Ecologic study of the effects of agricultural pesticides applications on the incidence of testicular germ cell tumors among men in the United States.

INTRODUCTION

Overview of TGCTs

- Human germ cell tumors (GCTs) are a heterogeneous group of neoplasms (1).
  - Most common group of cancers diagnosed in men between the ages of 15 and 44 years of age (2).
  - Typically classified into two histologic subtypes, seminomas and non-seminomas (1).
  - Considered as a prototypic malignancy of young adults (3).

1. Oosterhuis, J. W., & Looijenga, L. H. (2005).
2. 2. Znaor, A., Lortet-Tieulent, J., Jemal, A., & Bray, F. (2014).
3. 3. Hayes-Lattin, B., & Nichols, C. R. (2009).

Overview of TGCTs

- Arise from a precursor lesion called an intratubular germ cell neoplasia.
- Variations of TGCTs depend on the stage of differentiation and migration of germ cells at which the lesion occurs (3).
- Often associated with acquisition of excess genetic material from the short arm of chromosome 12 (3).

3. Hayes-Lattin, B., & Nichols, C. R. (2009).

Table 1. Estimated number of new testicular cancer cases and deaths by world area, 2008, for all ages (3).

Region	Male population size, in millions	Cases		Deaths	
		n	Age Standardized Rate	*n*	Age Standardized Rate
Africa	***492.1***	***1481***	***0.4***	***849***	***0.3***
Northern Africa	103.3	551	0.6	308	0.3
Eastern Africa	154.1	451	0.5	273	0.3
Middle Africa	60.7	66	0.2	37	0.1
Southern Africa	28	191	0.7	98	0.4
Western Africa	146	222	0.2	133	0.2
Americas	***454.8***	***16 845***	***3.5***	***1836***	***0.4***
Caribbean	20.6	154	0.7	52	0.2
Central America	73.7	2910	3.7	523	0.7
South America	190.3	4764	2.4	848	0.4
North America	170.2	9017	5.1	413	0.2
Asia	***2097.6***	***14 775***	***0.7***	***5525***	***0.3***
Eastern Asia	808.2	4182	0.5	817	0.1
Southeast Asia	286.4	2166	0.8	945	0.3
South-Central Asia	888.2	6661	0.8	3032	0.4
Western Asia	114.8	1766	1.5	731	0.6
Europe	***352.5***	***18 326***	***4.8***	***1627***	***0.4***
Central and Eastern Europe	137.7	4199	2.6	942	0.6
Northern Europe	48	3365	6.7	130	0.2
Southern Europe	75	3363	4.2	260	0.3
Western Europe	91.9	7399	7.8	295	0.2
Oceania	***17.5***	***895***	***4.9***	***37***	***0.2***
Australia/New Zealand	12.6	868	6.7	27	0.2
Melanesia	4.3	19	0.6	10	0.4
Micronesia/Polynesia	0.6	8	1.2	0	0
World	***3414.6***	***52 322***	***1.5***	***9874***	***0.3***

TGCTs Risk Factors

- Pre-existing medical conditions: cryptorchidism, inguinal hernias, testicular atrophy and family history of TGCTs (5).
- Perinatal risk factors: Increased maternal age, increased maternal weight, decreased parity, increased socioeconomic status and maternal smoking (7).
- Current etiology hypothesis: TGCTs are initiated during the fetal period
  - They could be susceptible to endocrine disrupting chemicals, which can affect proper development of the fetus (16).

5. Moller, H., Prener, A., & Skakkebaek, N. E. (1996).
7. McGlynn, K. A., Devesa, S. S., Graubard, B. I., & Castle, P. E. (2005).

Pesticide Use in the United States

- Common group of endocrine disrupting chemicals (17).
- Intended for the prevention, control or destruction of unwanted plants, vectors or animals during the production, transportation and storage of food (17).
- Examining the association between pesticide use and testicular germ cell tumor rates could provide additional information on the etiology of the disease (19-22).

17. Sengupta, P., & Banerjee, R. (2014).
19. Beranger, R., Le Cornet, C., Schuz, J., & Fervers, B. (2013).
20. Beranger, R., Perol, O., Bujan, L., Faure, E., Blain, J., Le Cornet, C., et al. (2014).
21. Frost, G., Brown, T., & Harding, A. H. (2011).
22. Enangue Njembele, A. N., Bailey, J. L., & Tremblay, J. J. (2014).

Study Objectives

- In this analysis, we used administrative cancer incidence (SEER, CDC Wonder) and pesticides application (U.S. Geological Survey System (USGS)) data to conduct an ecological study:
  - First, we used the CDC Wonder data to confirm racial and ethnic differences in TGCT incidence rates in the entire U.S. population (23)
  - Second, we used the CDC Wonder data in combination with the USGS data to determine if agricultural pesticides were associated with increased incidence of TGCTs.
  - We hypothesized that states with higher quantities of agricultural pesticide use would have higher incidence of TGCTs.

23. Markel, T. A., Proctor, C., Ying, J., & Winchester, P. D. (2014).

Materials and Methods

TGCT Incidence Data

- Publicly available through the Wide-ranging OnLine Data for Epidemiologic Research (WONDER) database (13).
- Obtained two population based age-adjusted TGCT incidence datasets from the CDC WONDER database.
  - The first CDC WONDER dataset was stratified by State, Year and Race, and was used to examine TGCT incidence trends for each race between 1999 and 2011.
  - The second CDC WONDER dataset included the overall TGCT incidence from 1999 to 2011 and was stratified by state and race only.
  - Incidence rates were calculated for each racial/ethnic group and graphed with Microsoft Excel 2013. We used the graphs for a qualitative analysis of differences among the different racial and ethnic groups (12).

12. Poynter, J. N., Amatruda, J. F., & Ross, J. A. (2010).
13. Siegel, R. L., Devesa, S. S., Cokkinides, V., Ma, J., & Jemal, A. (2013).

Agricultural pesticide use Data

- Annual county level pesticide use applied to agricultural crops in the United States from 1992 to 2009 called estimated Pesticide Use (EPest).
  - If use of a pesticide on a crop was not reported in a surveyed CRD, the EPest-low estimate treated the value as zero, whereas the EPest-high used rates from neighboring CRDs and in some cases, CRDs in the same USDA farm resource, to calculate the pesticide rate for the CRD (18).
- For this study, we included the five most commonly used agricultural pesticides, based on 2007 EPA estimates (25).
  - With the exception of Acetochlor and Metalochlor-S, annual estimates are available for 1992 through 2009. Acetochlor estimates were available beginning in 1994, when it was first registered for use, and S-metolachlor estimates became available in 1997 (18).

18. Thelin, G.P., and Stone, W.W., 2013.
25. Fishel, F. (2014).

Incidence Trends

- We used linear regression to examine trends in cancer incidence and pesticides among States.
  - We plotted age adjusted incidence rates by race from 1999 to 2011, and average quantities of pesticides used by state from 1992 to 2009

25. Fishel, F. (2014).

Spatial Mapping by State

- We constructed Maps for overall and race/ethnic specific TGCT incidence rates by state.

- We also constructed Maps for the distribution of the average quantity for the high and low estimates of each pesticide used.

- All Maps were constructed using ArcMAP GIS software version 10.2.

25. Fishel, F. (2014).

Ecologic Analysis

- The primary outcome measure of the study was the age adjusted incidence rate of TGCT.
  - Pearson correlation coefficients were computed for each race/ethnicity as a measure of a linear relationship between state specific TGCT incidence rates and the estimated quantity of pesticides used for the top 5 agricultural pesticides identified by the EPA.
  - Additionally, a linear model was used to assess the association between the age-adjusted incidence rates of TGCTs and the average quantities of agricultural pesticides used within each state.
  - A generalized Estimating Equation (GEE) method was used to account for within state correlation of average pesticide use, and the model also adjusted for race and ethnicity of the cases (23).
  - Average and Total Pesticide use was evaluated as a continuous variable, and then categorized into low level (25^{th} percentile), moderate level (Between the 25^{th} and 75^{th} percentile) and High Level (75^{th} percentile) for each State (23).

23. Markel, T. A., Proctor, C., Ying, J., & Winchester, P. D. (2014).

Results

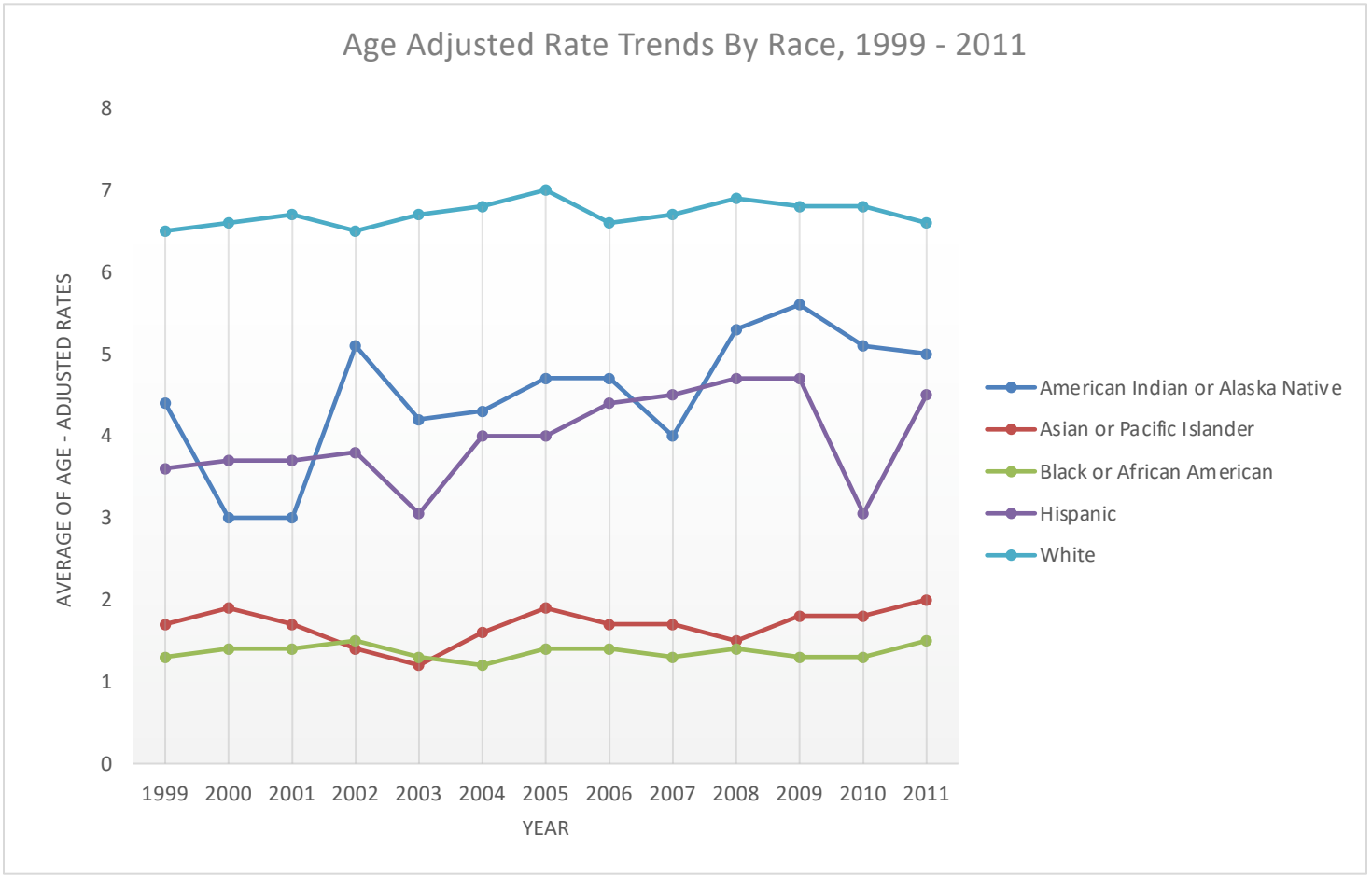
Incidence Trends

Table 2. Change in Incidence Rate trends for Testicular Cancer, 1999-2011 (CDC Wonder)

	American Indian or Alaska Native	Asian or Pacific Islander	Black or African American	Hispanic	White
Estimate	*	0.037	0.007	0.105	0.021
p-value	*	0.58	0.679	<.0001	0.111

*Unable to report due to low cases count and data restrictions

Figure 1. Age adjusted incidence trends of testicular cancer, by race, 1999 – 2011 (CDC Wonder)



Results

Incidence Maps

Figure 2. Choropleth map of age adjusted TGCT incidence rates (per 100,000) among all men of all ages, by state, 1999 – 2011 (CDC Wonder)

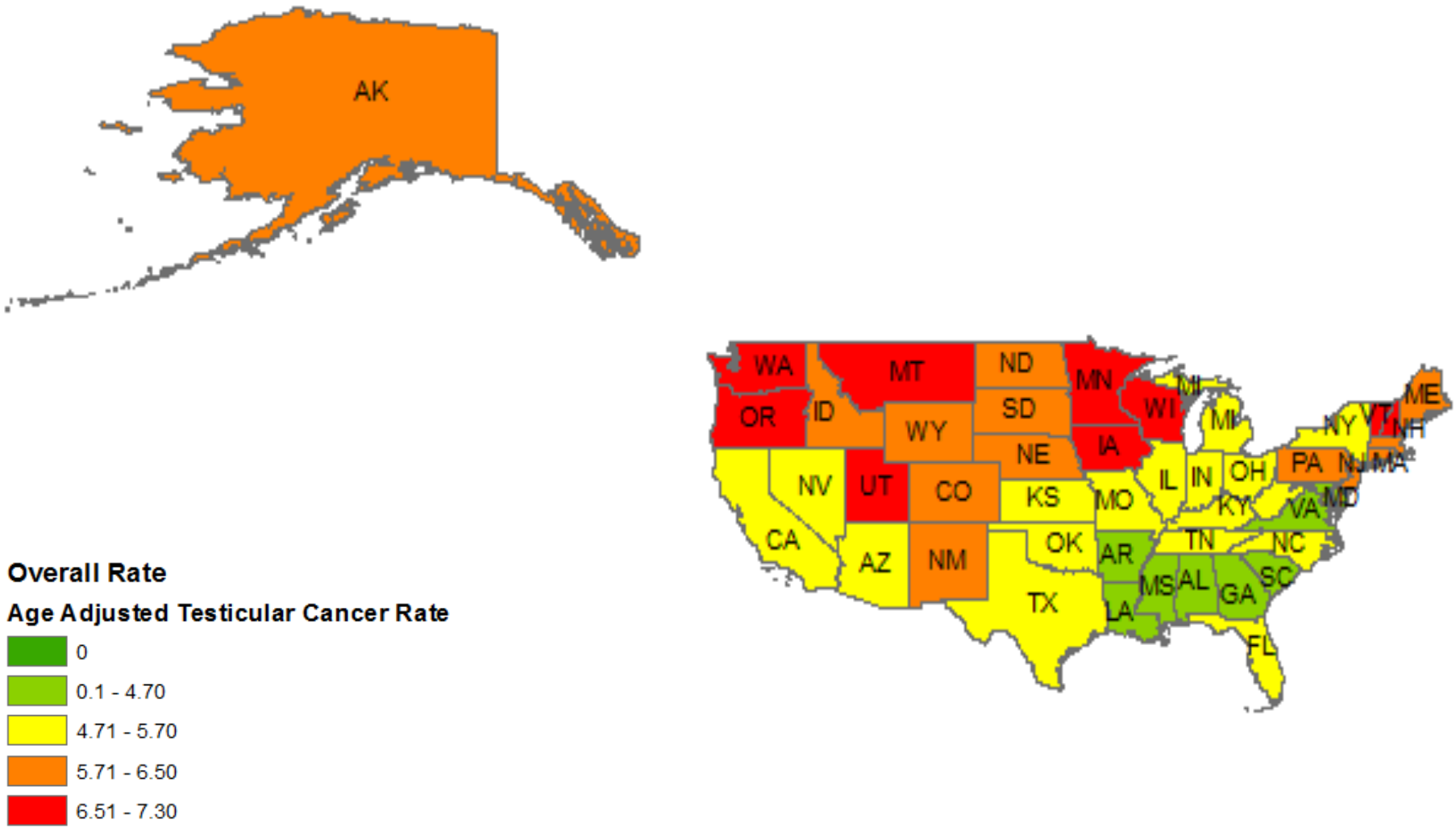


Figure 3. Choropleth map of age adjusted TGCT incidence rates (per 100,000) among American Indian and Alaska Native men, by state, 1999 – 2011 (CDC Wonder)

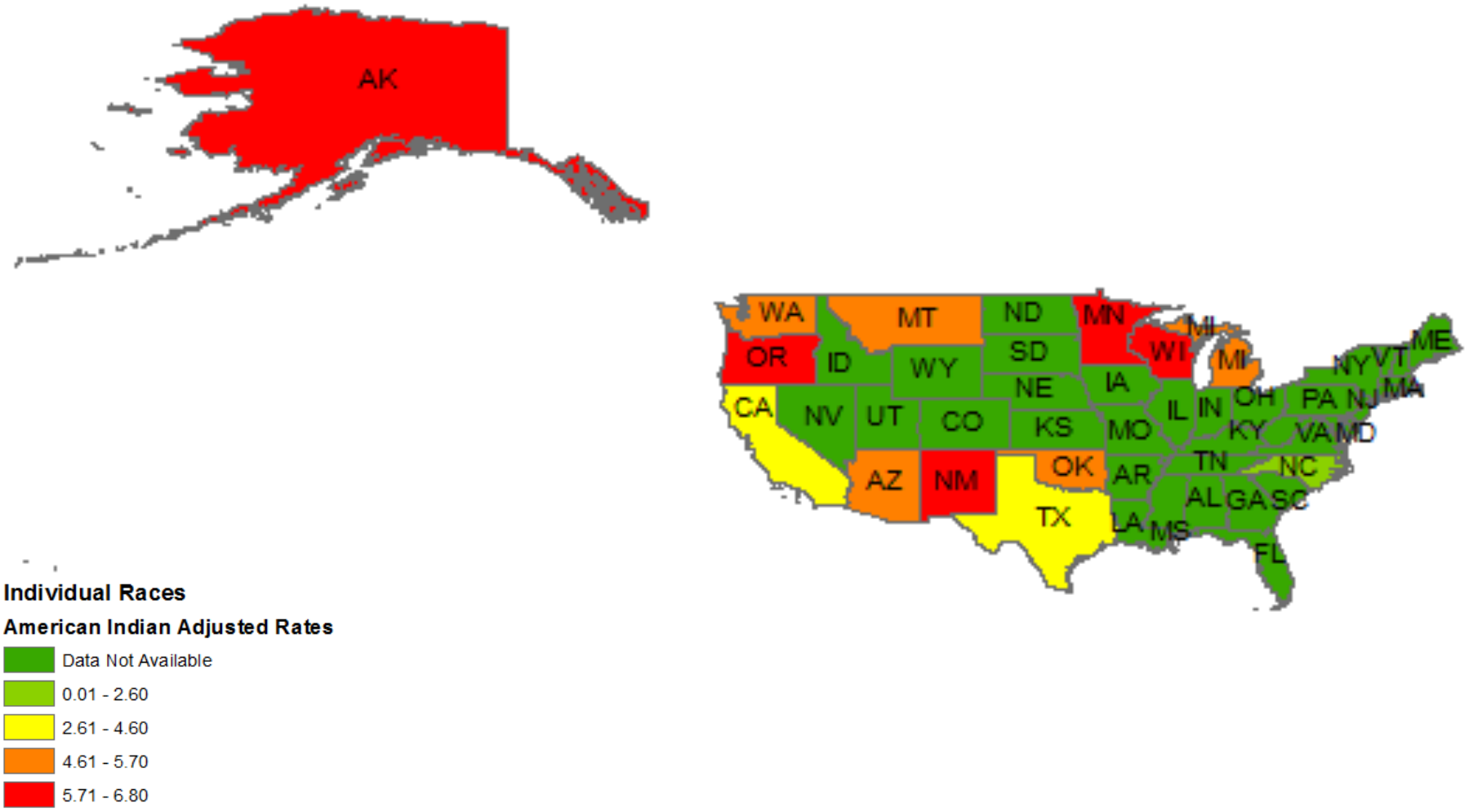


Figure 4. Choropleth map of age adjusted TGCT incidence rates (per 100,000) among Asian or Pacific Islander men, by state, 1999 – 2011 (CDC Wonder)

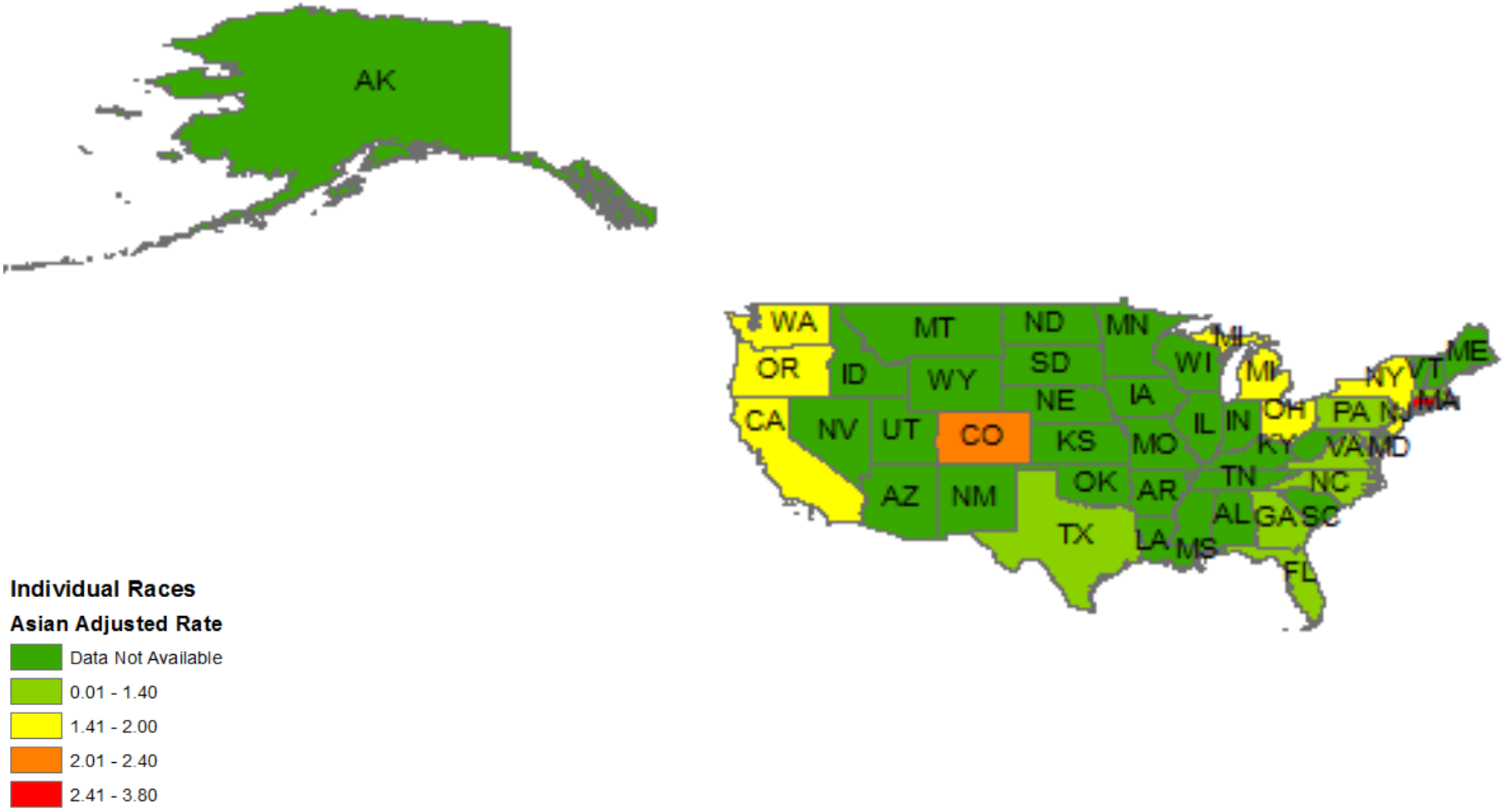
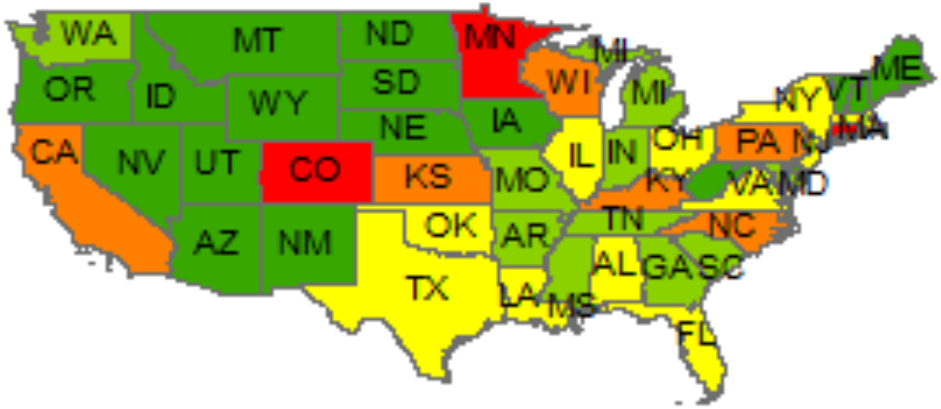


Figure 5. Choropleth map of age adjusted TGCT incidence rates (per 100,000) among Black and African American men, by state, 1999 – 2011 (CDC Wonder)



Individual Races

African American Adjusted Rate

- Data Not Available
- 0.01 - 1.20
- 1.21 - 1.50
- 1.51 - 1.80
- 1.81 - 2.20

Figure 6. Choropleth map of age adjusted TGCT incidence rates (per 100,000) among Hispanic men, by state, 1999 – 2011 (CDC Wonder)

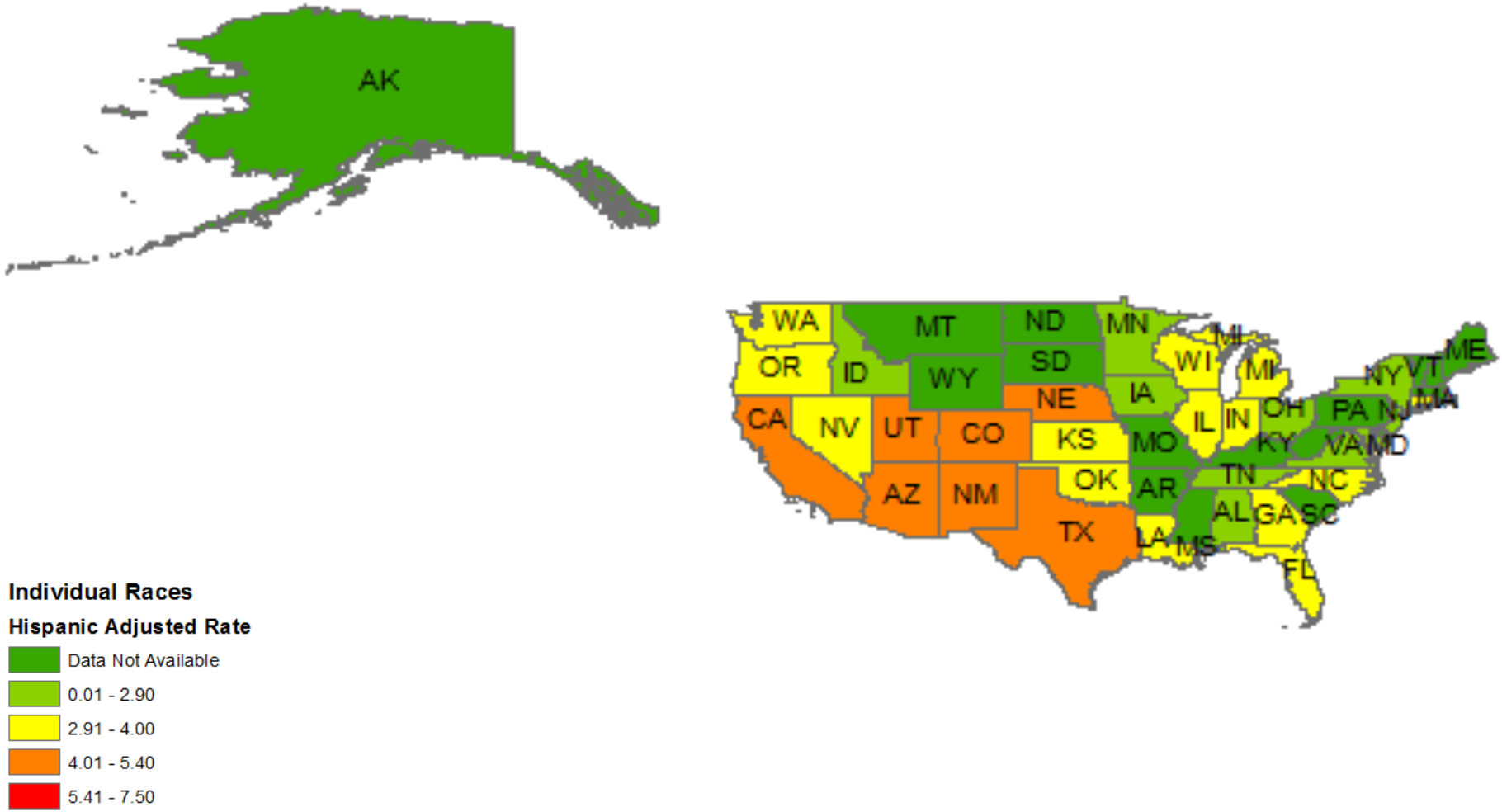
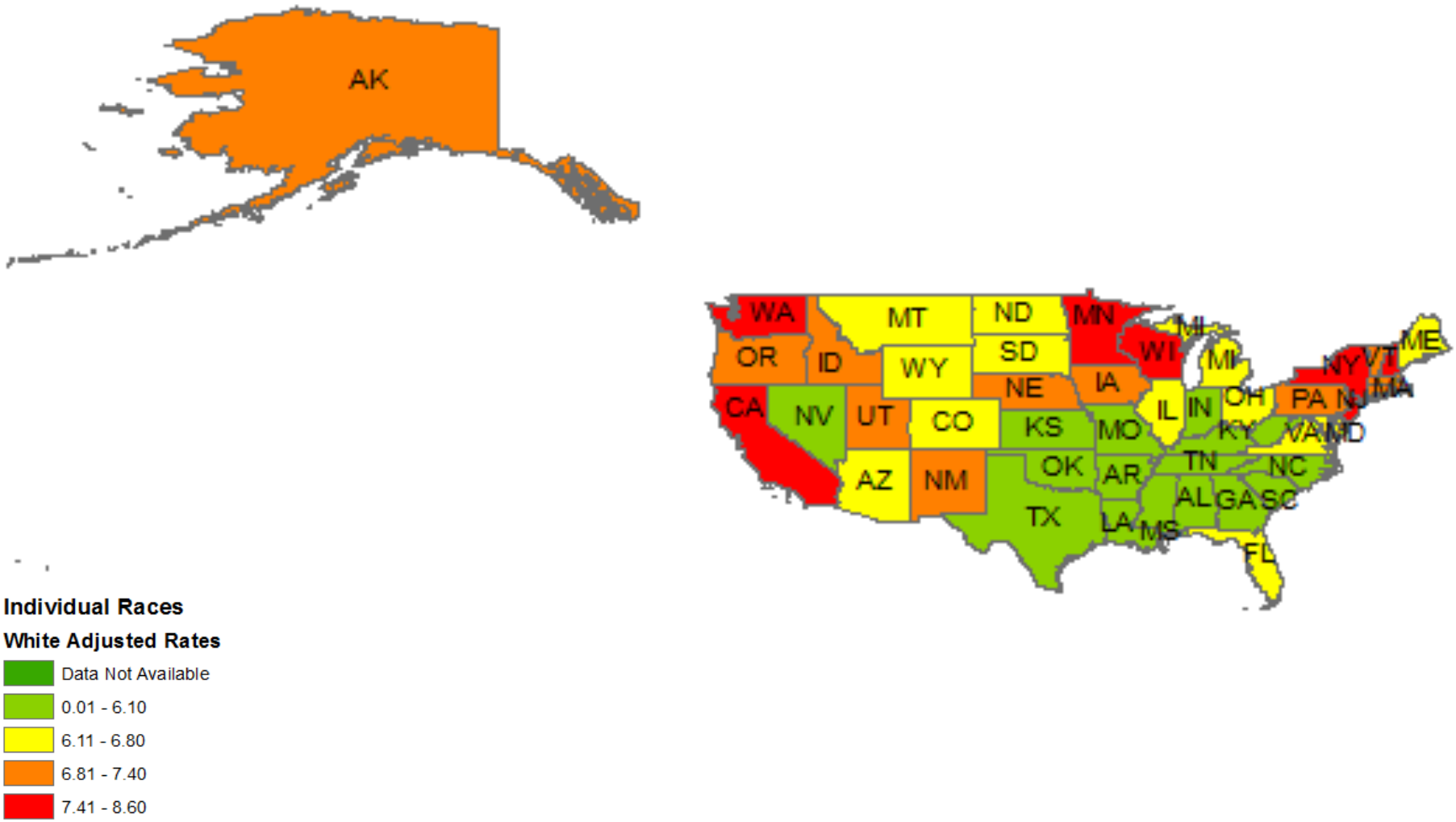


Figure 7. Choropleth map of age adjusted TGCT incidence rates (per 100,000) among White men, by state, 1999 – 2011 (CDC Wonder)



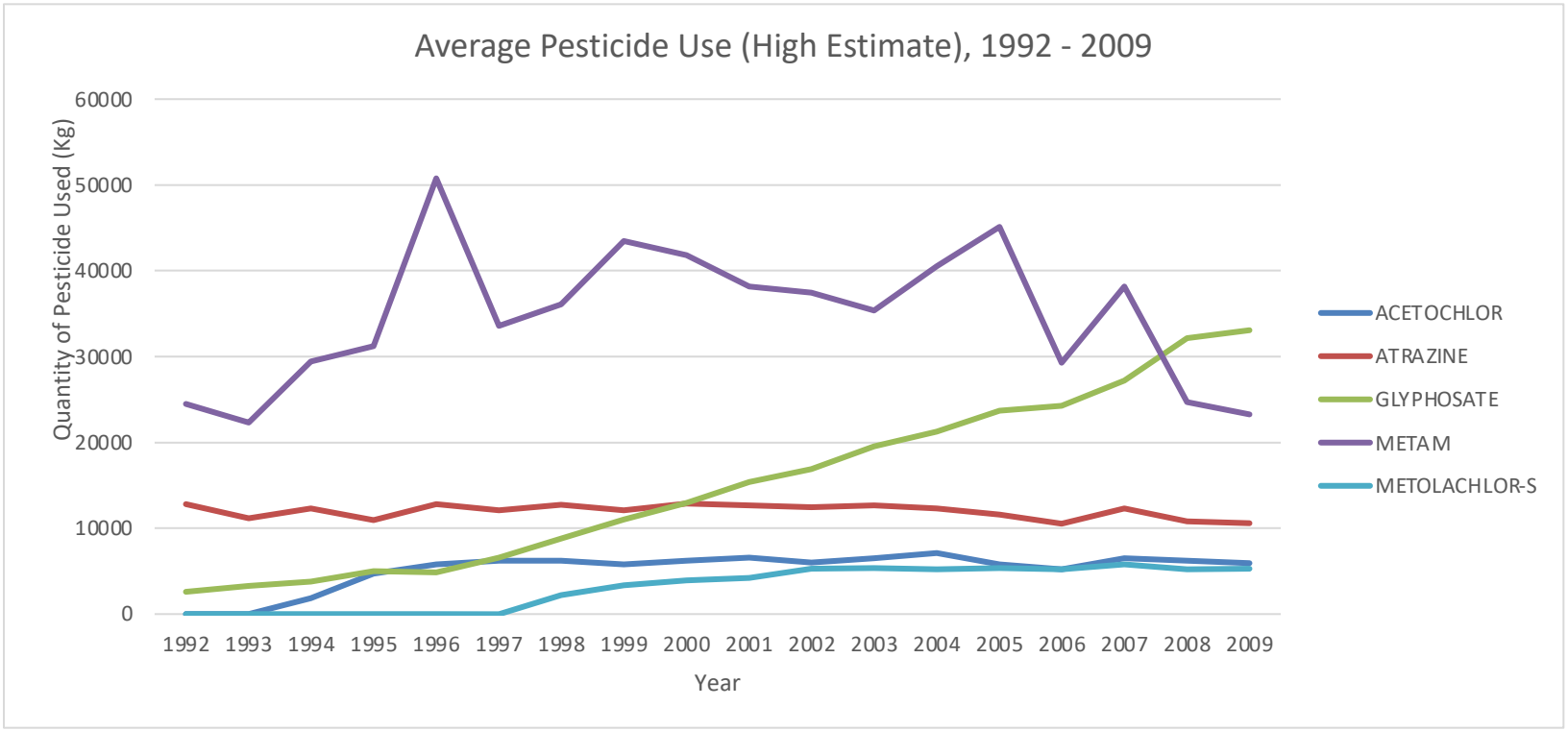
Results

Pesticide Trends

Table 3. Trend in Annual Average Pesticide Quantities (in Kg) used for the top 5 Pesticides in the U.S. (1992-2009)

	Atrazine	Acetochlor	Glyphosate	Metam	Metalochlor
High Pesticide Estimate	-78.571	91.8336	1872.053	79.3611	253.5587
p-value	<.0001	<.0001	<.0001	0.7381	<.0001
Low Pesticide Estimate	-71.2247	119.3176	1914.88	190.9958	244.0819
p-value	<.0001	<.0001	<.0001	0.6325	<.0001

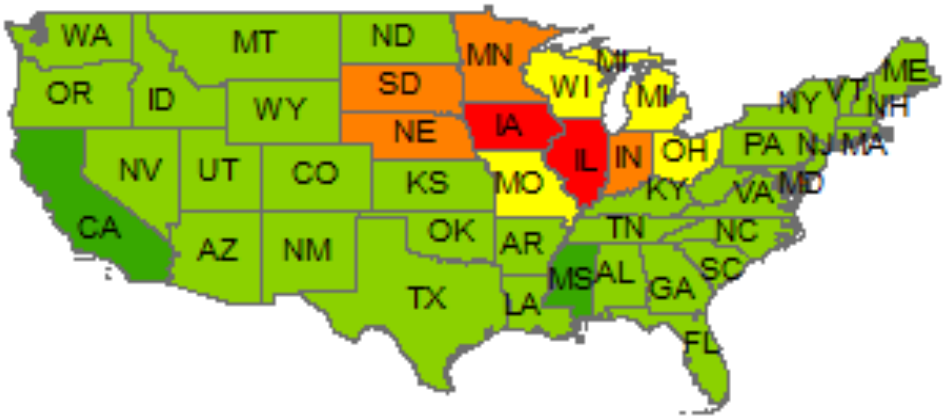
Figure 8. Trends of Annual Average Quantity (in Kg) of Pesticides Used 1992 – 2009 based on EPest High values (USGS)



Results

Pesticide Maps

Figure 10. Cloropleth map of average Acetochlor use (EPest High value), by state, 1992 – 2009 (USGS)



High Pesticide Exposure

Acetochlor

- 0.00
- 0.01 - 3704.65
- 3704.66 - 8839.44
- 8839.45 - 17892.10
- 17892.11 - 29775.80

Figure 11. Choropleth map of average Atrazine use (EPest High value), by state, 1992 – 2009 (USGS)

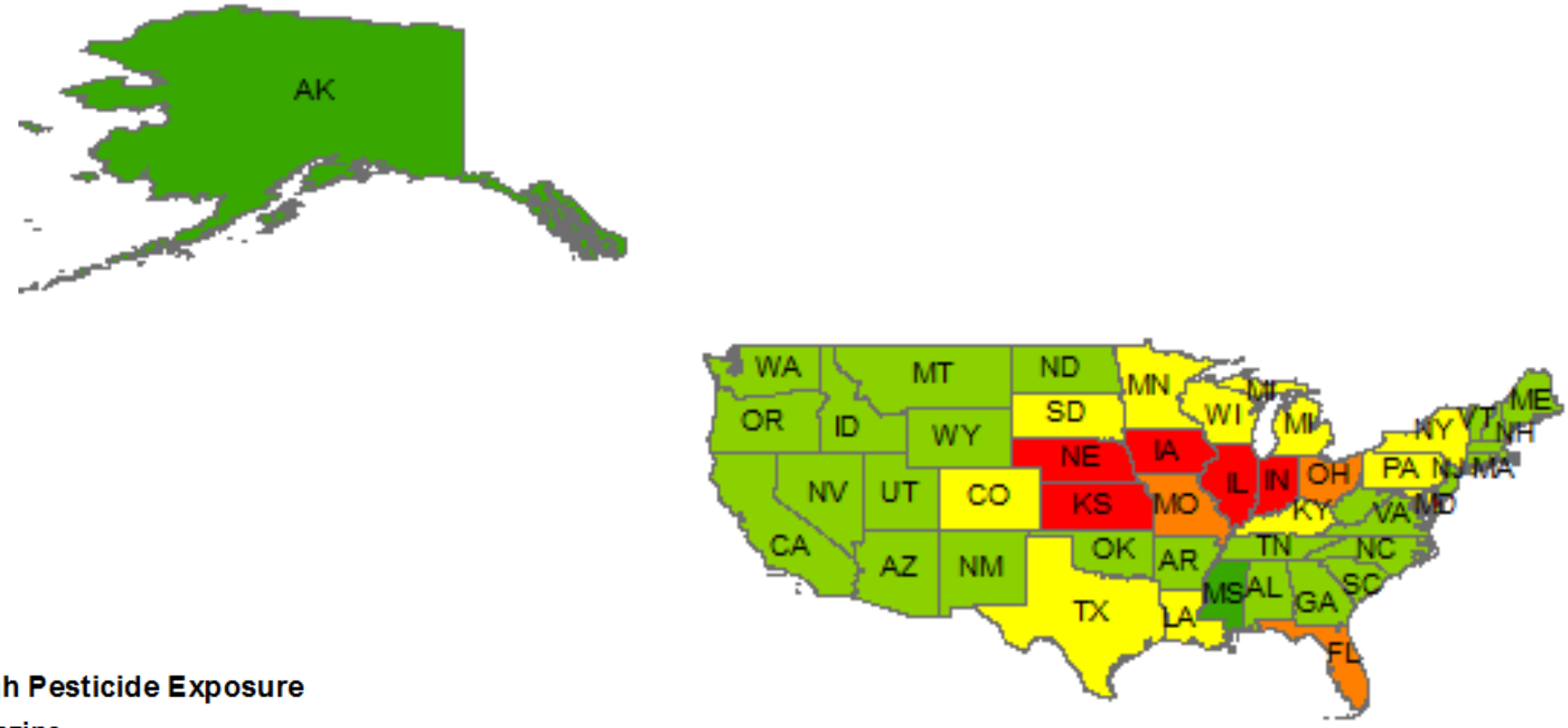
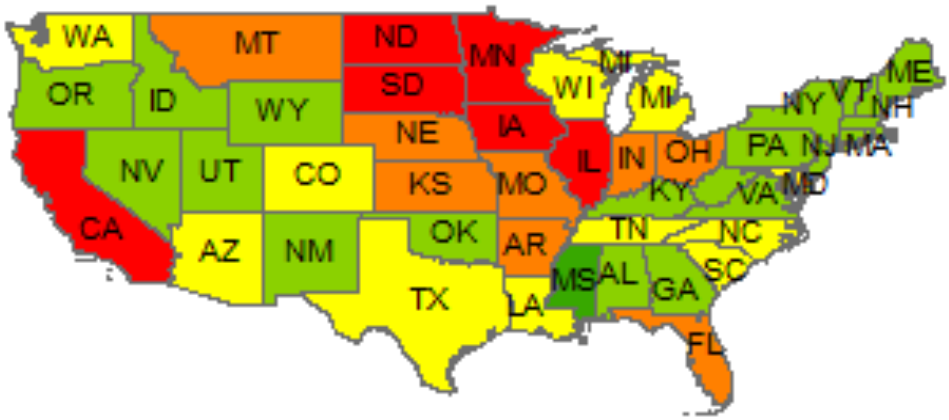


Figure 12. Choropleth map of average Glyphosate use (EPest High value), by state, 1992 – 2009 (USGS)



High Pesticide Exposure

Glyphosate

- 0.00
- 0.01 - 6912.39
- 6912.40 - 15768.40
- 15768.41 - 27164.75
- 27164.76 - 38205.38

Figure 13. Choropleth map of average Metam use (EPest High value), by state, 1992 – 2009 (USGS)

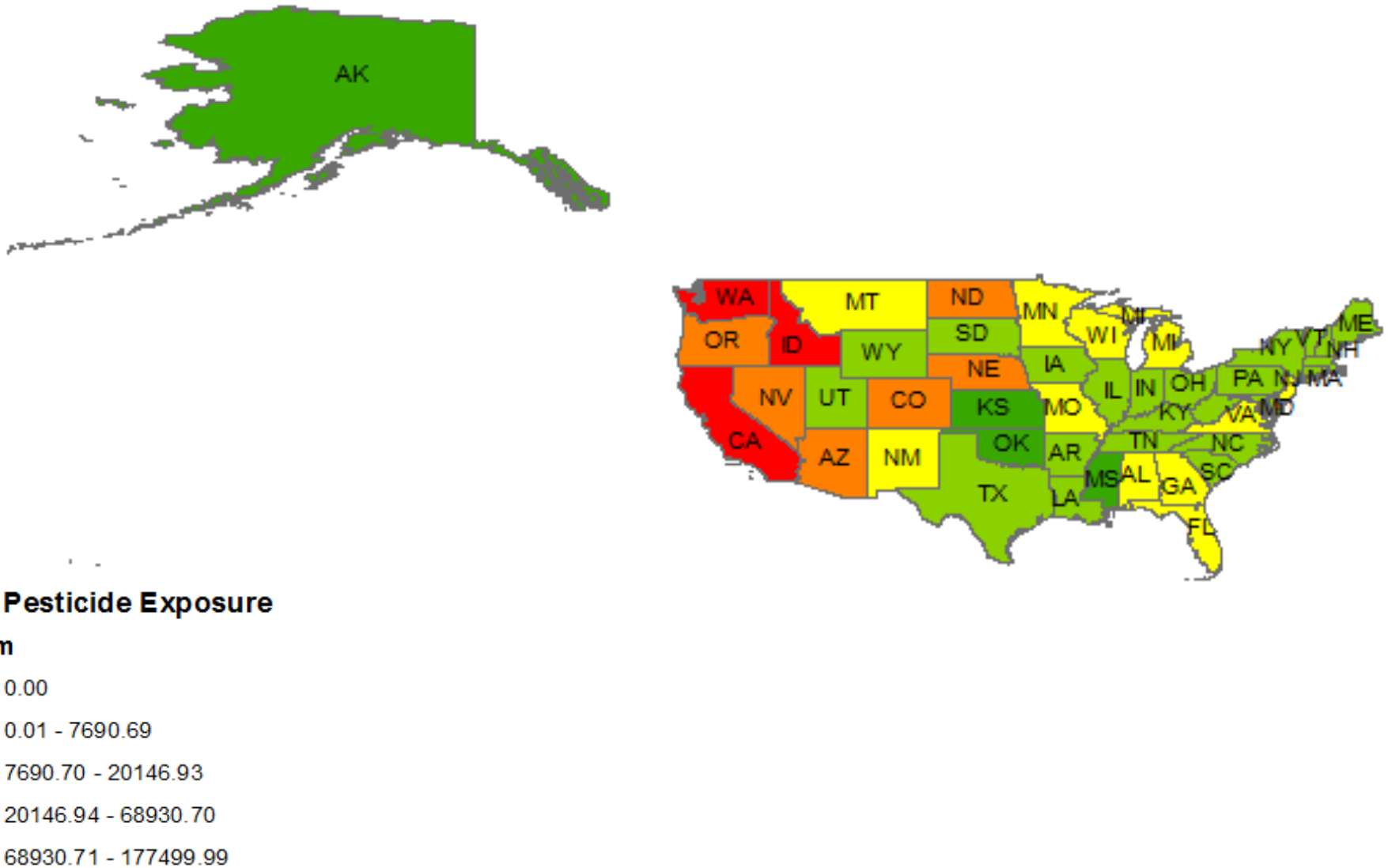
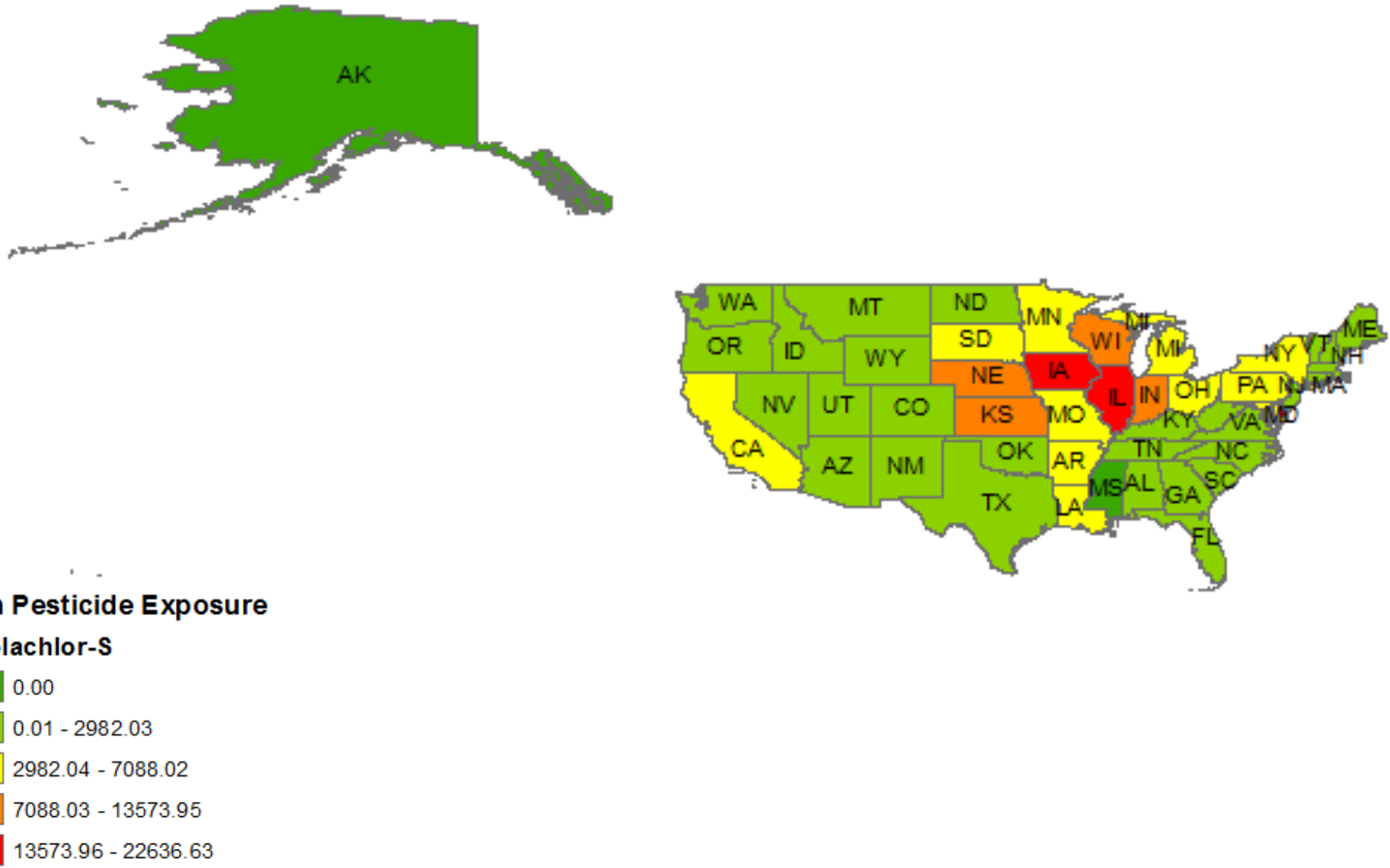


Figure 14. Choropleth map of average Metolachlor use (EPest High value), by state, 1992 – 2009 (USGS)



Results

Association of testicular germ cell tumors with pesticide use

Figure 15. Correlation between Average Atrazine use (in Kg) from 1992 to 2009 and TGCT incidence the United States from 1999 to 2011 among White Non-Hispanic Men.

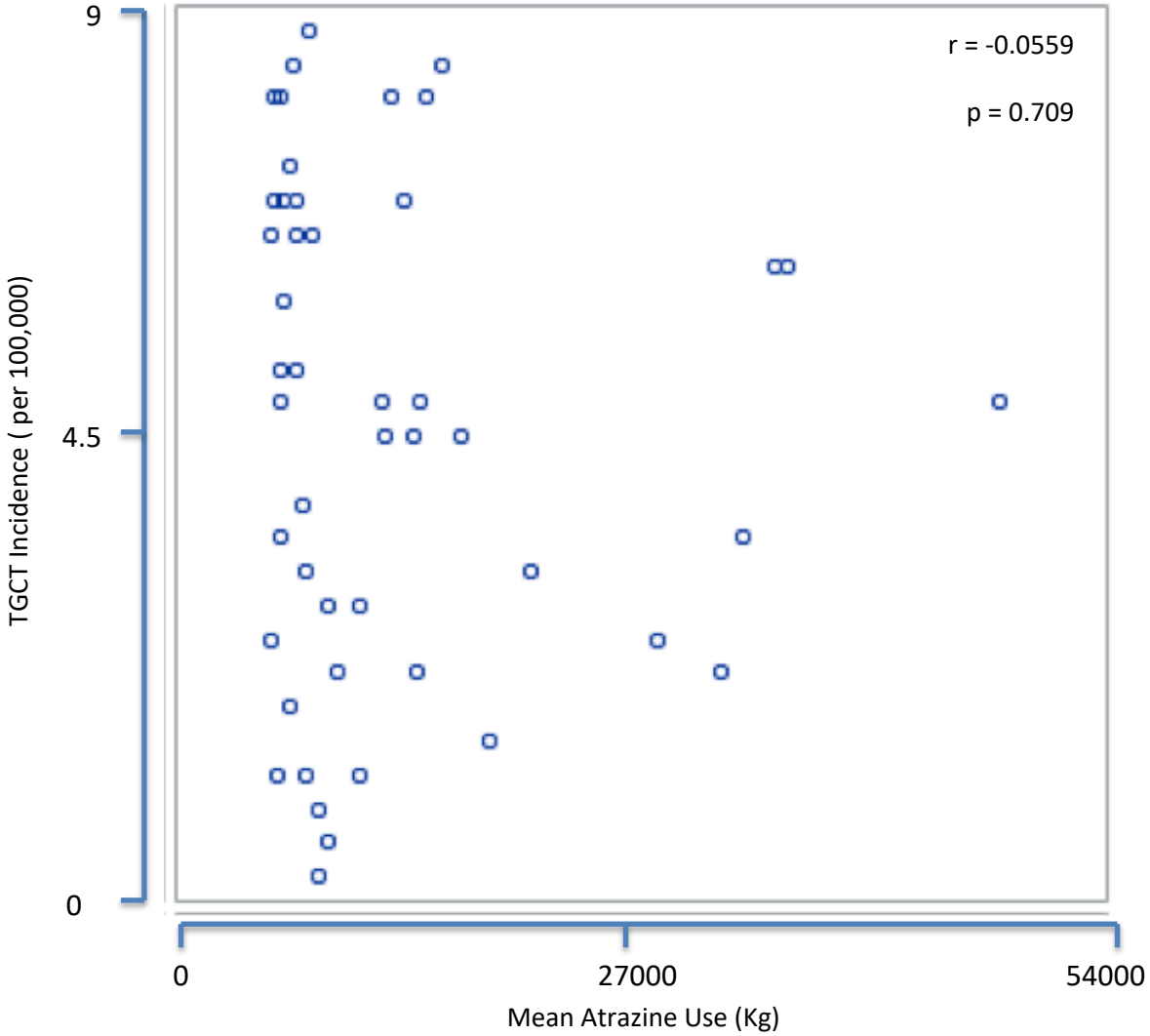


Figure 16. Correlation between Average Acetochlor use (in Kg) from 1992 to 2009 and TGCT incidence the United States from 1999 to 2011 among White Non-Hispanic Men.

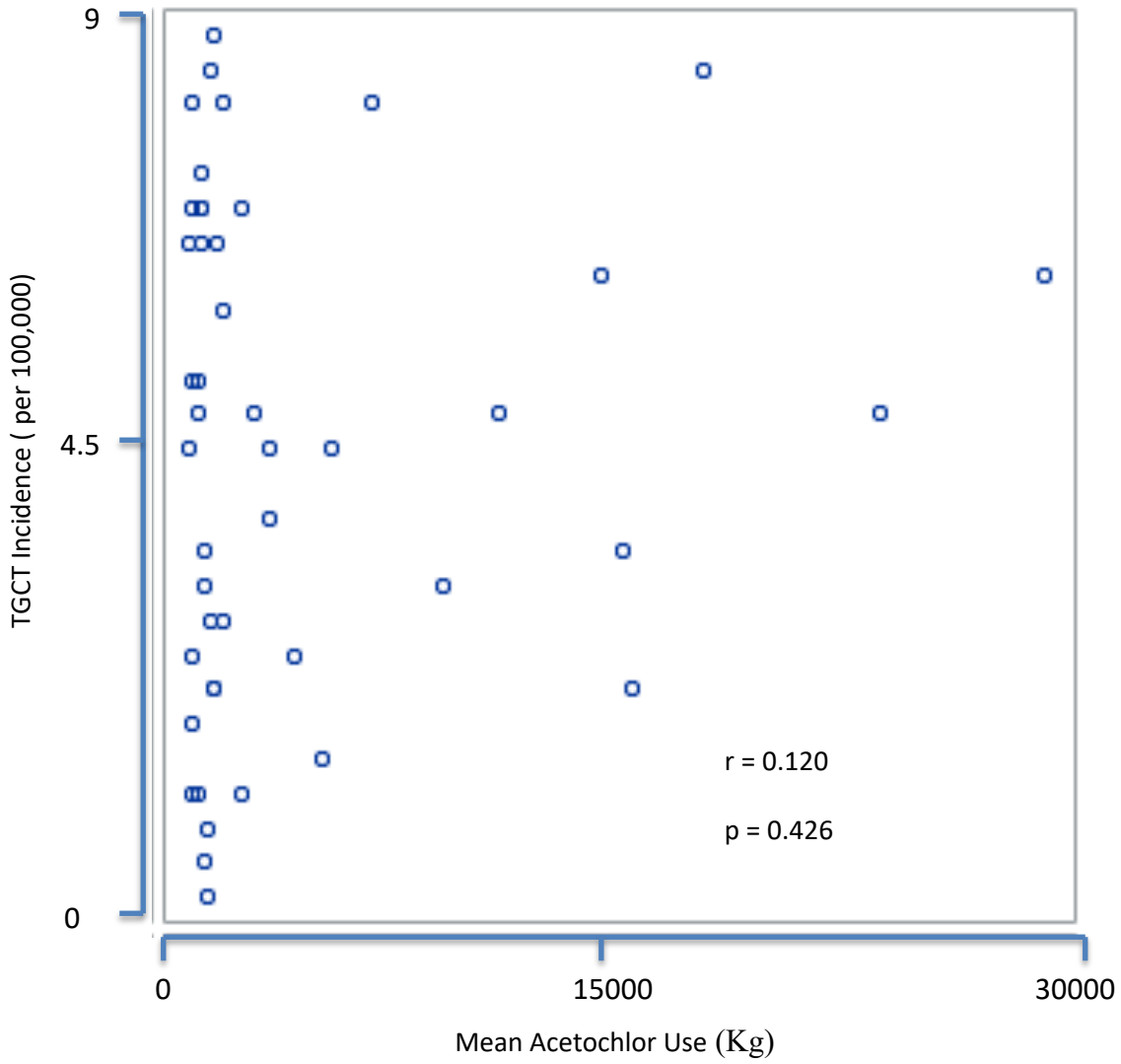


Figure 17. Correlation between Average Glyphosate use (in Kg) from 1992 to 2009 and TGCT incidence the United States from 1999 to 2011 among White Non-Hispanic Men.

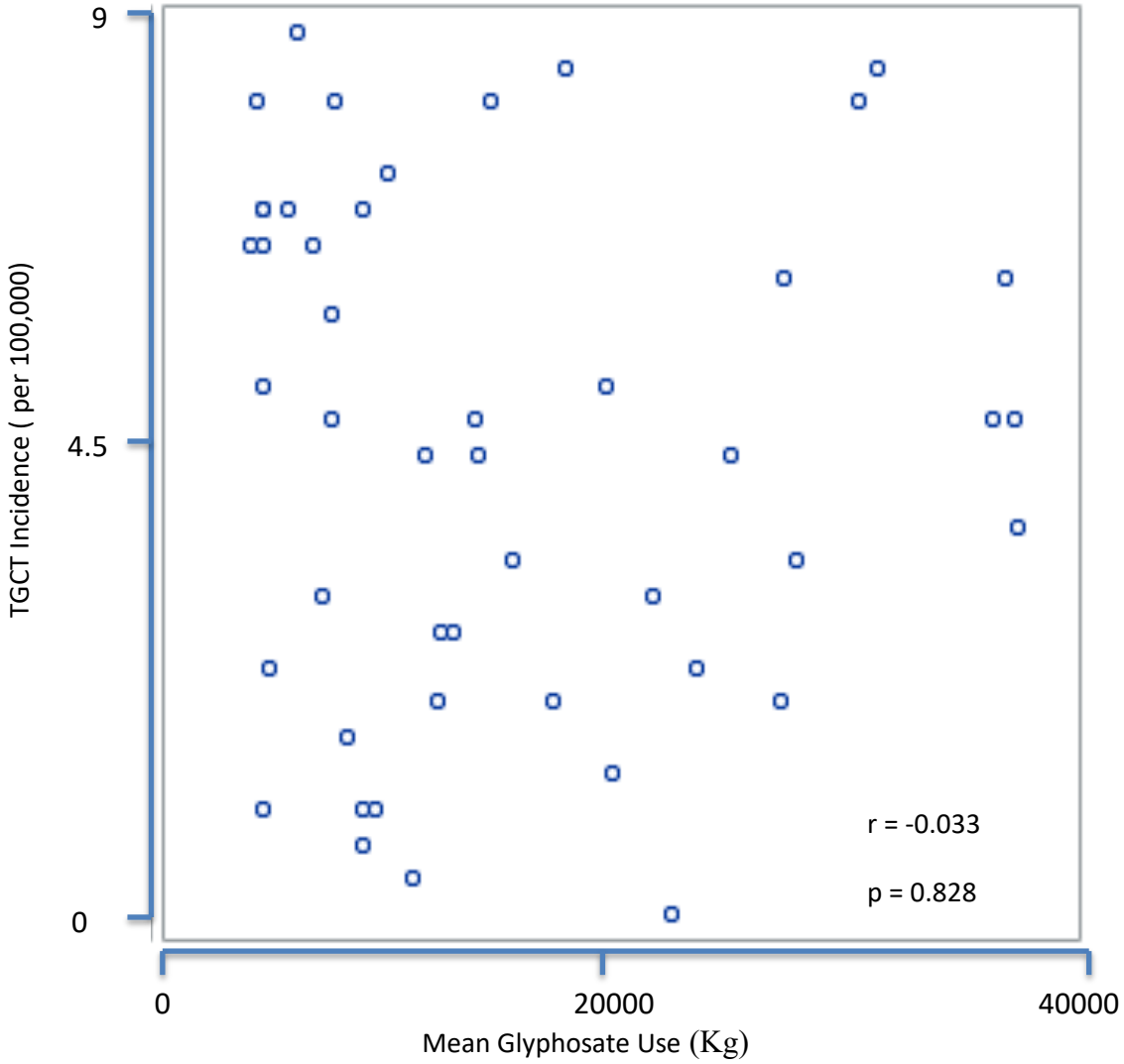


Figure 18. Correlation between Average Metam use (in Kg) from 1992 to 2009 and TGCT incidence the United States from 1999 to 2011 among White Non-Hispanic Men.

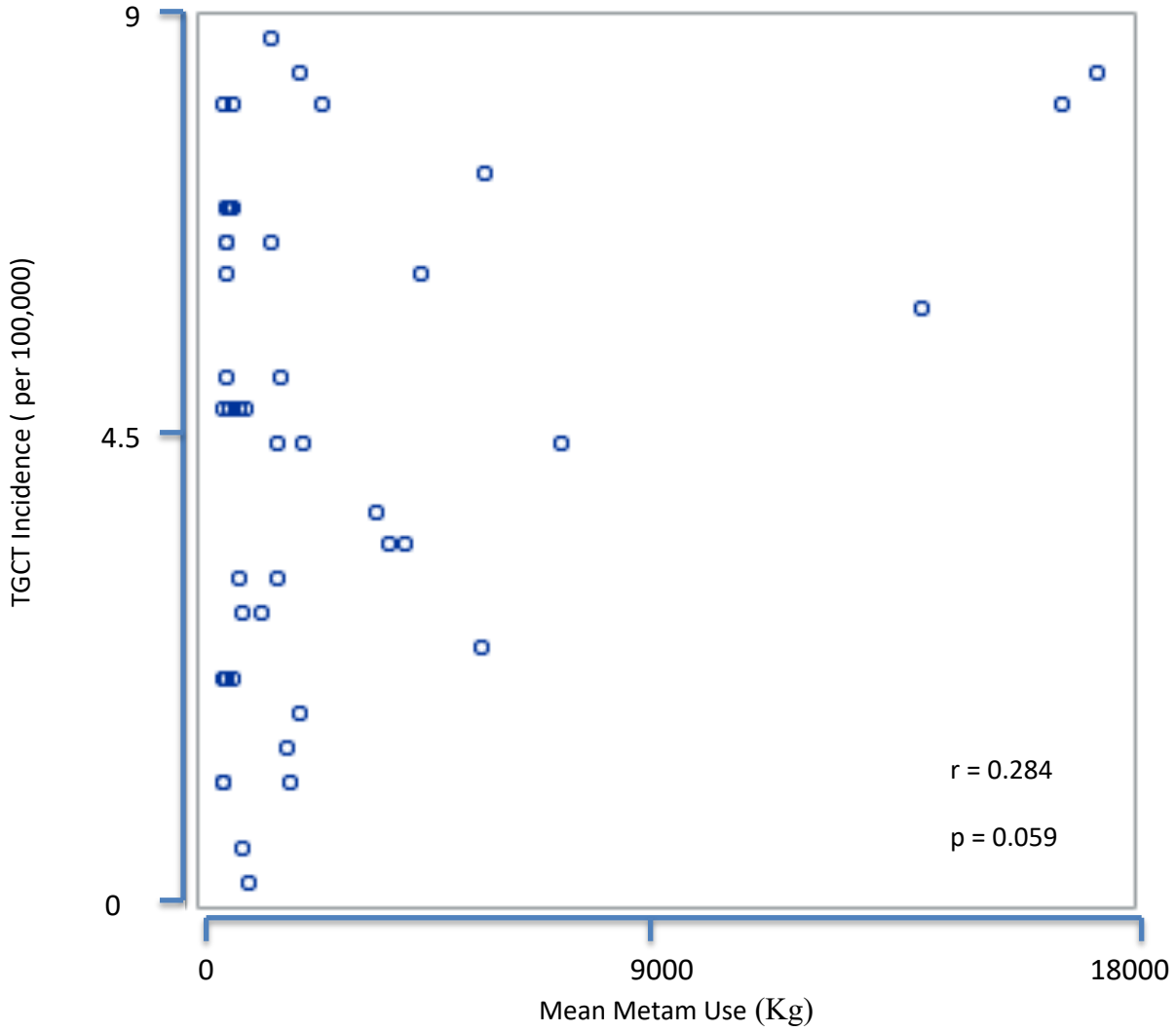


Figure 19. Correlation between Average Metolachlor use (in Kg) from 1992 to 2009 and TGCT incidence the United States from 1999 to 2011 among White Non-Hispanic Men.

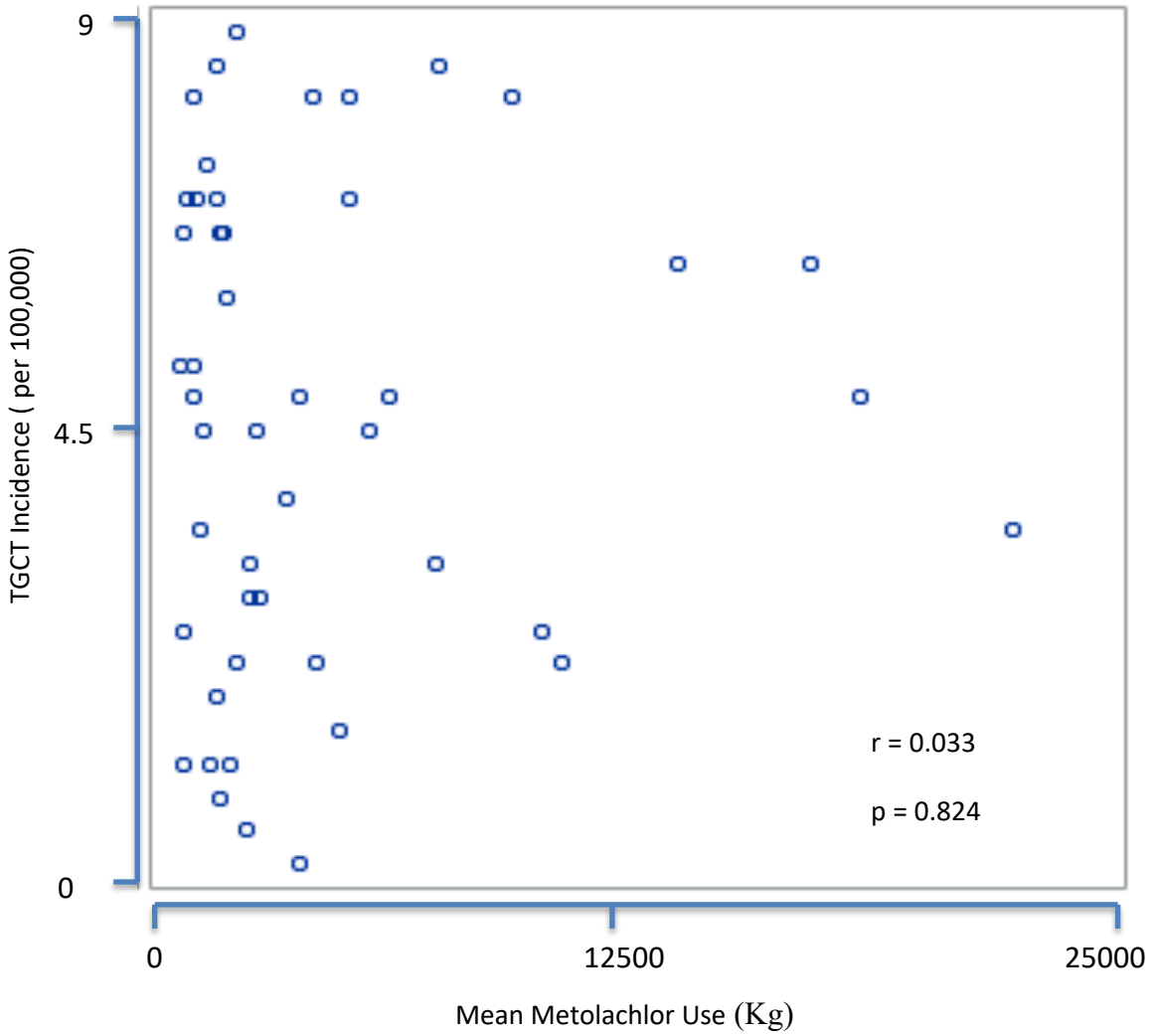


Table 4. Summary Table of Correlation Analysis Between Total Pesticide Use (Kg) from 1992 to 2009, and TGCT incidence (per 100,000) from 1999 to 2011

Race/Ethnicity	Variables Analyzed in Correlation		Correlation Estimate	95% Confidence Limits		p-Value
All races combined	Age Adjusted TGCT Incidence	Total Pesticide Use	0.11755	-0.185811	0.400458	0.4442
	Age Adjusted TGCT Incidence	Total Pesticide Use (Log Transformed)	-0.21483	-0.481034	0.087636	0.1575
American Indian or Alaska Native	Age Adjusted TGCT Incidence	Total Pesticide Use	0.02872	-0.611971	0.646654	0.9359
	Age Adjusted TGCT Incidence	Total Pesticide Use (Log Transformed)	-0.08837	-0.680152	0.573147	0.804
Asian or Pacific Islander	Age Adjusted TGCT Incidence	Total Pesticide Use	-0.07414	-0.549648	0.437646	0.7818
	Age Adjusted TGCT Incidence	Total Pesticide Use (Log Transformed)	-0.32599	-0.707388	0.202422	0.2076
Black or African American	Age Adjusted TGCT Incidence	Total Pesticide Use	-0.1001	-0.469256	0.29884	0.6231
	Age Adjusted TGCT Incidence	Total Pesticide Use (Log Transformed)	-0.1209	-0.485515	0.279543	0.5522
Hispanic	Age Adjusted TGCT Incidence	Total Pesticide Use	-0.01376	-0.366313	0.34225	0.941
	Age Adjusted TGCT Incidence	Total Pesticide Use (Log Transformed)	-0.12299	-0.457401	0.241887	0.5059
White	Age Adjusted TGCT Incidence	Total Pesticide Use	0.06109	-0.24015	0.351589	0.6919
	Age Adjusted TGCT Incidence	Total Pesticide Use (Log Transformed)	-0.21495	-0.481129	0.087514	0.1573

Table 5. Age Adjusted TCGT incidence by Individual Pesticide Use Among U.S. States (1999-2011)

Risk Factor	Category	Estimate	Standard Error	95% Confidence Limits		Z	Pr > |Z|
Total Atrazine Use (kg)	High Level of Pesticide Use vs. Low Level of Pesticide Use	-0.4347	0.2399	-0.9048	0.0355	-1.81	0.07
Total Atrazine Use (kg)	Moderate Level of Pesticide Use vs Low Level of Pesticide Use	-0.6304	0.2279	-1.0771	-0.1836	-2.77	0.0057
Total Atrazine Use (kg)	High Level of Pesticide Use vs. Moderate Level of Pesticide Use	0.1957	0.1656	-0.1289	0.5202	1.18	0.2373
Total Acetochlor Use (kg)	High Level of Pesticide Use vs. Low Level of Pesticide Use	-0.3606	0.2362	-0.8236	0.1024	-1.53	0.1269
Total Acetochlor Use (kg)	Moderate Level of Pesticide Use vs Low Level of Pesticide Use	-0.5346	0.2319	-0.9891	-0.08	-2.31	0.0212
Total Acetochlor Use (kg)	High Level of Pesticide Use vs. Moderate Level of Pesticide Use	0.1739	0.1688	-0.157	0.5048	1.03	0.3029
Total Glyphosate Use (kg)	High Level of Pesticide Use vs. Low Level of Pesticide Use	-0.4556	0.2365	-0.9192	0.008	-1.93	0.0541
Total Glyphosate Use (kg)	Moderate Level of Pesticide Use vs Low Level of Pesticide Use	-0.6124	0.2346	-1.0722	-0.1527	-2.61	0.009
Total Glyphosate Use (kg)	High Level of Pesticide Use vs. Moderate Level of Pesticide Use	0.1568	0.1542	-0.1455	0.4591	1.02	0.3092
Total Metam Use (kg)	High Level of Pesticide Use vs. Low Level of Pesticide Use	0.1042	0.2347	-0.3558	0.5643	0.44	0.6569
Total Metam Use (kg)	Moderate Level of Pesticide Use vs Low Level of Pesticide Use	-0.3299	0.222	-0.765	0.1052	-1.49	0.1373
Total Metam Use (kg)	High Level of Pesticide Use vs. Moderate Level of Pesticide Use	0.4341	0.1625	0.1156	0.7527	2.67	0.0076
Total Metolachlor Use (kg)	High Level of Pesticide Use vs. Low Level of Pesticide Use	-0.4179	0.2435	-0.8952	0.0594	-1.72	0.0861
Total Metolachlor Use (kg)	Moderate Level of Pesticide Use vs Low Level of Pesticide Use	-0.6044	0.2322	-1.0596	-0.1493	-2.6	0.0092
Total Metolachlor Use (kg)	High Level of Pesticide Use vs. Moderate Level of Pesticide Use	0.1865	0.1678	-0.1423	0.5153	1.11	0.2662
Total Pesticide Use (kg)	High Level of Pesticide Use vs. Low Level of Pesticide Use	-0.3439	0.2283	-0.7913	0.1035	-1.51	0.1319
Total Pesticide Use (kg)	Moderate Level of Pesticide Use vs Low Level of Pesticide Use	-0.4694	0.2157	-0.892	-0.0467	-2.18	0.0295
Total Pesticide Use (kg)	High Level of Pesticide Use vs. Moderate Level of Pesticide Use	0.1255	0.1672	-0.2022	0.4532	0.75	0.4528

Discussion

Discussion

- In this ecological study, we evaluated the association between pesticide use and TGCT incidence rates among men in the United States.
  - Pesticide use has been linked to an increase risk for certain diseases such as leukemia, non-Hodgkin's lymphoma, multiple (21,22).
  - Literature review of studies on occupational and environmental factors associated with TGCTs did not reach any clear conclusion on the existence of an association between pesticide use and TGCT risk, due to study design limitations (19).
  - Current studies on the role of pesticide exposure in the development of TGCTs include a case control study aiming to study the association of TGCTs and pesticide exposure by gathering more reliable domestic, occupational and environmental pesticide exposure (20).

17. Sengupta, P., & Banerjee, R. (2014).
19. Beranger, R., Le Cornet, C., Schuz, J., & Fervers, B. (2013).
20. Beranger, R., Perol, O., Bujan, L., Faure, E., Blain, J., Le Cornet, C., et al. (2014).
21. Frost, G., Brown, T., & Harding, A. H. (2011).
22. Enangue Njembele, A. N., Bailey, J. L., & Tremblay, J. J. (2014).

Discussion

- There is still no clear etiologic link to this increase in rates of TGCTs among men in the United States (26) and internationally (3): We evaluated the incidence of TGCTS between 1999 and 2011 using data from the SEER program and the CDC WONDER database. This dataset has allowed us to evaluate the overall incidence of TGCTs in men, and also in subgroups based on race and ethnicity (10).
  - We observed differences in the spatial distribution of TGCT incidence rates between states, with the highest rates observed in the Midwest and Northwest regions of the country, notably sin states such as Minnesota, Iowa, Wisconsin and Washington.
  - TGCT rates have been increasing in all racial/ethnic groups included in this study, but are still the highest among whites. Men of American Indian/Alaska Native, Asian/Pacific Islander, Black/African American and Hispanic origin all had an increase in TGCT rates, although this change was only statistically significant in men of Hispanic ethnicity during the study time period.
  - The strengths of the study include incidence data and pesticide use data for the entire United States population, but several limitations should be noted when interpreting the data from this study: The study is limited by small numbers of cases in some racial/ethnic groups.

Limitations

- The study also has limitations in estimating pesticide exposure.
  - No states with the exception of California require reporting of annual pesticide application, therefore the rates used in this study were estimated by the USGS and USDA.
  - The pesticide information used in the study represents estimates of the actual pesticide application on the crops so they should be interpreted with caution.
  - Futhermore, the EPest values are not a direct measurement of actual body pesticide burden, and no biomarkers were used to validate total body pesticides levels (23).

23. Markel, T. A., Proctor, C., Ying, J., & Winchester, P. D. (2014).

Limitations

- Additionally, the limitations of ecological studies should be taken into account.
  - Firstly, problems inherent with the ecological fallacy are well known. Such studies are based on aggregate population data rather than individual data: Due to this limitation, we were not able to determine if the individuals who were exposed to the pesticides were also the same individual who later developed TGCTs (15).
  - Previous studies looking at the effect of pesticides on the incidence rates of specific cancer often ascertained the exposure using questionnaires, and often focused on agricultural communities, but we were limited to using aggregate data for pesticide use (19-21).

19. Beranger, R., Le Cornet, C., Schuz, J., & Fervers, B. (2013).
20. Beranger, R., Perol, O., Bujan, L., Faure, E., Blain, J., Le Cornet, C., et al. (2014).
21. Frost, G., Brown, T., & Harding, A. H. (2011).

Future Research

- In summary, comparing the changes in TGCT incidence at the state level show that the rates of TGCTs are increasing among men in the United States, and that geographic and racial differences exist in incidence.

- We found that some agricultural pesticides were positively associated with the increased incidence of TGCTs within states, but these changes in environmental risk factors may have been initiated several decades ago.

- Further studies using more precise exposure ascertainment tools are needed to confirm these findings, and could provide more evidence to support the role of pesticide as an etiologic risk factor for TGCTs.

QUESTIONS

Table 6. Age Adjusted TCGT incidence by Race Among U.S. States (1999-2011)

Risk Factor	Category	Estimate	Standard Error	95% Confidence Limits		Z	Pr > |Z|
Race	American Indian or Alaska Native	-1.3359	0.2945	-1.9131	-0.7587	-4.54	<.0001
Race	Asian or Pacific Islander	-4.9135	0.1327	-5.1736	-4.6534	-37.03	<.0001
Race	Black or African American	-5.0851	0.1055	-5.2919	-4.8784	-48.21	<.0001
Race	Hispanic	-3.0519	0.1767	-3.3983	-2.7055	-17.27	<.0001

Table 7. Age Adjusted TCGT incidence by Overall Pesticide Use Among U.S. States (Univariate Model with Total Pesticide Use Only)

Risk Factor	Category	Estimate	Standard Error	95% Confidence Limits		Z	Pr > |Z|
Total Pesticide Use (kg)	High Level of Pesticide Use vs. Low Level of Pesticide Use	0.3018	0.3045	-0.2949	0.8986	0.99	0.3216
Total Pesticide Use (kg)	Moderate Level of Pesticide Use vs Low Level of Pesticide Use	-0.284	0.2852	-0.843	0.2751	-1	0.3194
Total Pesticide Use (kg)	High Level of Pesticide Use vs. Moderate Level of Pesticide Use	0.5858	0.3185	-0.0385	1.2101	1.84	0.0659

Table 8. Age Adjusted TCGT incidence by Pesticide Use Among U.S. States (Multivariate Model With All Pesticides)

Risk Factor	Category	Estimate	Standard Error	95% Confidence Limits		Z	Pr > |Z|	Risk Factor	Category	Z	Pr > |Z|
Total Atrazine Use (kg)	High Level of Pesticide Use vs. Low Level of Pesticide Use	0.0279	0.2267	-0.4163	0.4722	0.12	0.902	**Total Atrazine Use (kg)**	Continuous Use Between 1992 and 2009	-0.17	0.8648
Total Atrazine Use (kg)	Moderate Level of Pesticide Use vs Low Level of Pesticide Use	0.1169	0.214	-0.3025	0.5364	0.55	0.5848				
Total Acetochlor Use (kg)	High Level of Pesticide Use vs. Low Level of Pesticide Use	0.2526	0.2344	-0.2068	0.7119	1.08	0.2812	**Total Acetochlor Use (kg)**	Continuous Use Between 1992 and 2009	2.48	0.0131
Total Acetochlor Use (kg)	Moderate Level of Pesticide Use vs Low Level of Pesticide Use	-0.0086	0.2053	-0.411	0.3938	-0.04	0.9667				
Total Glyphosate Use (kg)	High Level of Pesticide Use vs. Low Level of Pesticide Use	-0.4926	0.2255	-0.9346	-0.0506	-2.18	0.0289	**Total Glyphosate Use (kg)**	Continuous Use Between 1992 and 2009	-2.45	0.0143
Total Glyphosate Use (kg)	Moderate Level of Pesticide Use vs Low Level of Pesticide Use	-0.5429	0.1889	-0.9131	-0.1728	-2.87	0.004				
Total Metam Use (kg)	High Level of Pesticide Use vs. Low Level of Pesticide Use	0.3642	0.2399	-0.106	0.8344	1.52	0.129	**Total Metam Use (kg)**	Continuous Use Between 1992 and 2009	2.16	0.031
Total Metam Use (kg)	Moderate Level of Pesticide Use vs Low Level of Pesticide Use	-0.2913	0.1413	-0.5682	-0.0143	-2.06	0.0393				
Total Metolachlor Use (kg)	High Level of Pesticide Use vs. Low Level of Pesticide Use	-0.1303	0.226	-0.5732	0.3126	-0.58	0.5642	**Total Metolachlor Use (kg)**	Continuous Use Between 1992 and 2009	-0.66	0.5104
Total Metolachlor Use (kg)	Moderate Level of Pesticide Use vs Low Level of Pesticide Use	-0.2625	0.1961	-0.6468	0.1218	-1.34	0.1807				