% of the samples collected in April, May, and June exceeding the MCL, and the median concentration increased from 2004 to 2005. In the Little River Basin in western Kentucky, 15 of the 24 pesticides detected were herbicides, with atrazine exceeding MCL in 17% of the samples.[8]

Epidemiologic research has suggested a possible link between atrazine exposure and other cancers, including breast, thyroid, and ovarian cancers.[17,21,38] However, these studies collectively have not provided adequate evidence to support the notion of an association with atrazine.[17,21,38] Fewer studies have specifically explored the association of atrazine exposure and cancers such as non-Hodgkin’s lymphoma (NHL). The majority of the research on links between occupational chemical exposure and NHL has focused on examining specific groups of pesticides such as organochlorine pesticides, organophosphates, or carbamate insecticides.[3] The findings of these studies have been mixed.[3] Fewer epidemiologic studies examining atrazine have been conducted. Results across these studies examining atrazine exposure and NHL have also been inconsistent, possibly due to small sample size, the absence of occupational or other exposure history, various methods of exposure assessment, and the inability to separate the effects of multiple coexposures.[3]

NHL is a heterogeneous disease that most often arises in the lymph nodes.[3] The malignant transformation of lymphocytes includes several subtypes with specific molecular and clinical characteristics.[3] From 1975 to 2012, the incidence rate of new NHL cases in the US increased from about 10 to 20 cases per 100,000.[1] In 2015, NHL was the seventh most common type of cancer in the US, representing 4.3% of all new cancer cases, with an estimated 71,850 new cases being diagnosed and an estimated

19,790 deaths due to NHL.[1] From 2006-2012, the US overall five-year survival rate of NHL was about 70%; however, it can range from about 62% to 82% depending on the stage of the cancer when diagnosed.[1] In 2013, the age-adjusted incidence rate of NHL in Kentucky was 20.9 per 100,000 compared to 19.0 per 100,000 in the US, while the NHL mortality rate was 7.2 per 100,000 compared to 5.9 per 100,000.[2,40,41] Figure 3 presents the crude rates of NHL in Kentucky from 1999 to 2010.

NHL disproportionately affects men in the US; the incidence of NHL from 2009 to 2013 for men and women was 23.7 per 100,000 and 16.1 per 100,000 respectively.[1] In Kentucky, the age-adjusted incidence rate from 2009 to 2013 was 25.4 per 100,000 for men and 17.1 per 100,000 for women. Among cancer deaths from 2009 to 2013, NHL was the eighth leading cause of death, accounting for 7.7 deaths per 100,000 in men and 4.7 deaths per 100,000 in women.[1] NHL also tends to affect older rather than younger people, with the majority of NHL cases (24.3%) being diagnosed in the 65 to 74 age category.[2]

Problem Statement

There have been inconsistent findings of whether atrazine exposure is associated with specific cancers such as NHL, mainly due to methodological limitations of previous studies.[22] Several of these previous studies made multiple comparisons in their statistical analysis, including exploring associations for several herbicides/pesticides and several types of cancers. Several of the previous studies may have observed some associations by chance alone.[13] Few studies examining associations have concentrated on a limited number of comparisons. Studies focusing specifically on NHL cancer and atrazine avoid the multiple comparison problems mostly encountered in environmental studies. Other studies have also reported findings based on small sample sizes, lacked detailed on exposure information, were underpowered to detect smaller effects, used self-reported data, and relied on proxies for exposure assessment. Additionally, few studies examined water data to assess atrazine exposure and its association with NHL. Those that did, however, did not consider atrazine exposure from both water and agricultural data (e.g., number of acres of corn-produced) to allow for an additional index to assess exposures in statistical modeling.

Purpose of Capstone

Therefore, the purpose of this study was to examine the association of atrazine and NHL in Kentucky. Data used in this study were obtained from the Kentucky Cancer Registry (KCR), the Kentucky Geological Survey (KGS), and Kentucky Department of Agriculture. Specifically, this study examined the incidence of NHL and two atrazine exposure metrics: agricultural corn production and atrazine in municipal water systems. First, a descriptive exposure analysis was conducted using the atrazine exposure database for Kentucky counties. The descriptive analysis included the examination of measures of direct and indirect atrazine exposure. Second, an ecologic study was conducted to examine the association of NHL and atrazine in Kentucky at the county level.

CHAPTER 2

LITERATURE REVIEW

Epidemiologic Studies

Among the studies conducted examining the association of NHL and atrazine, the findings have been mixed. Rusiecki et al. examined the NHL incidence among 53,943 participants in the Agricultural Health Study, a prospective 6.5-year study of licensed pesticide applicators in Iowa and North Carolina.[9] Researchers evaluated two exposure metrics: quartiles of lifetime days of exposure and quartiles of intensity-weighted lifetime days of exposure. When comparing the highest to the lowest atrazine exposure category, they observed an increased but statistically non-significant risk of NHL for both lifetime days (RR= 1.61, 95% CI: 0.62 - 4.16) and intensity-weighted lifetime days (RR= 1.75, 95% CI: 0.73 - 4.20).Tests for trend for increasing atrazine exposure were not statistically significant for either lifetime days (p=0.35) or intensity-weighted lifetime days (p=0.14). Although a strength of this study was the prospective design, there may have been recall bias due to using self-reported questionnaire data to assess atrazine exposure. Also, the study had limited information on the timing of exposure in relation to developing NHL.

Freeman et al. conducted a study using the same Agricultural Health Study prospective cohort.[19] However, they updated the study with an additional 6.5 years of follow-up data. Although Rusiecki et al. previously observed an elevated but non-significant risk, Freeman et al. only observed a slightly elevated non-significant risk for both lifetime days (RR=1.10, 95% CI= 0.71 - 1.70) or intensity-weighted lifetime days (RR=1.20, 95% CI= 0.78 - 1.86) in the second quartile exposure category. They observed a slightly negative, statistically non-significant association for all other quartiles of increasing exposure. When they evaluated the presence of effect modification by chemicals (alachlor, carbofuran, and diazinon) associated with atrazine and NHL, they observed no evidence of the interaction.

A multi-center, hospital-based case-control study conducted in France by Orsi et al. examined the association of occupational exposures to triazines and NHL among men.[26] Exposures were determined using questionnaires reviewed by occupational hygienists and interviews of triazine use. They reported an elevated but non-significant association (OR=1.9, 95% CI= 0.9 – 3.8). They also reported an elevated but non-significant association when they examined specific subtypes, diffuse large (OR=2.1, 95% CI= 0.8 – 5.0) cell and follicular (OR=2.3, 95% CI= 0.7 – 7.7) NHL. Another case-control study conducted by Cantor et al. among men in Iowa and Minnesota looked at the association of NHL and handling atrazine.[13] Men were diagnosed with NHL from 1980 to 1983, and detailed histories of their atrazine exposures were collected for those who had worked on farms at least six months. They found a slightly increased risk, although non-significant, for ever having handled atrazine (OR=1.2, 95% CI=0.9 – 1.8) and handled prior to 1965 (OR=1.3, 95% CI=0.7 – 2.5) among farmers compared to nonfarmers. When they examine triazine exposure and stratified the cases based on subtypes, they found an elevated risk of diffuse NHL (OR=1.6, 95% CI=1.0 – 2.6). They adjusted for vital status, age, state, cigarette smoking status, family history of lymphopoietic cancer, high risk occupations, and high risk exposures. Beyond the limitation of relying on cases and controls to recall exposure histories, this study also relied on proxies to get exposure histories for cases and controls. Additionally, because of the multiple comparisons in the study, many of the observed associations may have been due to chance alone. Furthermore, the study conducted by Orsi et al. did not have sufficient power to detect odds ratios smaller than 1.7.

A study conducted by Rhoades et al. among men and women assessed the association of public drinking water with atrazine alone and combined with nitrates and NHL in Nebraska.[15] They did not find an association (OR=1.0, 95% CI=0.7 – 1.4) when comparing ever atrazine use to never use. However when they examined the combination of atrazine and nitrates, they found an increased risk of NHL (OR=2.5, 95%CI=1.0 – 6.2) and specifically for the indolent B-cell subtype of NHL (OR=3.5, 95% CI=1.0 – 11.6). Another study conducted by MacLennan et al. investigating mortality due to in a cohort of triazine manufacture workers found an increased standardized mortality ratio of NHL (SMR=3.72, 95% CI=1.01 – 9.52).[10]

Hoar et al. in Kansas examined farm triazine (atrazine, cyanazine, metribuzin, prometone, propazine, terbutryn) usage and NHL in a population-based case-control study.[12] They observed a significant association for ever use of triazines (OR=2.5, 95% CI=1.2 - 5.4), although when they examined exposure to triazines with no phenoxyacetic acids or uracils, the association was not significant (OR=2.2, 95% CI=0.4 – 9.1). Zahm et al. also pooled three case-control studies conducted in Nebraska, Iowa and Minnesota, and Kansas to evaluate the association of atrazine and NHL.[24] Compared to nonfarmers, they found elevated risk associated with atrazine use (OR=1.4, 95% CI=1.1 – 1.8), personally handled atrazine (OR=1.4, 95% CI=1.0 – 1.8), and used but did not handle (OR=1.6, 95% CI=1.0 – 2.4) among farmers. However, when they controlled for use of additional pesticides (2, 4-D and organophosphates) the strength of association decreased (OR=1.2, 95% CI=0.9 – 1.7). When stratified by histological type, they observed a statistically significant association (OR=1.6, 95% CI=1.1 – 2.2). Zahm et al. evaluated the association in the same Nebraska case-control study among women only.[25] They did not find any statistically significant results for use on farms (OR=1.4, 95% CI=0.6 – 3.0) or personally handled (OR=2.2, 95% CI=0.1 – 31.5). Limitations of this study included the small sample size due to fewer women than men reporting using atrazine or personally handling atrazine.

De Roos et al. conducted a pooled analysis of same three case-control studies examining exposures to multiple pesticides, including atrazine and NHL in men.[14] However, they used hierarchical regression and controlled for several pesticides in their analysis. They found elevated risk in the hierarchical regression model (OR=1.5, 95% CI=1.0 – 2.2). When looking at the individual effects of pesticide combinations, they found an increased risk of NHL for atrazine combined with exposure to diazinon (OR=1.3, 95% CI=0.9 – 1.9), alachlor (OR=1.2, 95% CI=0.8 – 1.8), or dicamba (OR=1.0, 95% CI=0.5 – 2.0). However, the study had no information on the timing of pesticide usage in relation to NHL disease onset.

Few studies have examined agricultural practices as an indirect assessment of atrazine exposure. Orsi et al. examined the association of farming corn crops as an occupation and NHL.[26] They observed an increased risk of NHL (OR=1.9; 95% CI=1.0 – 3.7). Cantor et al. also examined the association of NHL subtypes and cultivation of corn crops.[13] They observed an elevated but non-significant association (OR=1.4; 95% CI=0.9 – 2.4) between small lymphocytic lymphoma and corn crop farming.

Due to NHL being a heterogeneous disease with multiple subtypes, some researchers have examined associations between atrazine exposures and NHL subtypes and have shown stronger associations when examining subtypes than NHL in aggregate. Schroeder et al. examined the association of atrazine and the NHL subtype, t(14;18), in farmers using archival biopsies of NHL cases in the Iowa and Minnesota case-control study.[16] The t(14;18) chromosomal translocation is a common somatic mutation suggested to be an early component step in the pathogenesis of t(14;18)-positive cases. They found the NHL subtype to be associated with atrazine (OR=1.7; 95% CI=1.0 – 2.8) among t(14; 18)-positive cases compared to the controls. This study's findings exploring a pathogenic component in the etiologic process may suggest greater support for studies examining NHL outcomes by specific subtype.

Since the time between exposure and the subsequent development of cancer varies depending on the specific cancer being studied, it is important to take into account the induction and latency period in the development NHL. However, there has been limited research conducted to understand the natural history of NHL. To date, very little is known about the latency period for environmental exposures and NHL.[32,33] What is known about NHL mainly concerns the development of NHL after treatment of Hodgkin's disease with chemotherapy or radiation. Among studies specifically examining association of NHL and atrazine, the period between exposure and disease slightly varied. For the case-control study conducted in Iowa and Minnesota, Cantor et al. reported associations for both men with past exposures at any time as well as exposures prior to 1965 to allow for 15- to 18-year latency period.[13] The case-control study conducted by Rhoades et al. in Nebraska allowed for a 20-year latency period.[15]

Experimental Studies

Among experimental studies examining cancer development, few studies have reported on atrazine exposure being associated specifically with lymphomas. Cantemir et al. examined p53 gene expression in peripheral lymphocytes of rats chronically exposed to atrazine.[31] Because the p53 gene is a tumor suppressor that negatively regulates cell proliferation through growth restriction, it plays a key role in tumorigenesis.[31] Overexpression, modification, or inadequate levels of p53 are known to accelerate the tumorigenesis process and alter cell response to agents that damage DNA.[31] They observed a modification in the p53 gene expression after long-term administration of atrazine in female Wistar rats. They reported a significant increase in the percentage of lymphocytes expressing the p53 protein and decreased sensitivity of p53. A study conducted by Donna et al. observed a significant increase in lymphomas one year after male Swiss mice were given atrazine.[30] Another study reported a dose-dependent increase in both lymphomas and leukemia among female Fischer 344/LATI rats after oral feeding of atrazine.[29]

However, given the review of the literature on experimental studies and the epidemiologic studies that have inconsistencies and methodological challenges, it is reasonable that the International Agency for Research on Cancer (IARC) categorizes atrazine in group 3 (not classifiable with regard to its carcinogenicity to humans).[27] Atrazine in currently under review by the EPA. The process includes re-evaluation of the literature to determine if there are any human or environmental risks from atrazine exposure.[28]

CHAPTER 3

EXPOSURE ASSESSMENT & ANALYSIS

Methodology

To estimate environmental atrazine exposure in Kentucky, two metrics were used at the county-level: agricultural corn crop activity and atrazine water metrics. The Kentucky Department of Agriculture (KDA) collects data on crop production by county annually. Variables of interest for this study included the number of acres and bushels of corn planted by county in 2002 and 2007. The KDA collects agricultural data every five years, with the most recently available for 2002 and 2007. Because atrazine herbicides are most commonly applied to corn crops, these variables were used as an indirect or proxy metric to assess atrazine exposure.

Data for groundwater and municipal water contamination with atrazine was collected from the Kentucky Geological Survey (KGS). As mandated by the US EPA, municipal water systems must be sampled periodically for concentrations of selected agrichemicals, including atrazine and other triazine herbicides. The KGS also maintains a database of the analytical results of all ground water and surface water samples including wells, springs, rivers, streams and municipal water sources, by county, for atrazine herbicides since 1991. These data were used to calculate the total number of samples collected in each county, the proportion of samples above the analytical limit of detection in each county, the highest concentration detected (maximum value) in each county, and the mean concentration level of the samples for each county.

The atrazine water database included atrazine sampled at five types of sites: rivers, streams, wells, springs, and municipal water sources from 1998 to 2009. To assess environmental exposures, rivers and streams water data were combined during the analysis to assess the environmental burden of atrazine in surface water. To assess human exposure to atrazine in water by route of ingestion of drinking water, municipal water data were combined with wells and springs data. The majority of the Kentucky population uses either municipal water or springs and wells for their drinking water.[44] Three different exposure metrics were used to examine both environmental exposures (river and streams) and exposure by ingestion of drinking water (municipal, wells, and springs).

Method 1 – Limit of Detection (LOD)

For this study, one-half of the lowest limit of detection (LOD) of all the analytical methods was substituted to detect atrazine in the water samples.[42] The lowest LOD recorded was 0.003 µg/mL, therefore for values recorded as below the LOD, we substituted 0.0015 µg/mL.[42] The proportion of samples above the LOD for each county was calculated by dividing the total number of samples taken that were above the LOD by the total number of samples collected for each county.

Method 2 – Mean concentration level

The mean concentration level for each county was calculated by taking an arithmetic average of the samples taken through the entire study period.

Method 3 – Maximum concentration level

The maximum concentration level was the sample with the highest concentration level for the entire sampling period for each county. The maximum concentration level for data on rivers and streams was also categorized into two groups based upon the national MCL equal to 0.003 µg/L standard set by the EPA. Counties were categorized based on having a maximum concentration level above or below 0.003 µg/L.

A three-level ordinal variable was created by combining data on the maximum concentration level for municipal, wells, and springs water sources to examine exposure by possible ingestion of atrazine in drinking water. Maximum concentration levels were categorized if the maximum concentration level for all samples from wells, springs, municipal water sources were measured to be above the MCL (high exposure), the maximum concentration level for either wells and spring or municipal water sources were measured above the MCL (moderate exposure), and if the maximum concentration level for neither wells or springs or municipal water sources were measured above the MCL (low exposure).

To determine atrazine exposure agricultural exposure metrics. Cutoff points were determined by plotting the data and visually observing natural breaks in the data (Figure 1 and Figure 2). The mean concentration level was categorized into a three-level variable for the wells, springs and municipal data: 0 µg/L, 0.00014 µg/L – 0.098 µg/L, and above 0.098 µg/L. For the rivers and streams data, the mean concentration level was categorized as: 0 µg/L, 0.00000538 µg/L - 0.4958 µg/L, and above 0.4958 µg/L.

The Shapiro-Wilk test was used to assess the normality assumption of all continuous exposure variables. Because all continuous variables were non-normal distributions, the non-parametric Spearman's rank correlation coefficients were used to measure the strength and direction of the linear relationship between continuous variables. Continuous variables included the number of bushels of corn produced, the number of acres of corn produced, the proportion of sample above the limit of detection, the mean concentration level of atrazine, and the maximum concentration level of atrazine.

Results

Tables 1 to 3 present the descriptive statistics for the atrazine exposure agricultural exposure metrics with cutoff points that were determined by plotting the data and visually observing natural breaks in the data. Among the river and stream samples, all reported spearman's rank correlation coefficients were statistically significant with the strongest correlation observed between the mean concentration level and the maximum concentration, followed by the proportion above the LOD and the mean concentration level. Because the correlation between bushels and acres of corn planted was very strong (r_s=0.997), the number of acres of corn produced was the only agricultural activity measure used in the analysis. Among the wells, springs, and municipal water samples, the strongest correlation was observed between the proportion of samples above the LOD and mean concentration level, followed by the mean concentration level and the maximum concentration level for the wells and springs.

Overall, the exposure analysis findings indicated that acres of corn and bushels of corn planted were highly correlated. Therefore, acres of corn was used in the regression analysis. Also, the mean was strongly correlated with the percentage of samples above the LOD and maximum concentration level. Among the correlations observed in the exposure analysis, the weakest were among the NHL cases and atrazine metrics. However, NHL cases and percent of samples above LOD and acres of corn planted were strongest among them. The total number of samples collected also varied across the state.

CHAPTER 4

MULTIVARIABLE REGRESSION ANALYSIS

Methodology

An ecologic study was conducted to examine the association of NHL and atrazine metrics in Kentucky. County-level data for atrazine exposure metrics and NHL cases were linked for all 120 Kentucky counties. The outcome variable was NHL cases. NHL cases, along with total population at risk of NHL, were obtained from the Kentucky Cancer Registry (KCR),[43] a population-based central cancer registry for the Commonwealth of Kentucky.[45] All Kentucky acute care hospitals and their associated outpatient facilities, health care facilities that either diagnose or treat cancer patients which include freestanding treatment centers, non-hospital (private) pathology laboratories, and physician offices are required to report all cancer cases to KCR.[45] The quality and accuracy of the data is enhanced through the extensive formal training programs of hospital-based registrars and reabstracting cases.[45] In addition, a formal quality assurance program was established to implement complete death clearance follow back and to ensure that all cases of cancer were systematically reported by non-hospital facilities.[45] KCR is also one of the expansion registries of the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program.[45] The SEER registries are the only comprehensive source of population-based information in the United States that includes stage of cancer at the time of diagnosis and patient survival data.[45] NHL cases (including nodal and extra-nodal) were newly diagnosed between 1999 and 2010. This time period was chosen to overlap with the atrazine water exposure data, and we assumed that atrazine exposure would remain relatively constant over time. Figure 1 displays crude rates of NHL for all Kentucky counties from 1999-2010.

Exposure metrics determined from the first analysis (Chapter 4) were used to estimate atrazine exposure in the ecological study. Additional county-level variables were obtained from the 2000 US census. Data from the 2000 census was used as the population distribution was very similar to the 2010 US census, and the year 2000 is included in the timeframe atrazine exposure (1998-2009) and NHL data were collected (1999-2010). Census variables included percentage of county population 25 years of age or older who have a bachelor’s degree or higher, median household income, the percentage of the county population below the poverty level, the percent of population 65 and older, and sex distribution.[46] These covariates were selected to be included in the final model even if they were determined not to be statistically significant since background literature on NHL and atrazine have established them as potential confounders. Additional data from the KGS used in the analysis included the estimated percentage of county population using public water sources.[47] KGS has estimated public water use for each Kentucky county only for the years 1998 and 2008.

An average was taken of the 1999 and 2008 estimates of the percent of the population using public water sources because some counties had significant differences in water usage from 1999 to 2008, while other counties remained relatively the same through the time period. After plotting the variables for percent of population 65 and older by atrazine exposure metrics separately and taking into consideration the mean age of diagnosis of NHL is in the 65 to 74 age group, it was determined that the

65 and older age variable should be categorized. Rather than include the percent of the population age 65 and older as a continuous variable in the model, it was categorized into a nominal variable: counties having 12% or more of their population 65 and older and counties having less than 12% of their population. The continuous variable, acres of corn planted, was categorized into tertiles for the final model.

A negative binomial regression model was used to assess the association between NHL and atrazine exposure metrics. Initially, a Poisson regression model was considered. However, there was evidence of overdispersion, and the negative binomial model was used instead. The negative binomial is a more flexible count data model with an additional variance parameter that can be used when the Poisson model does not fit the data well. SAS 9.3 PROC GENMOD (SAS Institute, Inc.; Cary, NC), which uses the linear variance parameterization of the negative binomial, was used to fit the model to the data. To calculate incidence rate ratios (RR), an offset determined by the natural log of the total population at risk in each county was included in the model. The unadjusted and adjusted RR, along with 95% confidence intervals, were reported for the NHL and each exposure metric. All statistical tests were evaluated using a significance level of 0.05.

A combined measure was created to assess the overall of atrazine exposure. Data for rivers and streams, wells and springs, and municipal water sources were combined. Using the combined data, three exposure metrics (maximum concentration level, mean concentration level, and percent of samples above the LOD) were used to examine the association of atrazine and NHL. Cutoff points were determined for the mean concentration level by plotting the data and visually observing natural breaks in the data (Figure 4). The mean concentration level was categorized into a three-level variable: 0 µg/L, 0.00000269 µg/L – 0.50 µg/L, and above 0.5 µg/L. There were four final models, each modeling atrazine exposure metrics and the agricultural exposure metric separately to avoid potential collinearity.

Results

Among the 120 Kentucky counties, atrazine samples collected ranged from 8 to 718 samples collected. Of the total number of atrazine samples collected, the mean and median were 115 and 78 respectively. Table 6 reports the results of the unadjusted model for rivers and streams, wells, springs, and municipal water sources combined. All unadjusted estimates were not statistically significant. Additionally, slightly protective unadjusted rate ratios were reported for the percent of samples above the LOD and for maximum concentration levels exceeding the MCL in all three samples.

Figures 5 – 8 display the four atrazine exposure variables in Kentucky at the county level. The majority of counties in the highest tertile for acres of corn planted were located in the western part of the state. However, the distribution of counties with highest mean concentration level, highest percent of samples above the LOD, and the highest maximum concentration were located throughout the western, northern, and central part of the state.

Tables 7 – 10 report the results of the adjusted models. After adjusting for potential confounders, the observed associations of the atrazine exposure metrics were similar to those reported in the unadjusted models. While the moderate category of acres of corn planted showed a slight elevated risk, a protective effect was reported in the highest exposure group. Therefore, counties with a moderate amount acres of corn planted had 1.02 times the rate of NHL compared to counties with the lowest amount of corn planted. While the rate ratio of NHL among counties with the highest amount of corn planted was slightly protective (RR= 0.96; 95 CI: 0.88 - 1.06). The other three models using atrazine water sampling reported statistically significant that were slightly protective. Additionally, all four models reported protective effects for percent of population with a bachelor's degree or higher, median household income, and percent of population below the poverty level. Although only slightly, all four final models reported elevated rate ratios for percent of population using public water sources, percent of population male, and percent of population 65 and older greater than twelve percent.

Spatial autocorrelation analysis to examine the potential for atrazine water samples taken from nearby counties to be related to each other and therefore not independent in this study was not addressed once the statistical analysis was completed for the final four models. Although, not addressing spatial autocorrelation may lead to incorrectly concluding a statistically significant relationship exists, that the relationship is stronger, and that the standard errors are smaller, it was determined that it was unnecessary to examine considering the majority of the rate ratios for the exposure variables were slightly protective and statistically insignificant.

CHAPTER 5

IMPLICATIONS FOR PUBLIC HEALTH

Overall, the study findings support the majority of previous research reporting no association of NHL and atrazine. This study examining the association of atrazine and NHL in Kentucky reported mostly statistically insignificant results. Furthermore, many of the adjusted rate ratios observed were slightly protective. When atrazine exposure was categorized into increasing exposure levels for acres of corn planted, mean concentration level, and samples above the maximum contaminant level, there was no evidence of increasing strength of association. However, slightly elevated associations were observed among percent of population using public water sources, percent of population male, and the percent of population 65 and older greater than twelve percent. This finding was expected as the incidence of NHL is higher among males and most new NHL cases occur in the 65 to 74 age group.

Strengths of this study include obtaining samples over a twelve year period (1998- 2009) to assess atrazine exposure for each county. Up to this point, this is one of the few studies that has assessed exposure by measuring the amount of atrazine in water. The majority of the research has consisted of occupational studies in which exposure was assessed through questionnaires. Additionally, the study used three different methods to assess atrazine in water and one agricultural exposure method. Mean concentration level and maximum concentration levels by county were used to create categorical variables to explore increasing exposure of atrazine in the water samples. This allowed for assessing a dose-response relationship when examining the association of atrazine and NHL. Another strength of this study was the absence of multiple comparisons unlike many previous studies that may have reported associations based on chance alone.

Although advantages of conducting an ecologic study include feasibility simply because obtaining individual-level exposure data may be time-consuming, expensive, or difficult, there are several limitations of this study that should be considered. Ecological studies examine the relationship between outcome and exposure at the population level instead of the individual level. As a result, associations or lack of associations observed at the county level in this study may not exist at the individual level. Because data collected in this ecologic study for NHL, atrazine, and covariates were all at the aggregate county level, confounding may not have been adequately controlled for.

Other key limitations encountered in this study was using atrazine water data that was not at the individual level, especially when assessing human atrazine consumption through wells, springs, and municipal water sources. Although the percent of the population by county served by public water sources was included in the study, the study did not have this information on the individual level. Therefore, this study lacked information on the specific amount of atrazine consumed by individuals living in each county as well as how much is absorbed and how atrazine is metabolized once it is ingested. This study also lacked data on current occupation and occupational histories of individuals in each county, including frequency and duration of exposure. Because atrazine exposure is associated with specific occupations, including pesticide applicators or pesticide is advantageous to control for occupation.[9,13,19] This study was also unable to account for or control for other pesticides that may have been present in the water samples. A previous study observed after controlling for exposure to other pesticides a reduced association of atrazine and NHL.[12] Other limitations include using number of acres of corn planted as an indirect measure of atrazine exposure. Although the majority of atrazine is used on corn crops, this proxy of exposure may not accurately provide the amount of atrazine that contaminates rivers, streams, wells, springs, or municipal water sources. Finally, because the exposure and outcome were concordant, this study did not allow for the ability to account for the latency period in developing NHL. Some previous studies have allowed for between 10 and 20 years of follow-up.

Findings of this study may be partially explained by the inaccuracies in the sampling of the atrazine and misclassification of exposure variables. Additionally, findings may have been affected by the small number of samples for the some of the atrazine water sample data. For example, several counties reported very few atrazine sampling values, while other counties had several samples taken during the study period.

Although this study had several limitations including the possible ecological fallacy, not adjusting for occupational exposures, and misclassification of exposures, results of this study add support to the growing body of evidence that the association of atrazine and NHL is unlikely. Study findings of elevated risk of NHL observed specifically among males as well as populations with greater than twelve percent 65 and older while protective effects for the atrazine exposure metrics and NHL further substantiate the notion that there is no evidence of an association between atrazine and NHL. With the growing lack of epidemiologic evidence showing no support that atrazine is a human carcinogen, future research should instead focus on exploring its association with poor reproductive outcomes and birth defects, as an endocrine disruptor.

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APPENDIX

TABLES

Table 1: Descriptive Statistics of Atrazine Exposure Metrics for Wells, Springs, and Municipal Water Sources, 1998-2009 (N=120 counties)

Characteristic	N (%)
Mean Concentration Level (µg/L) †	
High	15 (12.5)
Moderate	62 (51.7)
Low	43 (35.8)
Samples above MCL¥	
2	29 (24.2)
1	48 (40.0)
0	43 (35.8)

† Wells, Springs, and Municipal: High ≥0.098, Moderate 0.00014 – 0.098, Low 0;

¥ Maximum contaminant level (MCL): 0.003 µg/L

Table 2: Descriptive Statistics of Atrazine Exposure Metrics for River and Stream Water Sources, 1998-2009 (N=120 counties)

Characteristic	N (%)
Mean Concentration Level (µg/L) [†]	
High	14 (11.7)
Moderate	39 (32.5)
Low	67 (55.3)
Above MCL[¥]	
Yes	50 (41.7)
No	70 (58.3)

† Rivers and Streams: High >0.4958, Moderate 0.00000538 – 0.4958, Low 0

¥ Maximum contaminant level (MCL): 0.003 µg/L

Table 3: Descriptive Statistics of Agricultural Exposure Metrics in Kentucky, 2002 and 2007, (N=120 counties)

Characteristic	Mean (SD)
Acres of Corn Planted †	19.64 (36.01)
Bushels of Corn Planted ¥	2.29 (4.39)

† Acres of corn in thousands

¥ Bushels of Corn planted in millions

Table 4. Spearman Rank Correlation Coefficients of Atrazine Metrics for River and Stream Water Sources

Characteristic	Proportion above the LOD	Mean Concentration Level	Maximum Concentration Level	Acres of Corn	Bushels of Corn	NHL Cases
Proportion above the LOD	--	0.68969	0.54201	0.57532	0.55750	0.6509
Mean Concentration Level	0.68969	--	0.99217	0.32439	0.32246	0.00737
Maximum Concentration Level	0.54201	0.99217	--	0.28651	0.28536	0.00869
Acres of Corn	0.57532	0.32439	0.28651	--	0.99707	0.17236
Bushels of Corn	0.55750	0.32246	0.28536	0.99707	--	0.16549
NHL Cases	0.06509	0.00737	0.00869	0.17236	0.16549	--

***Values in red are not statistically significant (<.05)

Table 5. Spearman Rank Correlation Coefficients of Atrazine Metrics for Wells, Springs, and Municipal Water Sources

Characteristic	Proportion above the LOD	Mean Concentration Level	Maximum Concentration Level (Wells and Springs)	Maximum Concentration Level (Municipal)	Acres of Corn	Bushels of Corn	NHL Cases
Proportion above the LOD	--	0.92358	0.74174	0.60633	0.67068	0.65309	0.26840
Mean Concentration Level	0.92358	--	0.73352	0.72546	0.66458	0.65098	0.25396
Maximum Concentration Level (Wells and Springs)	0.74174	0.73352	--	0.23718	0.47192	0.46212	0.21724
Maximum Concentration Level (Municipal)	0.60633	0.72546	0.23718	--	0.51526	0.50253	0.16142
Acres of Corn	0.67068	0.66458	0.47192	0.51526	--	0.99707	0.17236
Bushels of Corn	0.65309	0.65098	0.46212	0.50253	0.99707	--	0.16549
NHL Cases	0.26840	0.25396	0.21724	0.16142	0.17236	0.16549	--

***Values in red are not statistically significant (<.05)

Table 6. Unadjusted Models of Atrazine Exposure Metrics and non-Hodgkin's Lymphoma

Characteristic	Unadjusted Estimate	P value	Unadjusted Rate Ratio	95% CI
Mean Concentration Level (µg/L)[†]				
High	0.09	0.19	1.10	0.95 -1.26
Moderate	0.01	0.79	1.01	0.92 -1.11
Low	--	--	--	--
% above the LOD	-0.00	0.39	1.00	1.00 - 1.00
Samples above MCL¥				
3	-0.02	0.80	0.98	0.86 - 1.12
2	0.07	0.20	1.07	0.97 - 1.18
1	0.05	0.36	1.05	0.95 - 1.16
0	--	--	--	--
Acres of Corn Planted*				
High	0.07	0.13	1.07	0.98 - 1.17
Moderate	0.08	0.10	1.08	0.99 -1.18
Low	--	--	--	--

†Rivers and Streams, Wells, Springs, and Municipal: High >0.50 , Moderate 0.00000269 – 0.5 , Low 0
¥ Maximum contaminant level (MCL): 0.003 µg/L
*Acres of Corn Planted: High >10,408, Moderate 1,656 – 10,408, Low <1,656

Table 7. Adjusted Model: Acres of Corn Planted

Characteristic	Estimate	Adjusted Rate Ratio	95% CI
Acres of Corn Planted *			
High	-0.04	0.96	0.88 - 1.06
Moderate	0.02	1.02	0.94 - 1.11
Low	--	--	--
Bachelor Degree or Higher	-0.00	01.00	0.99 - 1.00
Median Household Income	-6.01E-6	01.00	0.99 - 1.00
% Below the Poverty Level	-0.01	0.99	0.98 – 1.00
% Using Public Water Sources	0.00	1.00	0.99 - 1.00
% Male	0.01	1.01	0.98 - 1.04
12% or greater 65 and older			
Yes	0.16	1.17	1.07 - 1.28
No	--	--	--

* Acres of Corn Planted: High >10,408, Moderate 1,656 – 10,408, Low <1,656

Table 8. Adjusted Model: Mean Concentration Level

Characteristic	Estimate	Adjusted Rate Ratio	95% CI
Mean Concentration Level (μg/L)†			
High	-0.09	0.92	0.79 - 1.07
Moderate	-0.13	0.88	0.80 - 0.98
Low	--	--	--
Bachelor Degree or Higher	-0.00	1.00	0.99 - 1.00
Median Household Income	-3.84E-6	1.00	1.00 - 1.00
% Below the Poverty Level	-0.01	0.99	0.98 – 1.00
% Using Public Water Sources	0.00	1.00	1.00 - 1.01
% Male	0.01	1.01	0.98 - 1.04
12% or greater 65 and older			
Yes	0.18	1.19	1.09 - 1.30
No	--	--	--

†Rivers and Streams, Wells, Springs, and Municipal: High >0.50 , Moderate 0.00000269 – 0.5 , Low 0

Table 9. Adjusted Model: Percent of Samples above the Limit of Detection

Characteristic	Estimate	Adjusted Rate Ratio	95% CI
% of Samples above the LOD	-0.00	1.00	1.00 - 1.00
Bachelor Degree or Higher	-0.00	1.00	0.99 - 1.00
Median Household Income	-4.74E-6	1.00	1.00 - 1.00
% Below the Poverty Level	-0.01	0.99	0.98 – 1.00
% Using Public Water Sources	0.00	1.00	1.00 - 1.01
% Male	0.01	1.01	0.986 - 1.04
12% or greater 65 and older			
Yes	0.16	1.18	1.09 - 1.28
No	--	--	--

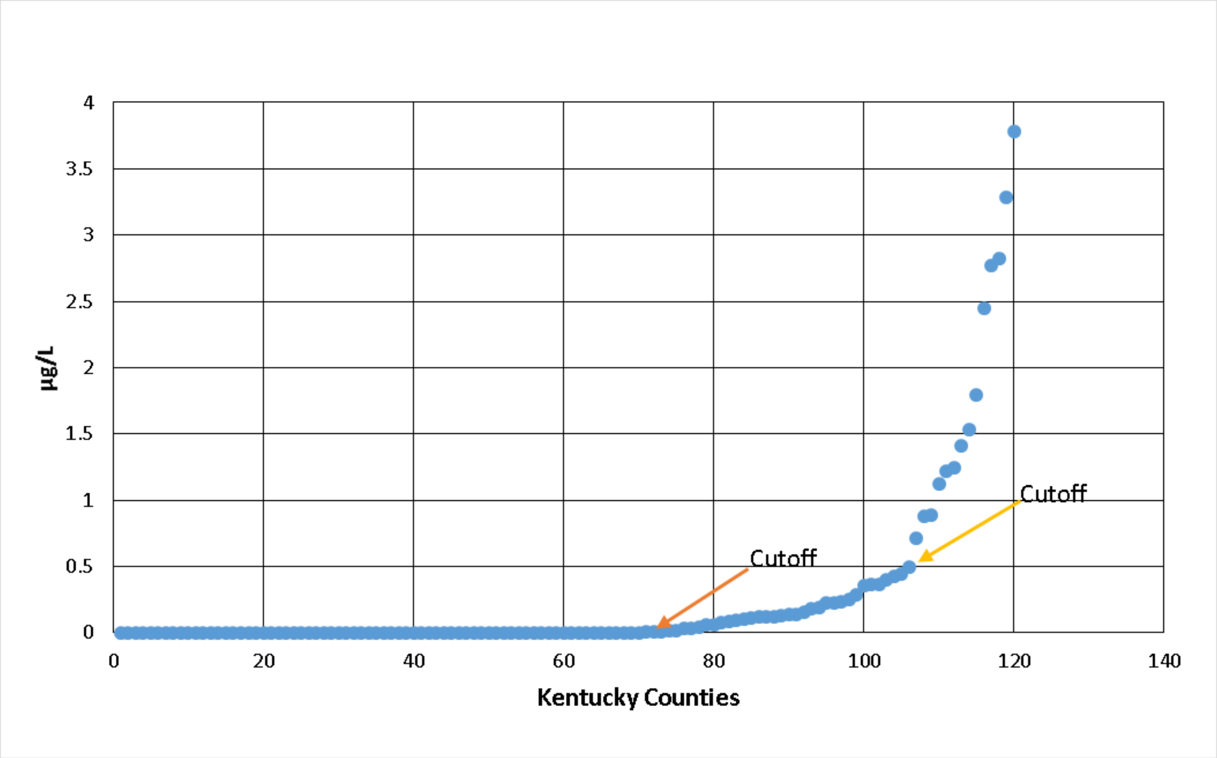
Table 10. Adjusted Model: Number of Samples above the Maximum Contaminant Level

Characteristic	Estimate	Adjusted Rate Ratio	95% CI
Samples above MCL¥			
3	-0.17	0.85	0.74 - 0.97
2	-0.12	0.89	0.79 - 1.00
1	-0.09	0.92	0.82 - 1.02
0	--	--	--
Bachelor Degree or Higher	-0.00	1.00	0.99 - 1.00
Median Household Income	-5.06E-6	1.00	1.00 - 1.00
% Below the Poverty Level	-0.02	0.99	0.97 – 1.00
% Using Public Water Sources	0.00	1.00	1.00 - 1.01
% Male	0.01	1.01	0.98 - 1.04
12% or greater 65 and older			
Yes	0.17	1.18	1.08 - 1.29
No	--	--	--

¥ Maximum contaminant level (MCL): 0.003 µg/L

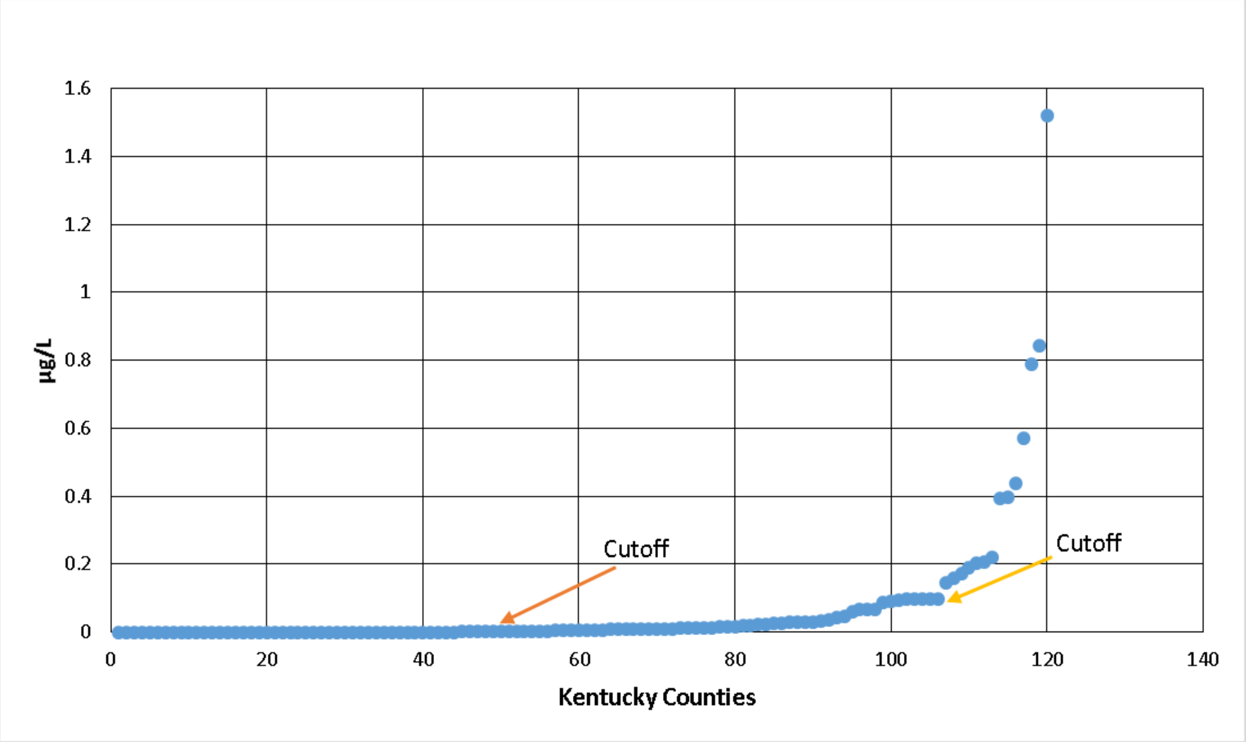
FIGURES

Figure 1. Plot of Mean Concentration Levels¥ for River and Stream Water Sources in Kentucky, 1998 – 2009



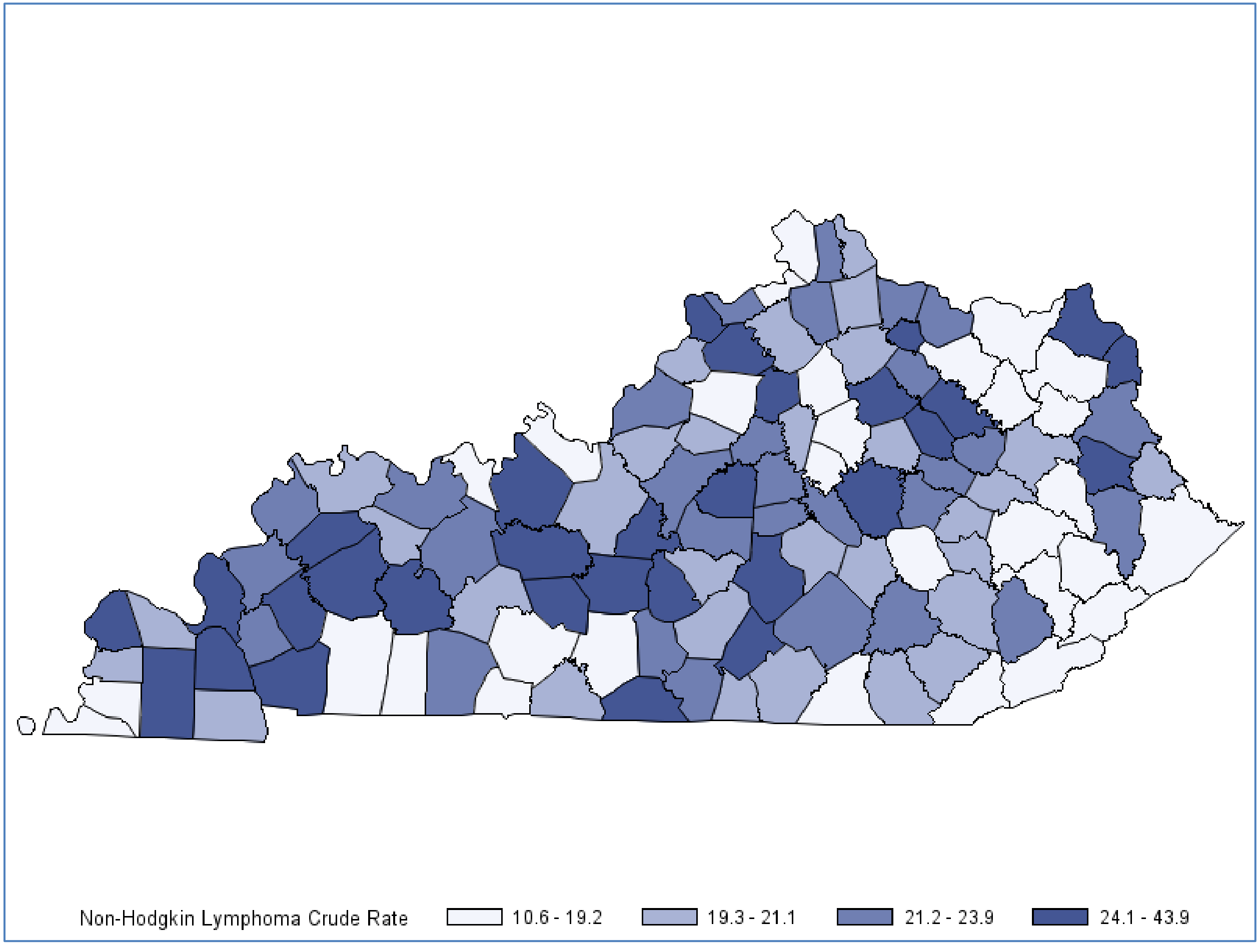
¥ Kentucky counties plotted from low to high mean concentration

Figure 2. Plot of Mean Concentration Levels[¥] for Wells, Springs, and Municipal Water Sources in Kentucky, 1998 – 2009



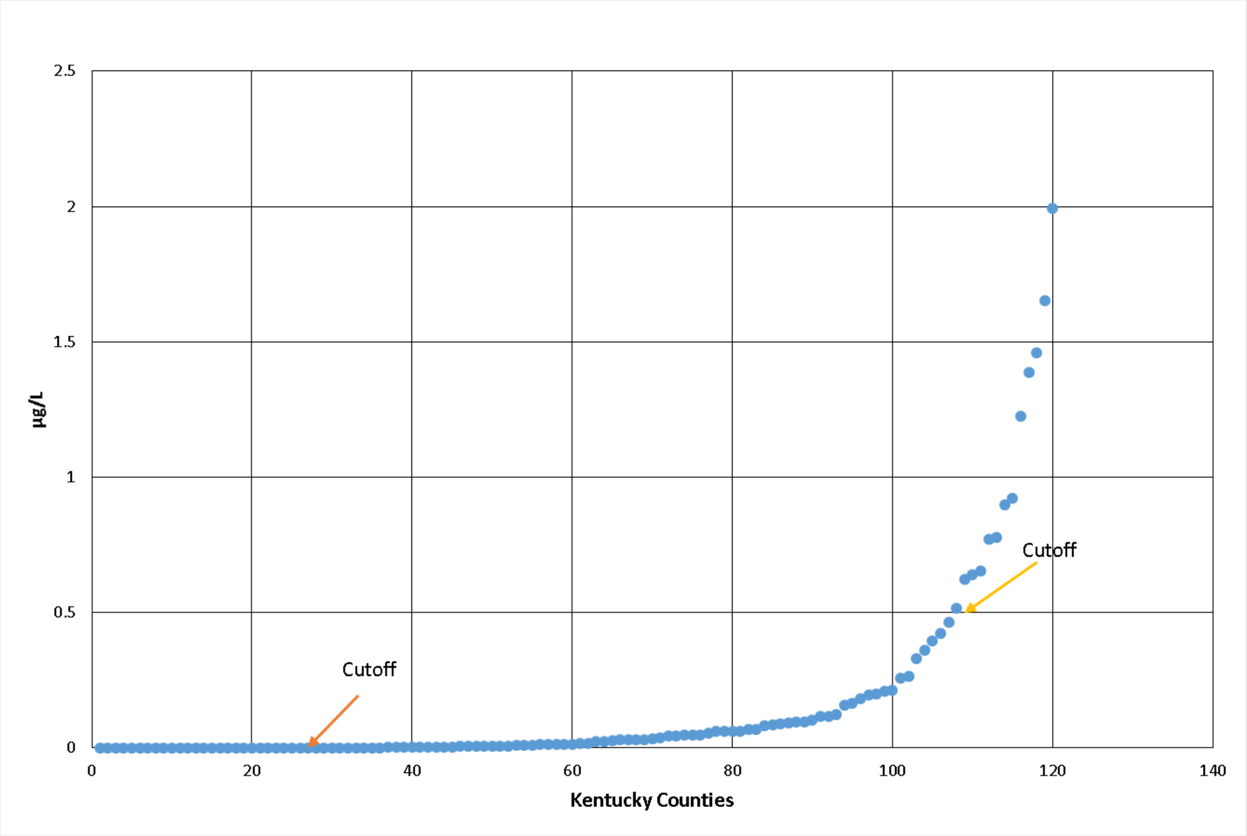
¥ Kentucky counties plotted from low to high mean concentration

Figure 3. Crude Rates[¥] of Non-Hodgkin Lymphoma in Kentucky, 1999 - 2010



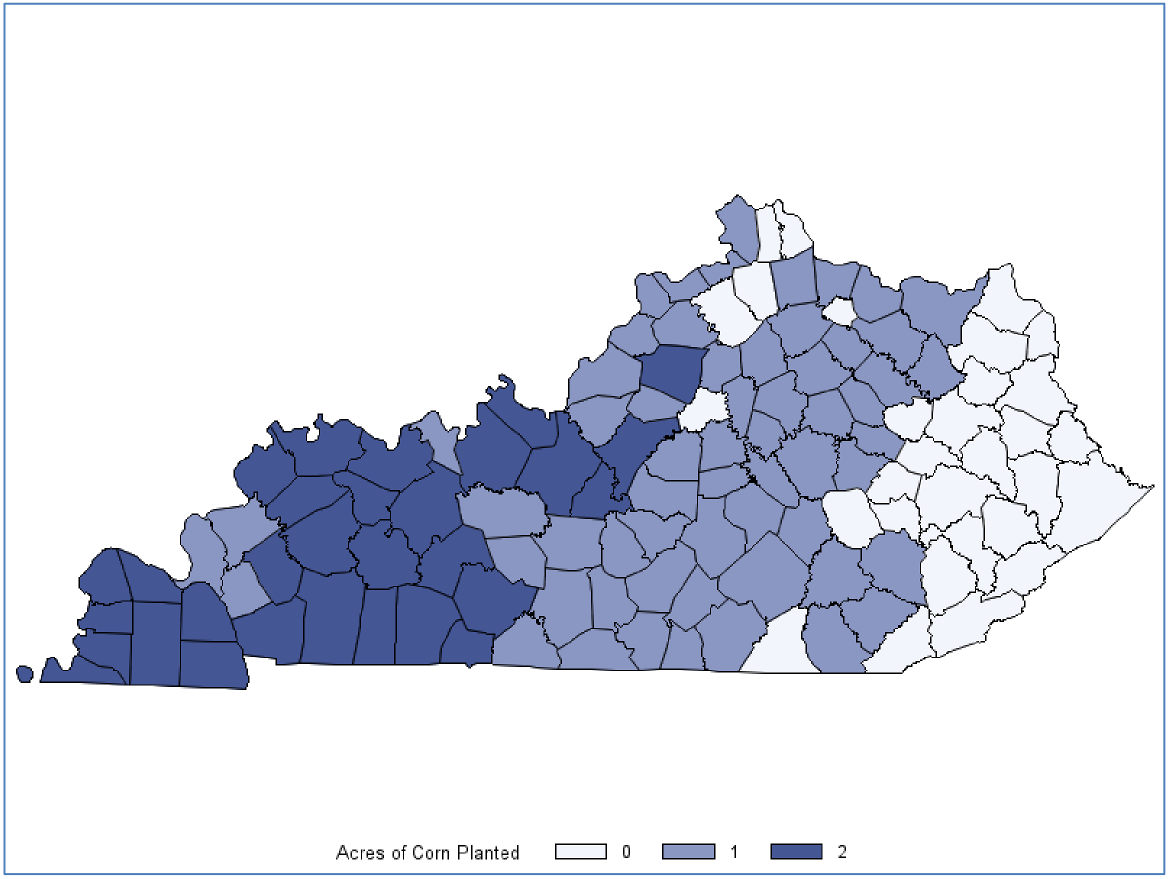
¥ Crude rates are per 100,000

Figure 4. Plot of Mean Concentration Levels¥for Rivers, Streams, Wells, Springs, and Municipal in Kentucky, 1998 – 2009



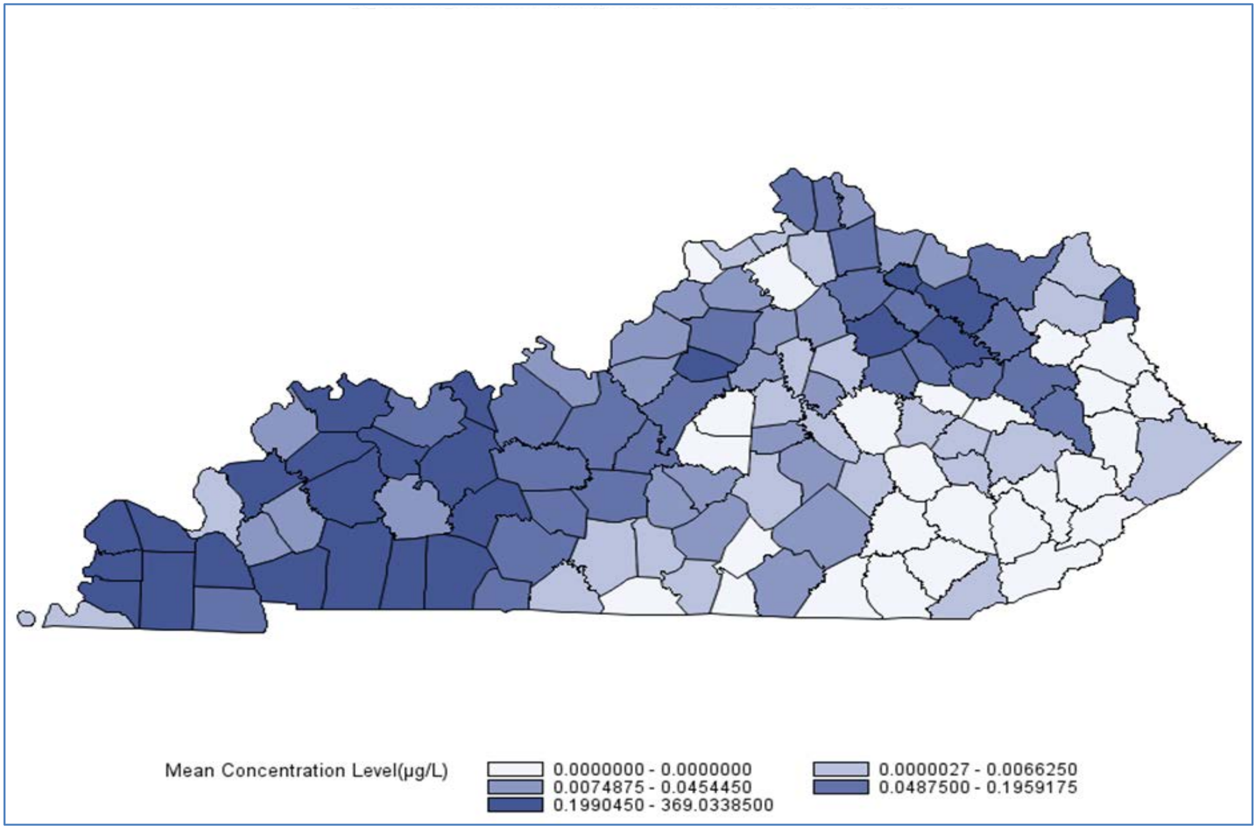
¥ Kentucky counties plotted from low to high mean concentration

Figure 5. Acres of Corn Planted[*] in Kentucky by Tertile: 2002 and 2007



* Acres of Corn Planted - 2: >10,408, 1: 1,656 – 10,408, 0: <1,656

Figure 6. Mean Concentration Levels of Atrazine in Kentucky, 1998 - 2009



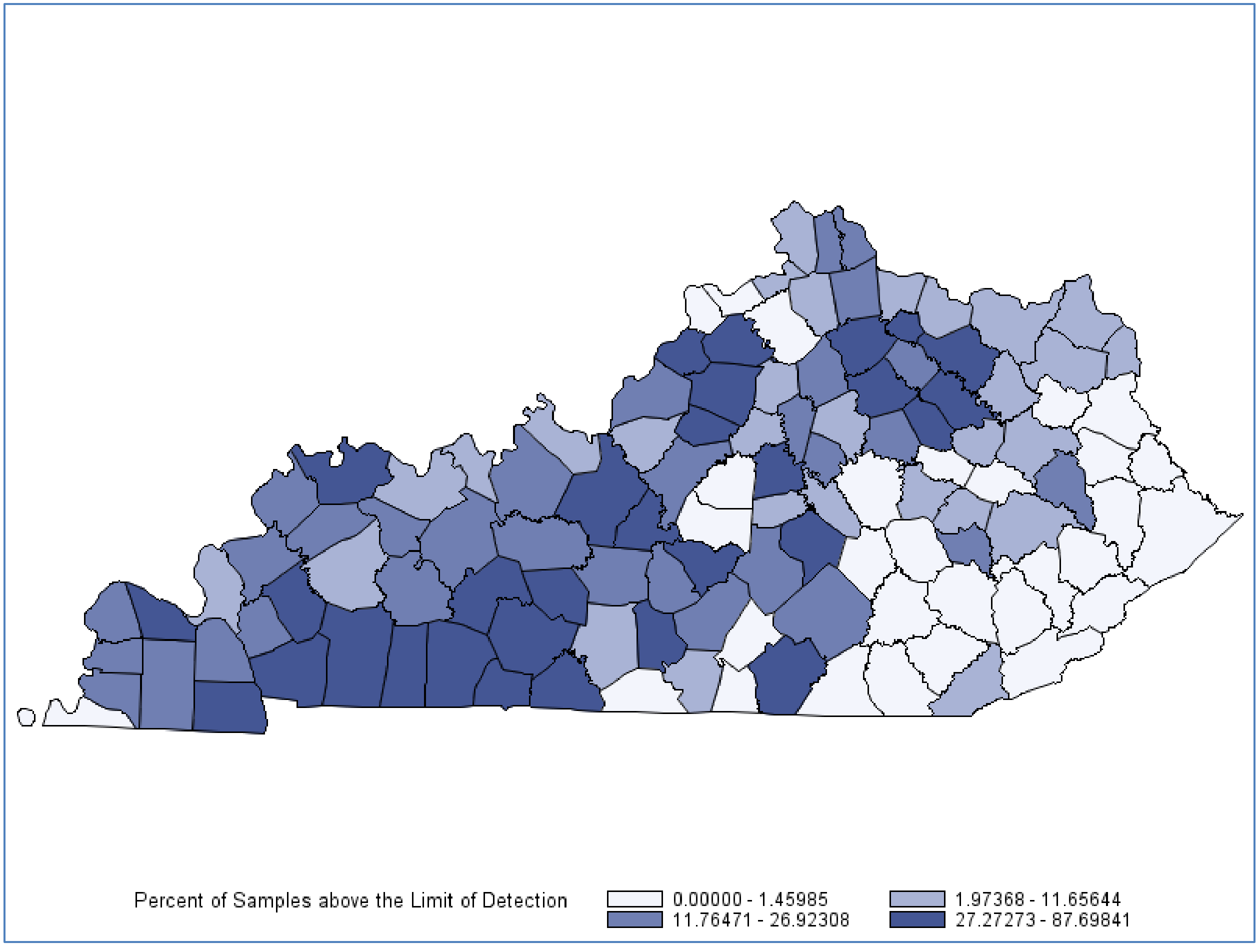
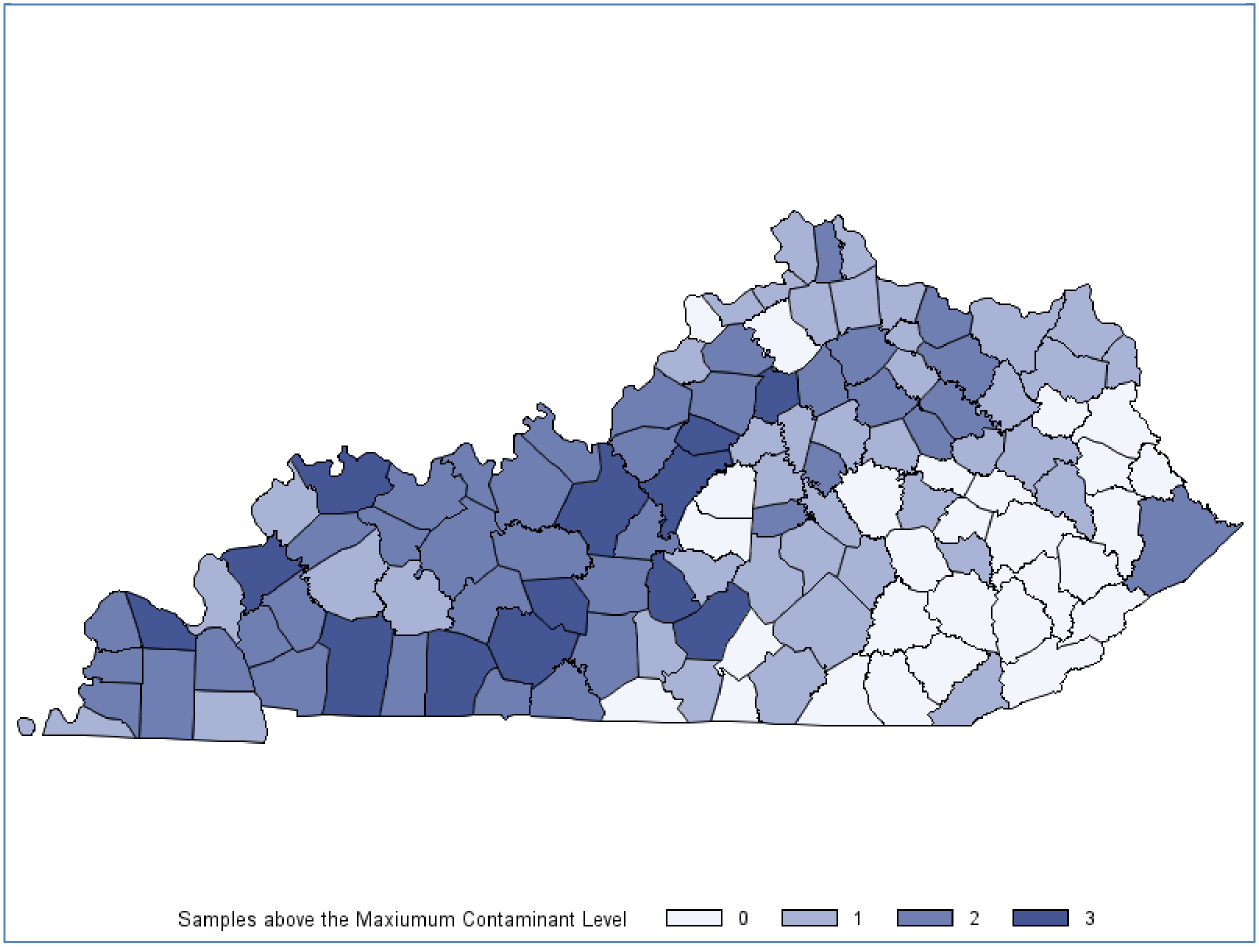


Figure 7. Percent of Sample above the Limit of Detection for Atrazine in Kentucky, 1998 – 2009

Figure 8. Number of Samples above the Maximum Contaminant Level¥ in Kentucky, 1998 - 2009



¥ Maximum contaminant level (MCL): 0.003 µg/L