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A Spatial Correlation Analysis of Broad Scale Use of Agricultural Pesticides and Infant Health Outcomes in the United States

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A Spatial Correlation Analysis of Broad Scale Use of Agricultural Pesticides and Infant Health Outcomes in the United States

by

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Thesis submitted to the Faculty of Graduate and Postdoctoral Studies, University of Ottawa, in partial fulfillment of the requirements for the M.Sc. degree in the

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Abstract

Introduction: Birth defects and low birth weight/preterm delivery are the leading causes of infant mortality in the United States. However, their etiologies remain mostly unknown. There is evidence suggestive of a link between exposure to pesticides and reduced infant health. We sought to answer the question of whether spatial variation in the incidence of infant mortality in the general population is correlated with variation in agricultural pesticide use. **Methods**: We examined the variation during 1996-2001 among 48 U.S. states of rates of infant mortality due to birth defects, and rates of infant mortality due to low birth weight or preterm delivery. We also examined the incidence of 41 specific birth defects through 1989-2001 in 33 states. We related these variables to the rate of agricultural pesticide use per state. **Results**: After controlling for socio-economic and behavioural risk factors, among-state variation in the rate of pesticide use accounted for over one quarter of the variation in infant mortality rates due to birth defects (r^2=0.29). We did not find a significant relationship between pesticide use and infant mortality due to low birth weight/preterm delivery. **Conclusion**: Our results support the hypothesis that adverse effects on infant health in the general population are associated with broad scale pesticide use. To overcome the inferential limitations of this study, further research using individual exposure and outcome data is needed.

Résumé

Introduction : Les anomalies congénitales et la naissance avant terme ou le poids insuffisant à la naissance sont les principales causes de la mortalité infantile aux Etats-Unis. Cependant, leurs étiologies demeurent inconnues. Il y a d'évidence suggestive d'un lien entre l'exposition aux pesticides et la santé infantile réduite. Nous avons cherché à répondre à la question de si la variation spatiale de l'incidence de la mortalité infantile dans la population générale est corrélée avec la variation de l'utilisation de pesticide agricole. **Méthodes** : Nous avons examiné la variation pendant 1996-2001 parmi les 48 états contigus des Etats-Unis de taux de mortalité infantile dus aux anomalies congénitales, ainsi que le taux de mortalité infantile dû au poids insuffisant à la naissance ou naissance avant terme. Nous avons aussi examiné l'incidence de 41 anomalies congénitales spécifiques dans 33 états entre 1989-2001. Nous avons comparé ces variables au taux de l'utilisation de pesticides agricoles par état. **Résultats** : Après avoir contrôlé pour des facteurs de risque socio-économiques et comportementaux, la variation entre états du taux d'utilisation de pesticide a compté pour plus d'un quart de la variation des taux de mortalité infantile dus aux anomalies congénitales (r^2=0.29). Nous n'avons pas trouvé un rapport significatif entre l'utilisation de pesticide et la mortalité infantile dû au poids insuffisant à la naissance/naissance avant terme. **Conclusion** : Nos résultats affirment l'hypothèse que des effets nuisibles sur la santé infantile dans la population générale sont associés avec l'utilisation de pesticide à grande échelle. Pour surmonter les limitations déductives de cette étude, davantage de recherche qui utilise des données d'exposition et de maladie spécifique aux individus est nécessaire.

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Mom and Dad, you cleverly cloaked a steady berating and hectoring of my unspeakable morals as an apparently insatiable interest in the obscure subject I was researching. We all knew it for what it was, and despite its ham-fisted nature, it worked. I got in, then I got it done anyway. Who knows? What I learned completing this thing may even serve me well some day:

"Doctor, this man's swallowed a litre of pesticide-spiked eggnog! His wife mixed it in on purpose. He knew it was poison, but who can resist the 'nog?"

"He's in the right hands. I did my thesis on a slightly related topic. Let's go ahead and pump this guy's stomach."

Lastly, I like to thank LPGB for her love, support, and encouragement. On the whole she probably detracted from my pace, but she certainly made the time better. We met in grad school.

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Table of Contents

List of Figures

List of Tables

Table 8: Pearson correlations between proportions of state land area treated with teratogenic pesticides (*Tera97*) and rates of individual birth defects. Note that a very high proportion (34 of 41) of specific birth defects are positively correlated with *Tera97*.

Table 9: Pearson correlations between proportions of state land area treated with teratogenic pesticides (*Tera97*) and rates of individual birth defects, grouped by common ontogeny. Note that a very high proportion (13 of 15) of specific birth defects are positively correlated with *Tera97*.

Table 10: Pearson correlations between all pesticides included in *Tera97* (N = 220) and rates of infant mortality due to birth defects. Note that a very high proportion (142 / 220) of the relationships between rates of use of individual pesticides and *BDmort* were positive.

Table 11: Pearson correlations between proportion of state land area treated with teratogenic pesticides (*Tera97*) and rates of individual birth defects. Only 25 of the 49 suspected teratogens showed a positive relationship.

Table 12: Pearson correlations between measures of pesticide use intensity. Note that all variables are highly collinear with Tera97 except %Farmland. In all cases N = 48 and $p < 0.00001$.

Introduction

Fetal mortality constitutes an important public health issue in the United States. Birth defects have remained the leading cause of infant mortality for the past twenty years, responsible for one fifth of infant (<1 year old) and neonatal (<1 month old) deaths (Petrini et al., 2002; NCHS, 2001). The March of Dimes defines a birth defect as any "abnormality of structure, function or metabolism present at birth that results in physical or mental disability, or is fatal" and estimates that 1 in 28 newborns are affected (March of Dimes Foundation, 2005). The economic impact of birth defects in the United States is estimated at over eight billion dollars yearly (Waitzman et al., 1995) and represents an important, and possibly preventable, cost to society.

The occurrence of congenital anomalies has been related to characteristics of individual mothers. These include natural factors, individual behaviours, as well as individual exposure to teratogens. Kalter's (2003) review of teratology asserts that known natural teratogenic substances are few; only the effects of prenatal iodine deficiency, as well as exposure to radiation, the rubella virus, and organic mercury are consistently confirmed. Other known risk factors associated with increased risk of fetal anomalies include maternal characteristics such as age, race, and to a lesser extent, smoking status, as well as prenatal exposure to manufactured chemicals such as thalidomide, certain anticonvulsants, retinoids, or folic acid antagonists. Alcohol, blighted potatoes, diethyl stilbestrol (DES), female sex hormones, lithium, pesticides, and even hyperthermia have all been cited as potentially teratogenic, although the evidence has not been firmly substantiated as yet. This said, incidence of birth defects is still not well

understood: prenatal exposure to known teratogens explains only from ~10% to <50% of observed congenital anomalies (CBDMP, 2005; Kalter, 2003).

The goal of the present study is to test whether a significant portion of the unexplained variance in the frequency of mortality due to birth defects may be linked to population-level exposure to pesticides, potential teratogens that are broadly distributed in the environment. Pesticides are ubiquitously used in agriculture, and market expenditures have increased steadily over the past several decades. Use of pesticides is widespread: 74% of American households and 66% of harvested American farms use pesticides (EPA, 2004). A total of 888 million pounds of active ingredient was applied in the United States in 2001. The pesticide use market includes sales of herbicides, insecticides, and fungicides, and is grouped by the EPA into three sectors: agricultural, commercial/industrial/governmental, and home & garden. Of these three, the agricultural sector has always been the majority contributor, totalling 76% of the total amount of active ingredient used and 67% of user expenditures in the 11 billion dollar pesticide market (2001 figures). Annual user expenditures have been steadily increasing in all market sectors since the EPA began tracking them in 1979.

A pesticide, as defined by the US Environmental Protection Agency (EPA), is "any agent used to kill or control undesired insects, weeds, rodents, fungi, bacteria or other organisms" (EPA, 2003). A particular pesticide formulation may be composed of a mixture of one or many active ingredients, the chemical responsible for the formulation's biocidic properties, together with any number of other ingredients. All pesticides are regulated by the EPA under FIFRA (the Federal Fungicide, Insecticide, and Rodenticide Act) and FFDCA (the Federal Food, Drug, and Cosmetic Act). Manufacturers of pesticides are required to furnish the EPA with detailed

toxicological information and animal testing results before registration of a new compound can be approved for general use. The US is the world's primary producer and consumer of pesticides, accounting for a fifth of the 5 billion pounds of conventional pesticides used worldwide from 1994-1997. During this time, there were nearly 900 different active ingredients (a.i.) registered for use in the US (EPA, 1997; 1999).

Pesticides are by nature toxic substances. Many commonly used agricultural pesticides are teratogenic or endocrine disruptors. Several of the most used active ingredients have been shown to elicit adverse pregnancy outcomes ranging from reduced fertility to the development of serious terata (birth defects) in animal testing species. Of the top 25 most commonly used a.i.'s in the US in 1997, one third are listed as developmentally toxic or teratogenic by either the Environmental Protection Agency's Toxics Release Inventory (TRI) list or by the State of California under the Safe Drinking Water and Toxic Enforcement Act of 1986, also known as Proposition 65 (Orme & Kegley, 2005). Another eleven of the top 25 are classified as known or suspected endocrine disruptors (*ibid.*). These lists use a weight-of-the-evidence approach, drawing on existing laboratory, animal, and epidemiological evidence to make decisions regarding the classification of various chemicals.

Other studies (see Garcia, 1997; Singleton, 2003; Wigle, 2003 and references therein) have discussed at length the mechanisms of teratogenesis and endocrine disruption, so I will only offer an introduction here. During specific periods of development (organogenesis in particular, which in humans happens during weeks 3-8 of pregnancy), the developing embryo is extremely susceptible to teratogenic agents or to small changes in endogenous hormone levels (Dolk &

Vrijheid, 2003). Chemicals with molecular weights less than 600 can readily cross the placental barrier and exert effects on the developing fetus (Schardein, 2000, p. 5). Only rarely do pesticides have molecular weights higher than 500, as most are in the 200-350 range (Miller, 2006). During the critical period, minimal exposure to pesticides can lead to teratogenic insults or interference with the embryo's chemical communication by endocrine disruptors. These very low-level exposures may introduce destructive static into biological signals and possibly lead to adverse pregnancy outcomes – terata in the case of teratogenic pesticides and abnormal growth or gestation in the case of endocrine-disrupting pesticides.

Experimental and epidemiological studies have suggested a link between prenatal exposure to pesticides and subsequent development of birth defects or other adverse reproductive outcomes in animals and in humans. Population declines, problems with sexual differentiation, terata, and other reproductive troubles have been observed in amphibians, reptiles, fish, and birds secondary to pesticide exposure (see Reeder *et al.*, 2005; Baatrup & Junge, 2001; Guillette *et al.*, 1995, and references therein). Among humans, exposure to herbicides has been associated with sub-lethal fertility troubles similar to those observed in nature, including reduced female fertility (Greenlee et al., 2003) and diminished semen quality (Swan et al., 2003). However, environmental pesticide exposure among humans has also been associated with more serious reproductive troubles such as elevated risk of spontaneous abortion and late fetal death (Arbuckle et al., 1999; Bell et al., 2001; Shreinemachers, 2003) as well as increased rates of terata among the offspring of persons occupationally exposed to pesticides (Garry, 1996). In a review of the literature, Wigle (2003) concluded that limited evidence for the link between maternal exposure to pesticides and subsequent development of birth defects, highlighting birth

defects affecting the central nervous system (henceforth CNS), cardiovascular system, or causing limb reductions or orofacial clefts. Garcia's (1997) review of occupational exposure to pesticides and incidence of congenital anomalies also reported increased risk of oral clefts, CNS, as well as defects of the musculoskeletal system as a result of occupational pesticide exposure. Other studies show elevated risk of limb anomalies associated with environmental or occupational exposure (Schwartz et al., 1986; Schwartz & LoGerfo, 1988; Lin et al., 1994). A third major review paper produced by the Ontario College of Family Physicians associated chronic exposure to pesticides with decreased fertility and fecundability, as well as increased risk of congenital CNS, heart, urogenital, orofacial, eye, and limb anomalies (Sanborn *et al.*, 2004). Commonalities in the organ systems detrimentally affected by pesticides emerge when meta-analyses are considered. The reproductive, nervous, cardiovascular, and skeletal systems represent those systems most vulnerable to the endocrine disrupting and teratogenic effects of pesticides.

Though exposure is highest for those occupationally exposed to pesticides, the surrounding general population is exposed to pesticides through the ambient environment; evidence of conventional crop pesticide residues are found in the water, air, soil, dust, and food of non-agricultural regions. The USGS National Water Quality Assessment (NAWQA) project has collected and analysed water samples across the US in an effort to determine the state of the nation's waters. Although concentrations of pesticide residues decrease as distance from the point source of application increases, residues have been detected in all U.S. regions studied, and low levels of long-lived pesticides are present in the waters and atmosphere throughout the year (Gilliom & Hamilton, 2005). Shorter-lived pesticide concentrations are seasonal and

proportional with regional agricultural and urban use. The NAWQA study found that pesticide concentrations in 9.6% of agricultural streams and 1.2% of agricultural groundwater sources exceeded allowable human health benchmarks. Urban stream and groundwater pesticide concentrations exceeded the benchmarks in 6.7% and 4.8% of the samples (*ibid.*).

Para-occupational exposure can be an important source of contamination for both the families of occupationally-exposed individuals as well as members of the general population. Exposure to pesticide-contaminated soil and dust either from pesticide-contaminated fields or domestic lawns or gardens is tracked into homes where residues become persistent because normal degradation processes through sunlight, rain, and soil microbial action are unavailable. Measurable pesticide residues in household dust have been reported in both agricultural and non-agricultural homes (Simcox et al., 1995; Lewis et al., 1999). Pesticide use is partly responsible for a low-level chemicalization of the environment such that those living and working in agricultural regions are exposed to residues at low, but persistent levels.

This leads to the hypothesis that exposure of the U.S. population at large to agricultural pesticides has negative impacts on human health. Clearly, a causal link at this scale would be very difficult to demonstrate. However, the hypothesis makes a testable prediction: that the spatial variation in the incidence of adverse pregnancy outcomes in the general population (not just among individuals with known pesticide exposure) is positively correlated with local pesticide use (after controlling for other known risk factors).

Methods

To test the predictions outlined above, we examined the variation among U.S. states of rates of infant mortality due to birth defects and low birth weight/prematurity, and of the incidence of specific birth defects. We related these variables to the rate of agricultural pesticide use per state. Because individual-level data on pesticide exposure and health outcomes were unavailable to us, we used a geographic (or ecological) study design. All statistics were performed on the SYSTAT v.10 and Statistix 7 statistical software packages.

Data on agricultural pesticide use were obtained from the National Center for Food and Agricultural Policy's (NCFAP) circa 1992 and circa 1997 national pesticide use databases (Gianessi & Anderson, 1995; 2000). The authors compiled data from 108 pesticide use surveys conducted by federal and state agencies to formulate the circa 1992 database, and released an update of agricultural practices circa 1997 in 2000. The NCFAP pesticide datasets are (to my knowledge) the only comprehensive compilation of information on agricultural pesticide use at the national scale. Various measures of agricultural pesticide use are detailed in 20,886 individual records, including year, state, crop type, pesticide name, pesticide class, acres treated, and weight of pesticide used, among others. The circa 1992 edition contains information on 200 active ingredients for 87 crops for the 48 contiguous U.S. states during 1990-1993 (appendix 1). The updated circa 1997 edition contains information on 235 active ingredients for the same 87 crops across 48 contiguous US states for the 1995-1998 year range (appendix 1). The NCFAP pesticide use totals are comparable with U.S. pesticide use estimates calculated by the EPA in a separate publication (Aspelin & Grube, 1999).

I calculated the number of acres treated with pesticides (all crops) as a proportion of the total land area of each state. I did this for each of four groups of products: potentially teratogenic pesticides used in 1990-1993 (*Tera92* – Appendix 2), potentially teratogenic pesticides used in 1995-1998 (*Tera97* – Appendix 3), potentially endocrine-disrupting pesticides used in 1990-1993 (*ED92* – Appendix 4), and potentially endocrine-disrupting pesticides used in 1995-1998 (*ED97* – Appendix 5). An acre was considered treated if any volume or concentration of a given pesticide was applied to it. Thus, the same acre could be counted more than once if it was treated on multiple occasions by the same or by a different pesticide. The NCFAP pesticide database takes pesticide treatments with multiple a.i.'s into account by counting the treated acreage twice, once for each a.i.

Pesticide use was reported in the NCFAP dataset as total weight of pesticide applied (in lbs.), as well as acres treated. As in previous studies (Pepin, 2005; Mineau & Whiteside, 2006), we chose to use acres treated rather than pounds per acre as our measure of pesticide use. The concentration of a given active ingredient per pound of commercial product can vary considerably because the weight of a given product is a function of its formulation (e.g. emulsion, powder, aqueous solution, fumigant, etc.) and does not relate to toxicity. For instance, in aqueous solutions, most of the weight is water. In a powder, the weight is principally active ingredient. Since the formulation determines the weight of a pesticide, and the active ingredient determines toxicity, it would be meaningless to combine rates of application by weight of different pesticides. We assumed that an application of a given pesticide over an area represented the appropriate quantity to achieve pest control and felt that calculating acres treated better reflected agricultural pesticide use intensity than calculating some measure using the weight of pesticides used per acre.

We calculated the number of acres treated per state as a proportion of state area. Our dataset considered an acre as "treated" separately for each individual active ingredient in a formulation, and for each separate application. Note that this means it is theoretically possible that the total number of acres treated with pesticides exceed the total acreage of a state. State land areas were taken from http://www.infoplease.com/ipa/A0108355.html on March 17, 2005 and verified against http://quickfacts.census.gov/qfd/index.html. Proportions of state land area treated with potentially teratogenic or endocrine disrupting pesticides during years 1991-1994 and 1995-1998 are given in Table 1.

Pesticides were divided into four categories (Appendices 1-5) based on the NCFAP year ranges and the classifications of the Pesticide Action Network (PAN) Pesticide Database. PAN manages a database that provides toxicological information on all pesticides used in California (www.pesticideinfo.org). We classified compounds as teratogenic if they were listed on either the California Proposition 65 list (Safe Drinking Water and Toxic Enforcement Act, 1986) or the US EPA Toxics Release Inventory of reproductive or developmental toxins. The listing of chemicals is done via a weight-of-the-evidence approach using best-available laboratory, animal, and epidemiological evidence. A substantial fraction of pesticides in use have not been adequately re-assessed by the EPA with up-to-date testing protocols for teratogenicity and none have been officially tested for endocrine-disruption properties (National Coalition Against the Misuse of Pesticides, 2005). Consequently, absence of a pesticide from either of these two lists does not necessarily mean that it is not teratogenic or incapable of endocrine disruption.

I analyzed three infant health outcomes from two separate databases to examine the association between pesticide use and infant health in this study: infant mortality due to birth defects (*BDmort*), infant mortality due to low birth weight (*LBWmort*), and incidence per 10,000 live births of 41 specific birth defects.

Infant mortality rates due to birth defects and low birth weight/prematurity were obtained via a database produced by the Center for Disease Control's National Center for Health Statistics (NCHS) and made available by the March of Dimes. The National Center for Health Statistics compiles a dataset of individual birth certificates linked to matching death certificates for each infant in the United States. Information from the birth certificate includes age, race, and Hispanic origin of the parents, birthweight, period of gestation, plurality, prenatal care usage, maternal education, live birth order, marital status, and maternal smoking. Additional information from the death certificate includes age at death and underlying and multiple cause of death. For this study, NCHS data on average rates of infant mortality per state from 1996 to 2001 (N= 48) according to cause of death (birth defects & low birth weight/preterm delivery) were obtained online from the March of Dimes Foundation perinatal statistics information database (www.marchofdimes.com/peristats).

Data on rates of the 41 specific birth defects were compiled and published by the National Birth Defects Prevention Network (NBDPN, 2003). Rates per 10,000 live births of up to 45 anomalies were reported for 33 states. However, not every state registry was able to provide data for all conditions. Nor were all registries identical in terms of case definition, ascertainment method, cohort size, years of available data, coding system, or follow-up age

range (Table 2). I therefore eliminated the three states that reported on half or less of the 45 conditions, and I eliminated those conditions that were reported by less than 80% of states (Table 3). The remaining data represented 41 anomalies in 30 states, among which 2% of the data were missing. For the purposes of multivariate analyses in which missing values are not tolerated, missing rates were filled in using the average incidence rate calculated from values of all reporting states.

The original raw NBDPN datasets were divided into two separate time periods: from 1989-97 and 1997-2001. Occurrence of given birth defects are statistically rare events. To reduce stochastic variability associated with analysis of smaller numbers, I combined the data in two ways to make two separate datasets. First, I combined the deaths due to all birth defects in the 1989-97 and the 1997-2001 datasets into a set spanning the entire 1989-2001 period. Since 1997 yearly totals were included in both of the original datasets, I subtracted the appropriate number of counts for all defects where the 1997 year was counted twice (N=15 states) in order to correct for double-counting. In a second analysis, I classified birth defects over 1989-2001 according to organ system (N = 16 groups) on the basis of common embryological ontogeny (Table 4). Grouping related birth defects in this manner increases the statistical sensitivity of subsequent analyses by lumping categories with small numbers of cases into a few categories with larger numbers of cases, as has been done in other studies (Scheuerle & Tilson, 2002).

To control for possible confounding effects of among-state variation in socioeconomic, demographic, and public health conditions, I obtained data on these factors from publications by the US national census, the Center of Disease Control, and the March of Dimes (Table 5 &

Appendix 6). Correcting for variance in maternal characteristics such as age, race, and smoking status, as well as measures of affluence, education, abortion rates, and health care quality takes the most important known predictors of adverse birth outcomes into account (reviewed in Luo et al., 2006). This has two beneficial effects. It reduces error variance in statistical procedures, allowing detection of the effects of pesticides and it reduces the risk of hidden effects of collinear variables. Our tests of the pesticide hypothesis therefore become more conservative.

The statistical methodology and justification of this study is as follows. Following data collection, observation showed that many of the variables in this analysis were strongly positively skewed. In these cases, a power transformation was applied: $X' = X^b$. For each variable, the exponent b was varied from 0 to 1 to find the distribution of X' that most closely conformed to normality, as assessed with Komolgorov-Smirnov (KS) tests. Collinearity among independent variables (state rates of pesticide use, socioeconomic and health indicators) was assessed with Pearson correlations.

Relationships between dependent variables (measures of infant health) and the independent variables were tested with simple regressions and multiple regressions. Residuals from the regressions were tested for normality with KS tests.

Results

Per state rates of infant mortality due to birth defects vary among states by a factor of 2.7. The highest rates are concentrated approximately in the prairies of the mid-western states and through the Mississippi delta (Figure 1). Per state rates of infant mortality due to low birth weight/preterm delivery vary by a factor of 5.8. The highest rates are concentrated in the eastern

United States (Figure 2). Pesticide use intensity varies by a factor of 358. The states with the highest rates of pesticide use are the same states whose economies depend highly on agriculture. Pesticide use is concentrated along the west coast states and in the states comprising the areas commonly known as the corn belt, the wheat belt, and the soy belt - states of the upper mid-west and south of the great lakes running down the Mississippi river floodplain (Figure 3).

Temporal variability

Relative rates of pesticide use among states were relatively similar through the study period. Average rates of use of pesticides included in the NCFAP pesticide database classified by the Pesticide Action Network as "endocrine disruptors" for the years 1991-1994 and 1995-1998 (hereafter referred to as *ED92* and *ED97*) are highly correlated ($r = 0.98$, $p < 10^{-5}$). Also, average rates of use of pesticides classified as "teratogens" are also highly correlated between the years 1991-1994 and 1995-1998 (hereafter *Tera92* and *Tera97*) ($r = 0.97$, $p < 1 \times 10^{-5}$). Thus, inter-annual variations in rates of pesticide use per state are unlikely to influence results.

Relative rates per state of infant mortality attributable to congenital anomalies from 1996-2001 were also reasonably stable. We averaged these rates over 1996-2001 in order to reduce stochastic variability.

Infant mortality and pesticide use

Per-state rates of infant mortality due to birth defects (averaged over 1996-2001 for the 48 conterminous US states, hereafter referred to as *BDmort*) are significantly related to the proportion of the state treated with teratogenic pesticides (averaged over 1995-1998: *Tera97*)

(Figure 4; r = 0.33, p = 0.022, n = 48). Per-state rates of infant mortality due to low birth weight/preterm delivery (averaged over 1996-2001 for the 48 conterminous US states, hereafter referred to as *LBWmort*) are also significantly related to the proportion of the state treated with suspected endocrine-disrupting pesticides (averaged over 1991-1994: *ED92*) (r = 0.37, p = 0.010, n = 48).

To test the possibility that the mortality-pesticide relationships reflected collinear variation among states between pesticide use and other known risk factors, we carried out multiple regressions. We included socio-economic, demographic, and public health variables in the model, in addition to the pesticide use. Infant mortality due to birth defects (*BDmort*) was significantly related to teratogenic pesticide use, independently of other known risk factors. In a multiple regression, the rate of infant mortality was related to four variables out of the twelve tested: average state-wide rates of teratogenic pesticide use from 1995-98 (*Tera97*), average household income, the percentage of females aged 18-44 who smoke, and state abortion rates (model adjusted $R^2 = 0.71$, n = 48; Table 6). The partial correlation of *BDmort* and *Tera97*, after controlling for the influence of the other variables in the model, was r = 0.54 (Figure 5). Since the collinearity of *Tera97* with the non-pesticide variables is low (see tolerances in Table 6), this partial correlation is unlikely to be biased by other variables in the model. In sum, over one quarter ($r^2 = 0.29$) of the variation in mortality rates that is not related to socio-economic and behavioural variables can be statistically attributed to variation in the rate of pesticide use. Based on the regression model, the relative risk of infant mortality due to birth defects in the state with the highest rate of use of teratogenic pesticides is 1.31 times higher than in the state with the lowest rate of use (Appendix 7).

In contrast, mortality due to low birth weight (*LBWmort*) was not significantly related to pesticide use (*ED92)* after controlling for socioeconomic variables in a multiple regression. In a multiple regression including the same twelve variables used in the previous model, *ED92* became non-significant ($F = 3.74$, $p = 0.144$), mainly due to inverse collinearity with *percentage of state population of non-Hispanic white origin.* The R^2 of the model which excluded *ED92* was not significantly affected, dropping from 0.56 (AIC = -82.17) to 0.53 (AIC = -79.96).

It is possible, but unlikely, that the relationship between *BDmort* and *Tera97* reflects some aspect of agricultural intensity that is collinear with teratogenic pesticide use. Pesticide use is likely to be related to agricultural intensity in general: greater tilling, irrigation, fertilization, servicing with diesel fume emitting tractors, etc. For example, pesticide use (*Tera97*) is correlated with the *percentage of land area in farms* ($r = 0.65$, $p < 10^{-5}$, $n = 48$). However, infant mortality was not significantly associated with *percentage of land area in farms* in the multiple regression models when included at the same time as *Tera97* (Table 7). Significantly more variation is explained by a model that includes *Tera97* (adjusted $R^2 = 0.71$, AIC = -46.07, $n = 48$) vs. *percentage of land area in farms* (adjusted $R^2 = 0.65$, AIC = -36.54, $n = 48$).

Pesticide use and incidence of specific birth defects

After finding a general positive association between overall state use of teratogenic pesticides and the incidence of mortality due to birth defects, we were interested in determining whether certain terata were more related to pesticide use than others. However, relationships between incidence rates of specific individual birth defects and *Tera97* were not detectable with

these data. We tested the relationships between *Tera97* and the rates of individual birth defects (Table 8). The strongest individual correlation was between choanal atresia and *Tera97* ($r = 0.40$, $p = 0.027$). When the probabilities were corrected for multiple comparisons ($n = 41$), none of the associations remained significant.

Although relationships between the rates of individual birth defects and pesticides are weak, they are positive far more often than would be expected by chance if there was no effect of pesticides on rates of birth defects. Among the specific congenital anomalies, a very high proportion (34 of 41) showed positive associations with *Tera97* (Table 8). When grouped by affected organs sharing a common embryology as detailed in Table 4, 13 of 15 systems showed positive associations with the rate of pesticide use, again making up a very high proportion (Table 9). Since these comparisons are not independent (as they were carried out each time on the same set of states), a p-value cannot be attached to the proportion. However, this result is consistent with a non-specific tendency for increased incidence of most types of birth defects in areas with higher rates of teratogenic pesticide use. It is also possible that the incidence of birth defects in different organ systems covary in among-state comparisons for reasons having nothing to do with pesticides. This result requires confirmation due to the potential for artefacts or other error leading to non-specific positive, but small and non-significant, correlations.

Mortality due to birth defects and specific pesticides

We did not find that infant mortality due to birth defects was related to use of specific pesticides. We tested Spearman correlations between the variation of *BDmort* and rates of use of individual pesticides among states (Table 10). We found that the strongest correlations were

individually significant (highest was 2,4-D: $r = 0.44$, $p = 0.0016$), but after correcting for multiple comparisons ($n = 220$), these became non-significant.

Pesticides classified as teratogenic were not more likely to show significant or stronger positive correlations with *BDmort* than those not classified as teratogenic. Only 25 of the 49 suspected teratogens showed a positive relationship (Table 11). Because state-wide rates of use of different pesticides are often strongly collinear, it would be very difficult to associate infant mortality with any particular pesticides.

Discussion

Presumably, concern about possible health effects of exposure to pesticides motivated the regulation of pesticide use in North America. In addition, public concern has motivated the organic food industry as well as efforts to ban cosmetic use of pesticides (e.g., Hudson, Québec 1991 by-law 270; House of Commons of Canada 2001 Private Member's Bill C388). Although it is believed that, "approximately 25% of health problems are already environmental in origin" (Jameton and Pierce 2001), evidence of a direct link between the health of the population at large and pesticide use is still tenuous. Because measuring exposure to pesticides in the general population would be extremely difficult, we chose to carry out a preliminary test of this hypothesis using an "ecologic" study. Though cause-and-effect cannot be inferred from correlative studies of this sort, it is nonetheless well situated to consider questions of "population interventions" (Morgenstern, 1982), which broad scale pesticide applications certainly are.

In this study, we found that, after controlling for socio-economic and behavioural risk factors, among-state variation in the rate of pesticide use could statistically account for over one quarter of the variation in the rates of infant mortality due to birth defects ($r^2 = 0.29$). Our analyses of the spatial correlation between pesticide use and incidence of birth defects, and mortality due to birth defects, were done using independent sets of data. Our pesticide database, and data on infant mortality due to birth defects were much more reliable than the data on birth defect incidence (see sources of error below). Analyses of both datasets independently provide support commensurate with the quality of their data to the prediction that increased rates of birth defects and mortality due to birth defects would be seen in areas where pesticide use is high.

We did not find that any individual pesticide or class of pesticides could be pinpointed as particularly hazardous or particularly safe. The fact that all measures of pesticide use in this study are highly inter-correlated (Table 11) make it impossible to determine that associations between birth defect incidence and mortality were correlated with any specific pesticides or groups of pesticides.

Clearly, a correlative study relating infant mortality to rates of pesticide is insufficient to establish a causal link between the two. However, several other lines of evidence have shown that exposure to pesticides under more controlled conditions has a detrimental effect on infant health. Retrospective case-control studies have found increased incidence of musculoskeletal birth defects (Schreinemachers, 2003; Engel et al., 2000; Kristensen et al., 1997), multiple anomalies (Lin et al., 1994, Garcia et al., 1999), CNS defects (Kristensen et al., 1997; Garcia et al., 1999), oral clefts (Garcia et al., 1999), respiratory/circulatory defects (Schreinemachers,

2003), and birth defects in general (Zhang et al., 1992; Nurminen et al., 1995; Hureen et al., 2003) in children born to parents occupationally exposed to pesticides. Garry et al. (2002a; 2002b) noted that offspring conceived among farm families during the pesticide spraying season are disproportionately afflicted by birth defects and spontaneous abortions. Arbuckle et al. (1999; 2001) also found an association between pesticide exposure and spontaneous abortion in Ontario farmers. Shaw et al. (1999) showed positive associations between professional domestic pesticide application and incidence of neural tube defects (NTDs) and limb reduction defects. In addition, they found that NTD incidence was positively related to residential proximity to agricultural crops. Bell et al. (2001) noted an increase in fetal mortality due to birth defects for mothers exposed to restricted use pesticides during organogenesis (weeks 3-8 of pregnancy), the period most vulnerable to teratogenesis. Wigle's (2003) overall review of published evidence for the link between maternal exposure to pesticides and birth defects concluded that it is reasonably consistent, especially for birth defects affecting the CNS and cardiovascular systems or causing limb reductions or orofacial clefts.

Members of the general population are exposed to pesticides and their breakdown products. Measurable concentrations of various pesticides and their residues are found in the water, air, and soil of both agricultural and non-agricultural regions of the US (Gilliom & Hamilton, 2005). Pesticide residues are also present on food and in the tissues of the general population. Most importantly, where child and fetal health is concerned, residues and their metabolites are measurable in adult reproductive tissues and fetal tissues. The seminal fluid, ovarian follicular fluid, amniotic fluid, maternal blood, placental blood, umbilical cord blood, breast milk, and infant meconium all contained measurable quantities of many commonly used pesticides in the U.S. (see Colbourn, 2006 and references therein).

The preponderance of evidence for the teratogenicity of certain pesticides has led to the listing of 64 of the 235 (27%) agricultural pesticides included in this study on either the California Proposition 65 (a.k.a. the Safe Drinking Water and Toxic Enforcement Act of 1986), or the U.S. EPA Toxics Release Inventory Lists. Another 58 of 235 (25%) are classified as suspected endocrine disruptors. Exposure to sufficient quantities of these chemicals is thought to cause reproductive and developmental harm.

It is possible that the relationship observed in our study is due to unobserved variables that co-vary with pesticide use (rural life, for example). However, we believe that it is pesticide use which is responsible for the relationship with infant mortality. Our measures of agricultural intensity are shown in Table 12. Mortality due to birth defects was most strongly related to the percentage of state land treated with teratogenic pesticides. Mortality was less strongly correlated with *percentage of state land area in cropland* (i.e., cultivated land and land used for pasture or grazing, whether or not treated with pesticides), and even less strongly related to the *percentage of state land area in farms* (which also includes woodland and wasteland, as well as acres in the Conservation Reserve and Wetlands Reserve Programs (http://www.nass.usda.gov/Census_of_Agriculture/index.asp). These additional areas included in farmland acreage are less likely to be treated with pesticides (Mark R. Miller, National Agriculture Statistics Service, USDA, *personal communication*). Since the agricultural intensity variables with higher pesticide inputs were increasingly highly correlated with *BDmort*, and the variable with lowest pesticide input was not significantly correlated with *BDmort*, this suggests

that pesticide use intensity is the variable underlying the relationship between agricultural intensity and birth defects.

We are also not aware of any other aspect of agriculture which has been related to incidence of birth defects in more controlled studies that could explain our results. Exposure to nitrates in fertilizers have been linked in epidemiological studies to adverse reproductive outcomes such as increased risk of developing CNS birth defects, spontaneous abortion, intrauterine growth retardation, and prematurity (see Ward et al., 2005 and references therein). Recently, research has also found that the mycotoxin zearalenone, a mycotoxin produced by *Fusarium* molds, has teratogenic effects on swine. Zearalenone has estrogenic effects but at this time its human health effects are unknown (Barrett, 2000).

Sources of error

This study followed an ecologic design, and all variables used were aggregate-level measures. The incidence of birth defects is related to several risk factors including parents' genetics, health, diet, and stance on abortion, in addition to population-level factors such as the reporting practices of their state of residence, abortion laws, health care access, etc. These factors vary strongly within states, and they are likely to differ among subgroups of the state population. Therefore, while one might wish to estimate risk at the individual level, our aggregate data apply only at the population level. Inferences at any lower level (individuals or groups within states) would potentially be subject to strong cross-level biases.

It has been pointed out that use of regression modeling to control for confounders can affect both magnitude and direction of the results. However, this problem arises only if the covariates are not independent. The high tolerances in our regression model (Table 6) attest to the independence of our variables and to the robustness of our results with regard to this source of error.

That said, it is likely that pesticide effects on infant mortality are stronger than this study identifies, since many characteristics of ecologic studies tend to add random noise. Possible sources of error include:

1) Data quality: mortality due to birth defects – U.S. state birth defect registry data are quite poor, which limited our ability to pinpoint specific birth defects. There are efforts currently underway to standardize reporting policies and practices, most notably by the National Birth Defects Monitoring Program, which is currently developing a set of national reporting standards (www.nbdmp.org). However, states' reporting standards vary considerably, as demonstrated by Table 2, because individual state birth defect registries evolved without coordinated reporting guidelines. This makes comparison and interpretation of results problematic. For instance, registries differ in their surveillance methods, be they active, passive, or mixed. Passive surveillance involves searching for relevant cases in hospital discharge records, whereas active surveillance methods involve screening possible medical data sources (hospitals, private clinics, nursing homes, abortion clinics, for example) for relevant entries, and generally yields more accurate results (Piriyawat et al., 2002).

   Registries differed in other important respects as well. As seen in Table 2, some registries did not include stillbirths (82% did), cases prenatally diagnosed (64% did), or

elective terminations (42% did) in reported birth defect incidence rates, despite the known confounding effect of these practices. A study of the impact of prenatal diagnosis on surveillance rates of neural tube defects (NTDs) in 6 states showed that between 9-42% of pregnancies were terminated following positive prenatal diagnosis of a NTD (Cragen *et al.*, 1995). An Australian study showed that excluding elective terminations from fetal mortality calculations had the effect of reducing rates of fetal mortality due to birth defects by 44% (Davidson et al., 2005). Studies by Hobbs et al. (2001) and by Correa-Villasenor et al. (2003) concluded that although some true differences in birth defect incidence rates are reflected by registry data, the largest variability is attributable to differences in surveillance methods. Differing state surveillance practices would be most likely to obscure any association between the variability of birth defect incidence rates due to exposure to teratogenic pesticides. A spurious positive relationship would arise only if states where high quantities of pesticides are used also more systematically report incidence and mortality due to birth defects. Despite these limitations, this database is the only (nearly) comprehensive source of state birth defect incidence for the time period of interest.

2) Data quality: pesticides – There are notable gaps in the pesticide data. The NCFAP pesticide use database accounts for conventional pesticides used on agricultural row crops only. Agricultural conventional pesticide use accounts for ~75% of total conventional pesticide use. The remaining ~25% is made up by the commercial and residential sectors and was unaccounted for in this study.

Another concern is that updated toxicity testing has yet to be performed on all of the pesticides included in the NCFAP dataset. The EPA called for re-registration of all active ingredients registered for use before 1988 in order to maintain pace with evolving technological and regulatory requirements. By 2004, 22% of active ingredients currently in use still required re-registration for teratogenicity (EPA, 2004). One of the hypotheses we were interested in testing was whether regions with higher use of pesticides classified as teratogenic or endocrine disrupting also had higher rates of infant mortality. Since 22% of pesticides have not been classified using up to date EPA assays, we cannot trust that our results regarding the specific effects of teratogenic vs. non-teratogenic pesticides are representative.

3) State-level aggregations of data – States are demographically and culturally diverse, delineated by geographic and political considerations unrelated to the causes and prevalence of birth defects. Aggregation over these units will tend to obscure birth defect - pesticide relationships. Further, there exists a relatively high rate of domestic migration (inter-state movement) within the US – the Bureau of the Census estimated an average domestic migration rate of 15.4% for the period of 1995-2000, meaning that, on average, 1 in 7 Americans moved out of their state of residence in this five-year span (2000). In general, interstate mixing would also be likely to obscure the relationships we sought to test.

County-level fetal health and pesticide use information could have provided a potentially stronger test of our hypothesis; however, sufficient data were not available. On the other hand, because birth defects are rare events, using the state as the unit of

analysis integrated our analysis over a sufficiently large population to avoid extremely local confounding effects.

4) Use of mortality as a response variable – Though infant mortality is unambiguous and can be accurately diagnosed, measures of birth defect-induced mortality and birth defect incidence are situated at the tail end of the extended time period required for development of a human baby, which makes underestimation likely. Birth prevalence should not be assumed to be true total incidence. In choosing as our fetal health gauge the measure of infant mortality due to birth defects, we have used a practical, but conservative guide. Forty to 60% of spontaneously aborted fetuses are afflicted with chromosomal anomalies and another 40-50% are morphologically abnormal, meaning that approximately 80% suffer from one or the other (Kalter, 2003). To determine the effect of environmental exposures on congenital anomalies, it would be desirable to include data on regional rates of miscarriage and stillbirth. However, most of the estimated 15% of pregnancies that miscarry go unrecognized and/or unreported (Wilcox, 1983). Consequently, use of end-of-term measures such as the ones used in this study to approximate birth defect mortality and incidence are likely to underestimate pesticide effects.

Given the number of factors that would tend to blur the associations investigated in this study, it is noteworthy that a significant association from best-available, independent datasets was found which supports the hypothesis that infant health in the general population is adversely affected by broad scale pesticide use.

Future Research

Our results underline commonalities between teratogenic pesticides and all pesticides, and these may be traceable to harmful common ingredients in pesticide formulations. Commercial pesticide formulations include not only the biocide, or "active ingredient", but also any number of so-called "inert ingredients" included to enhance the stability or activity of the formulation. It is known that many of these inert ingredients have teratogenic or endocrine-disrupting properties independent of the active ingredient, and several authors have hypothesized that links between pesticide use and human health effects may be due to exposure to the "inert", rather than to the "active", ingredients (Blair and Zahm, 1995; Petrelli et al., 1993; Danish EPA, 1999). Our results are consistent with this idea, but cannot speak directly to it since our data did not include measures of inert ingredients. The Food Quality Protection Act of 1996 required residue tolerance reassessments for all pesticide formulations – including inert ingredients – registered for use before 1988 (Fenner-Crisp, 2001; p. 686), but available agricultural pesticide use data are limited to active ingredients only. The EPA has now begun to subject other pesticidal ingredients to the same regulatory scrutiny as the active ingredients. Future efforts should quantify the use of these ingredients and their effects on human health. In addition, we would be interested to see a large case/control study comparing pesticide residues in the tissues of mothers of infant mortality cases, versus mothers of healthy infants.

Given the limitations of ecological studies, specifically ecological bias, cross-level bias, and relatively low inferential strength of results, our results must be seen as generating new hypotheses to be tested, and as providing direction for future studies. The next step would be a

study of pesticide exposure and infant health using individual level data, which are not available without proper justification due to privacy concerns. It is in support of such studies that this project was undertaken. Macroecologic studies using aggregate-level data will continue to be done, however, due to their low cost, speed, and a desire to make best use of available data to benefit public health.

We are grateful for the publicly available databases used in this study. Specifically, the infant health databases maintained by the March of Dimes and the Center for Disease Control's National Center for Health Statistics, the pesticide use database maintained by the National Center for Food and Agricultural Policy (www.ncfap.org), as well as the pesticide information database maintained by the Pesticide Action Network (www.pesticideinfo.org). The California Birth Defects Monitoring Program and the Canadian Institute for Health Information refused to release data on rates of birth defects in California and individual health records in Canada for the purposes of this study. This study was funded by a grant from the Natural Science and Engineering Research Council of Canada.

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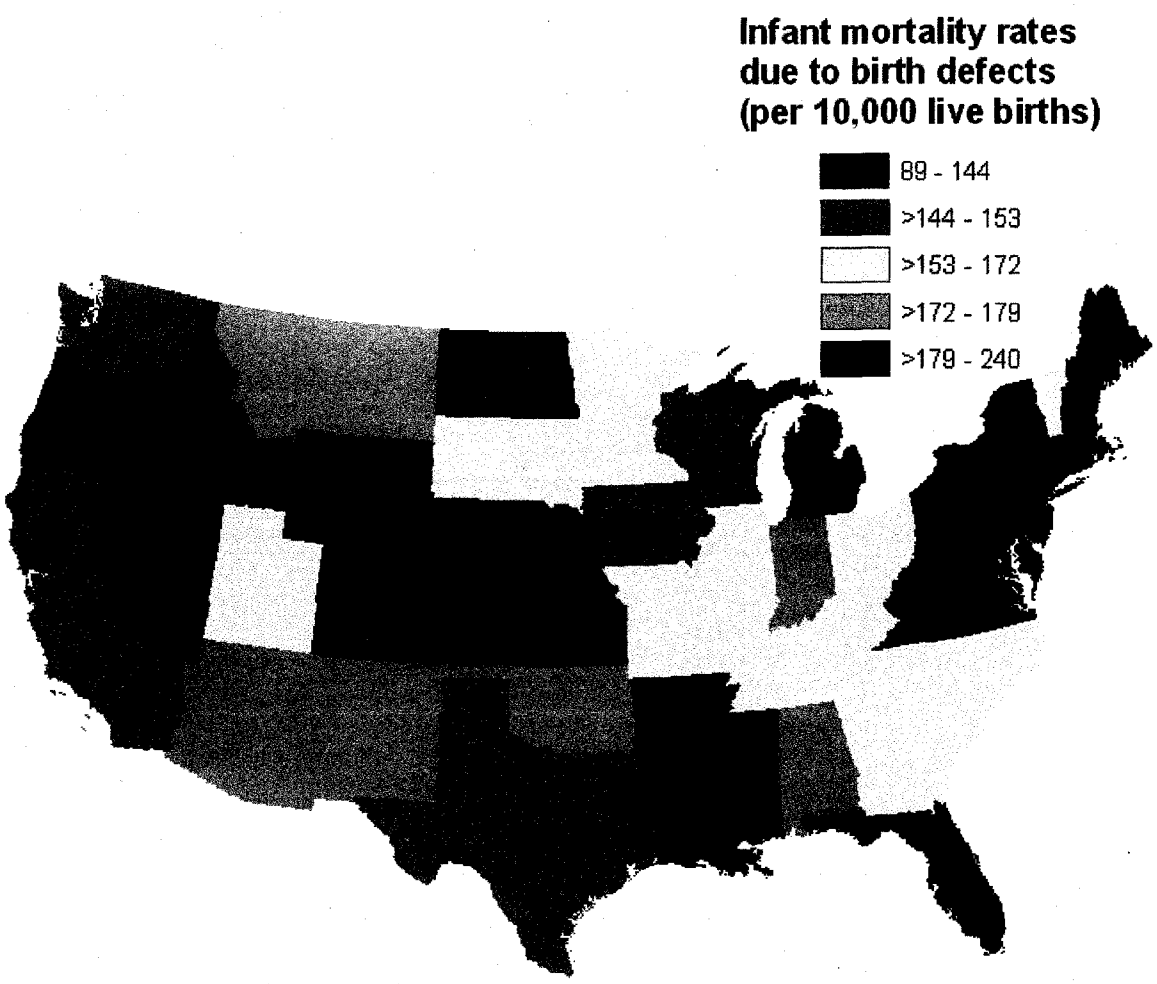

Figure 1: Distribution of state infant mortality rates due to birth defects. Rates are calculated per 10,000 live births. States coloured dark green or light green have infant mortality rates due to birth defects below the national average. Yellow states have an average amount. Orange and red states have above average rates of infant mortality due to birth defects.

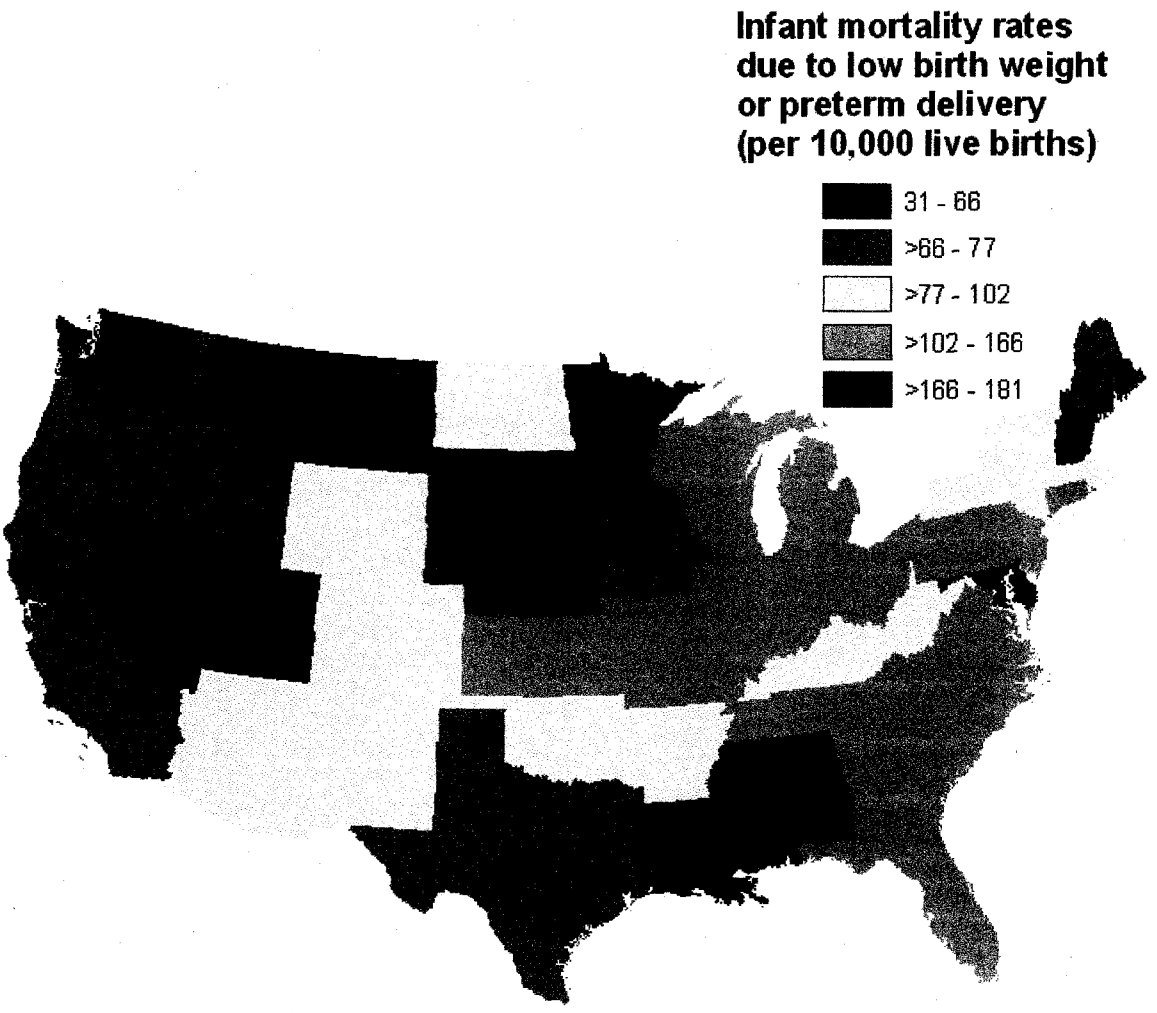

Figure 2: Distribution of state infant mortality rates due to low birth weight or preterm delivery. Rates are calculated per 10,000 live births. States coloured dark green or light green have infant mortality rates due to low birth weight or preterm delivery below the national average. Yellow states have an average amount. Orange or red states have above average rates of infant mortality due to low birth weight or preterm delivery.

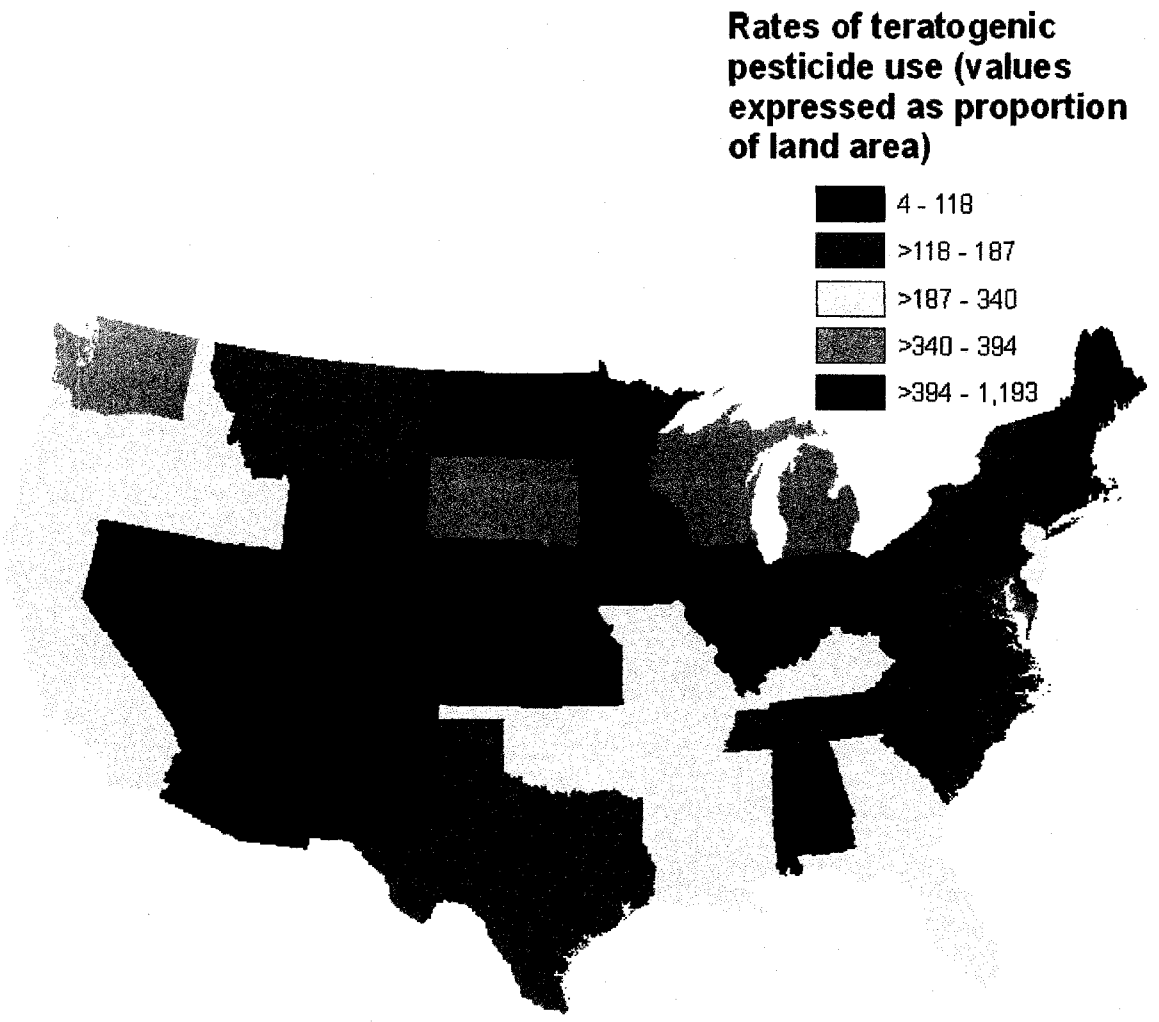

Figure 3: Distribution of teratogenic pesticide use. Pesticide use is expressed as a function of total land area of the state. Green states use an amount of teratogenic pesticides below the national average. Yellow states use an average amount. Orange and red states use a greater than average amount of teratogenic pesticides.

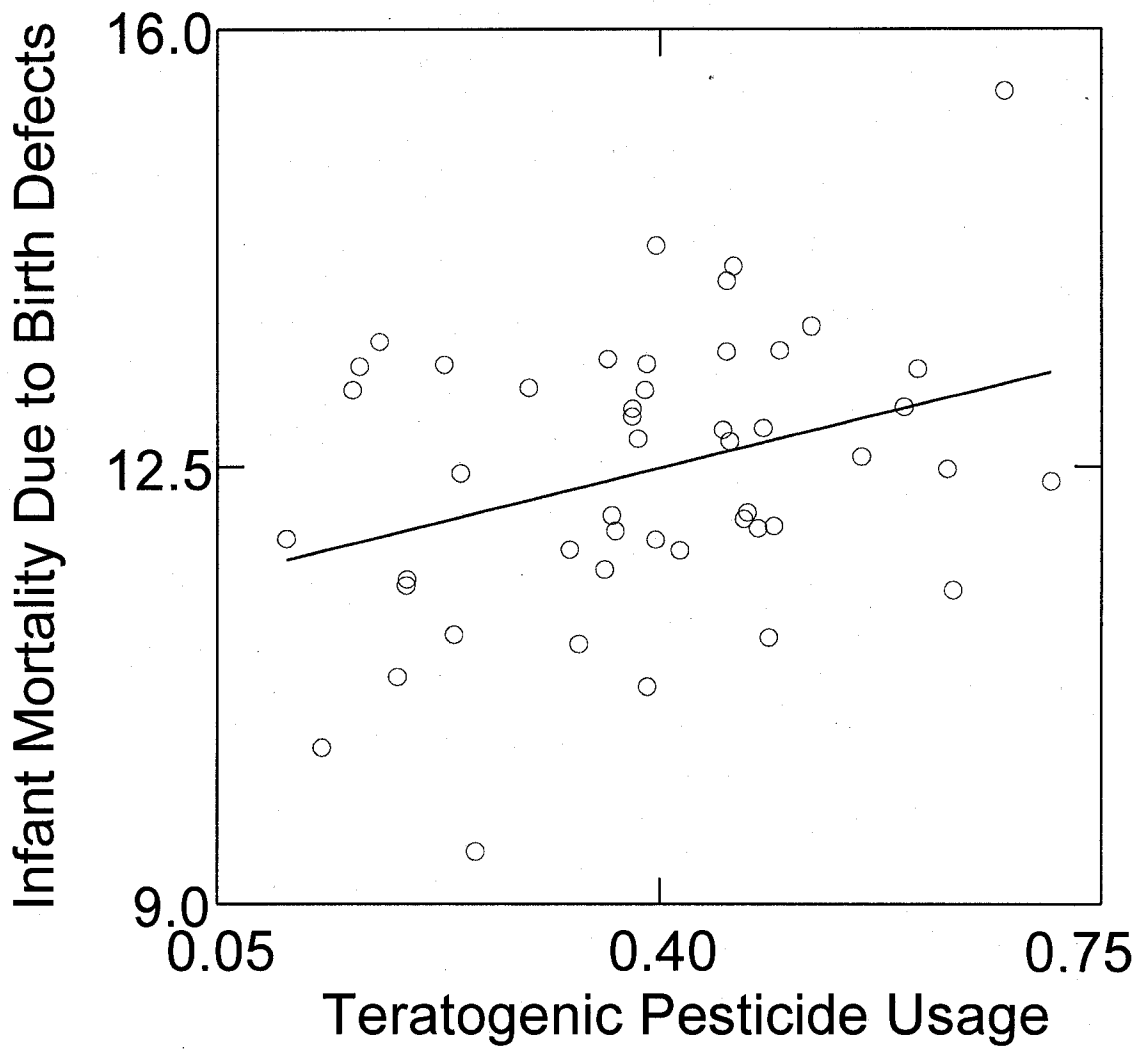

Figure 4: Per-state rate of infant mortality due to birth defects as a function of the proportion of state area treated with teratogenic pesticides ($r = 0.33$, $p = 0.022$, $n = 48$).

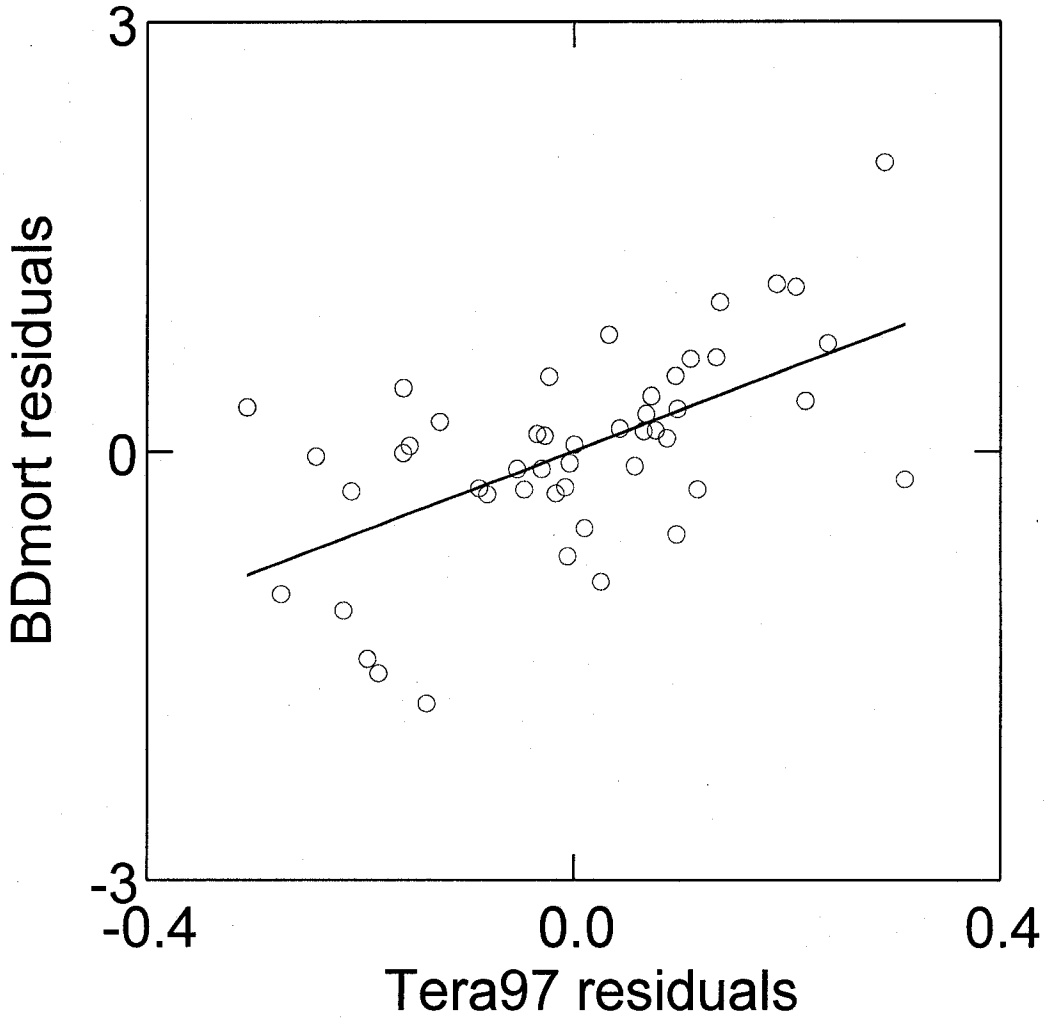

Figure 5: Residuals of the per-state rate of infant mortality due to birth defects as a function of the residuals of the proportion of state area treated with teratogenic pesticides, both controlled for socio-economic and behavioural variables.

Table 1: Total number of acres treated with potentially teratogenic or endocrine disrupting pesticides during years 1991-1994 and 1995-1998 as a fraction of the total acreage of the state (N = 48).

State	EDs92	Teras92	EDs97	Teras97
Alabama	0.142	0.046	0.099	0.026
Arizona	0.071	0.014	0.031	0.012
Arkansas	0.269	0.146	0.243	0.093
California	0.114	0.088	0.128	0.102
Colorado	0.138	0.028	0.060	0.035
Connecticut	0.044	0.014	0.036	0.013
Delaware	0.835	0.269	0.744	0.253
Florida	0.121	0.092	0.099	0.072
Georgia	0.214	0.078	0.207	0.095
Idaho	0.067	0.053	0.057	0.063
Illinois	0.904	0.361	0.865	0.248
Indiana	0.773	0.308	0.770	0.221
Iowa	0.916	0.449	0.949	0.358
Kansas	0.299	0.125	0.361	0.141
Kentucky	0.179	0.071	0.189	0.059
Louisiana	0.325	0.155	0.244	0.093
Maine	0.021	0.011	0.013	0.008
Maryland	0.380	0.144	0.301	0.115
Massachusetts	0.031	0.016	0.027	0.016
Michigan	0.255	0.145	0.246	0.109
Minnesota	0.313	0.258	0.310	0.210
Mississippi	0.402	0.172	0.239	0.097
Missouri	0.314	0.119	0.317	0.091
Montana	0.068	0.037	0.070	0.046
Nebraska	0.477	0.171	0.544	0.122
Nevada	0.001	0.001	0.003	0.001
New Hampshire	0.010	0.004	0.008	0.002
New Jersey	0.142	0.057	0.119	0.059
New Mexico	0.045	0.004	0.016	0.004
New York	0.118	0.065	0.155	0.038
North Carolina	0.226	0.093	0.224	0.054
North Dakota	0.339	0.197	0.327	0.305
Ohio	0.473	0.262	0.441	0.176
Oklahoma	0.159	0.119	0.159	0.059
Oregon	0.044	0.061	0.057	0.062
Pennsylvania	0.150	0.061	0.177	0.049
Rhode Island	0.025	0.010	0.019	0.007
South Carolina	0.171	0.085	0.183	0.056
South Dakota	0.263	0.131	0.268	0.112
Tennessee	0.196	0.078	0.158	0.054
Texas	0.136	0.032	0.209	0.047
Utah	0.047	0.006	0.010	0.004
Vermont	0.049	0.019	0.047	0.014
Virginia	0.125	0.054	0.130	0.045

Washington	0.104	0.102	0.140	0.118
West Virginia	0.017	0.007	0.018	0.006
Wisconsin	0.216	0.130	0.201	0.104
Wyoming	0.012	0.005	0.011	0.008

Table 2: Characteristics of surveillance systems in the National Birth Defects Prevention Network (NBDPN) dataset. Large differences in reporting standards & guidelines affect data quality and preturb comparison analyses across registries.

	Number	%
Number of registries[a]	33 states	100%
Case definition		
Number of registries including fetal deaths[b]	27 states	82%
Number of registries including elective terminations	14 states	42%
Number of registries including prenatal diagnoses	21 states	64%
Registries reporting >=90% of the 45 NBDPN conditions	28 states	85%
Registries reporting >=80% of the 45 NBDPN conditions	30 states	91%
Case ascertainment method		
Active	9 states	27%
Passive	13 states	39%
Mixed	11 states	33%
Cohort size		
<20000	5 states	15%
20,000 to 49,999	7 states	21%
50,000+	21 states	64%
Registries with statewide representation	30 states	91%
Average yearly size	80,430	
Total number of births included (all years)	24,075,982	
Range	7,676 - 365,000	
Number of years of available data[c]		
2-4	6 states	18%
5+	27 states	82%
Average # of years	8.27	
Monitored age range		
Neonatal	4 states	12%
1 yr	13 states	39%
> 1 yr	16 states	48%

[a]The following state registries were included, taken from either the 2001 or 2004 NBDPN datasets: Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia (MACDP), Illinois, Iowa, Kentucky, Maryland, Massachusetts, Michigan, Mississippi, Missouri, Montana, New Jersey, New Mexico, New York, North Carolina, North Dakota, Oklahoma, Rhode Island, South Carolina, Tennessee, Texas, Utah, Virginia, Washington, West Virginia, and Wisconsin.
[b]Missouri was reported as having no inclusion of terminations, though in reality they do include terminations of fetuses affected with neural tube defects.
[c]Refers to the number of years of a possible 13 (1989-2001) for which data was reported.

Table 3: Adjustments made to the raw National Birth Defects Prevention Network (NBDPN) dataset in order to reduce number of empty cells for the purposes of conducting multivariate analysis. The 25 empty cells that remained following these adjustments were filled in using average values calculated from all other reporting registries.

Culling order – Action taken (culled registries or birth defect, *non-empty cells / total # of cells*)
0 - (none, 1325 / 1485)
1- Removed birth defects monitored by less than half of registries from analysis (amniotic bands, *1310 / 1452*)
2- Removed state registries monitoring less than half of birth defects from analysis (South Carolina, Maryland, *1295 / 1364*)
3 – Removed rates of gastroschisis and omphalocele and Fetal alcohol syndrome birth defects from analysis (*1231 / 1260*)
4 – Removed North Dakota because of low (51%) reporting rate (*1205 / 1230*)

Table 4: Birth defect conditions used in this study grouped by organ system (N = 45). Adapted from Scheuerle & Tilson (2002).

Face and Neck	**Central Nervous System**	**Cleft Lip/Palate**	**Conotruncal Heart Defects**
Aniridia	Anencephaly	Cleft lip with and without cleft palate	Common truncus
Anophthalmia/microphthalmia	Encephalocele	Cleft palate without cleft lip	Tetralogy of Fallot
Anotia/microtia	Hydrocephalus		Transposition of great vessels
Choanal atresia	Spina Bifida		
Congenital cataract			
Obstructive Heart Defects –Right side	**Obstructive Heart Defects – Left side**	**Heart – Other Defects**	**Other Circulatory System**
Ebstein's anomaly	Aortic valve stenosis	Atrial septal defect	Patent ductus arteriosis
Pulmonary valve atresia/stenosis	Coarctation of aorta	Endocardial cushion defects	
Tricuspid valve atresia/stenosis	Hypoplastic left heart syndrome	Ventricular septal defect	
Gastrointestinal – Upper	**Gastrointestinal – Lower**	**Renal and Urinary System**	**Genitourinary – Male**
Esophageal atresia / Tracheoesophageal fistula	Biliary atresia	Bladder extrophy	Hypospadias & epispadias
Pyloric stenosis	Hirschsprung's disease	Obstructive genitourinary defect	
	Rectal and large intestinal atresia/stenosis	Renal agenesis/hypoplasia	
Musculoskeletal – Other	**Chromosomal Anomaly**	**Limb Reduction Defects**	**Other organs and organ systems**
Congenital hip dislocation	Down's Syndrome	Limb reduction defect, lower	Amniotic bands[A]
Diaphragmatic hernia	Trisomy 13	Limb reduction defect, upper	Fetal alcohol syndrome[A]
Microcephaly	Trisomy 18		
Gastroschisis[A]			
Omphalocele[A]			

[A]These conditions were omitted from the analysis because they were only rarely monitored by individual registries

Table 5: Socioeconomic control variables included in the regression model. These variables were included to account for potential co-linearity with rates of pesticide use.

Public Health	***Socioeconomic***	***Demographic***
-doctor coverage per 100,000 individuals [1]	*-unemployment rate* [7]	*-Caucasian % of population* [10]
-% of births to mothers aged 20-39 [2]	*-average household income* [8]	
-% of population consuming more than 5 servings of fruits and/or vegetables per day [3]	*-% of population with bachelor degree* [9]	
-% of live births to mothers who did not receive pre-natal care in the 1st trimester [4]	*- state abortion rate per 1000 women (1996 and 2000)* [11]	
-% of new mothers who smoked during pregnancy [5]		
-% of females 18-44 who smoke [6]		

[1] Obtained online March 17, 2005 @ http://www.census.gov/statab/www/ranks.html
[2] Obtained online May 24, 2005 from www.marchofdimes.com/peristats
[3] Obtained online May 24, 2005 from http://apps.nccd.cdc.gov/brfss/
[4] Obtained online May 24, 2005 @ http://www.cdc.gov/nchs/fastats/prenatal.htm
[5] Obtained online February 9, 2005 @ http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5339a1.htm
[6] Obtained online May 24, 2005 from www.marchofdimes.com/peristats
[7] Obtained online March 17, 2005 @ http://www.census.gov/statab/www/ranks.html
[8] Obtained online March 17, 2005 @ http://www.census.gov/statab/www/ranks.html
[9] Obtained online March 17, 2005 @ http://www.census.gov/statab/www/ranks.html
[10] Obtained online March 17, 2005 @ http://www.census.gov/popest/race.html
[11] Obtained online March 3, 2007 @ www.abortiontv.com/Misc/AbortionStatistics.htm#United%20States and http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5212a1.htm

Table 6: A multiple regression model of determinants of infant mortality due to birth defects*. N = 48, F = 30.0, and adjusted $r^2 = 0.71$ for the complete model.

Independent Variables	Coefficient	SE	Tolerance	Variable p
Household Income[a]	-1.30×10^{-4}	2.00×10^{-5}	0.652	$<10^{-5}$
Smoking Rates (♀)[b]	-9.27×10^{-2}	2.45×10^{-2}	0.768	$<10^{-3}$
Tera97[c]	2.82	0.597	0.982	$<10^{-4}$
Abortion Rates[d]	-4.46×10^{-2}	1.64×10^{-2}	0.742	0.009

**BDmort* = 1996-2001 average state rates per 100,000 live births of infant mortality due to birth defects (square root transformed to better satisfy normality).

[a]*Household Income* = state average median household income in 1999 (US$).

[b]*Smoking Rates* (♀) = 1999-2003 average state percentage of females aged 18-44 having ever smoked 100 cigarettes in a lifetime and currently smoking everyday or some days.

[c]*Tera97* = 1995-1998 average state acreage treated with teratogenic pesticides as a proportion of the total land area of the state (third root transformed to better satisfy normality)

[d]*Abortion Rates* = state abortion rate per 1000 women, averaged data from 1996 and 2000

SE = standard error of the coefficient.

Table 7: Regression model of the determinants of infant mortality due to birth defects*, including the collinear variables *Tera97* and *%FRMLNDRT3*. *%FRMLNDRT3* was not significantly related to the dependent variable, implying that the relationship between pesticide use and infant mortality due to birth defects is independent of other agricultural practices. N = 48, F = 23.5, adjusted $r^2 = 0.71$ for the model.

Independent Variables	Coefficient	SE	Tolerance	Variable p
Household Income[a]	-1.30×10^{-4}	2.00×10^{-5}	0.542	$<10^{-5}$
Smoking Rates (♀)[b]	-9.11×10^{-2}	2.55×10^{-2}	0.727	$<10^{-3}$
Abortion Rates[c]	-4.38×10^{-2}	1.69×10^{-2}	0.716	0.013
Tera97[d]	2.66	0.870	0.472	0.004
%Farmland[e]	5.13×10^{-2}	0.193	0.415	0.791

**BDmort* = 1996-2001 average state rates per 100,000 live births of infant mortality due to birth defects (square root transformed to better satisfy normality)

[a]*Household Income* = state average median household income in 1999 (US$).

[b]*Smoking Rates* (♀) = 1999-2003 average state percentage of females aged 18-44 having ever smoked 100 cigarettes in a lifetime and currently smoking everyday or some days.

[c]*Abortion Rates* = state abortion rate per 1000 women, averaged data from 1996 and 2000

[d]*Tera97* = 1995-1998 average state acreage treated with teratogenic pesticides as a proportion of the total land area of the state (third root transformed to better satisfy normality), *SE* = standard error of the coefficient.

[e] *%FRMLNDRT3* = 1997-2002 average state percentage of land area used for farmland (third root transformed to better satisfy normality).

Table 8: Pearson correlations between proportions of state land area treated with teratogenic pesticides (*Tera97*) and rates of individual birth defects. Note that a very high proportion (34 of 41) of specific birth defects are positively correlated with *Tera97*.

Birth Defect	Correlation Coefficient with *Tera97*	P value
Anencephaly	0.279	0.136
Aniridia	-0.088	0.644
Anophthalmia/microphthalmia	0.100	0.599
Anotia/microtia	-0.053	0.781
Aortic valve stenosis	0.160	0.399
Atrial septal defect	0.029	0.881
Biliary atresia	0.124	0.515
Bladder extrophy	0.212	0.261
Choanal atresia	0.404	0.027
Cleft lip with and without cleft palate	-0.128	0.501
Cleft palate without cleft lip	0.190	0.314
Coarctation of aorta	0.047	0.806
Common truncus	-0.078	0.684
Congenital cataract	0.118	0.534
Congenital hip dislocation	0.077	0.687
Diaphragmatic hernia	0.096	0.612
Down's Syndrome	0.079	0.678
Ebstein's anomaly	-0.225	0.231
Encephalocele	0.109	0.566
Endocardial cushion defects	0.010	0.957
Esophageal atresia / Tracheoesophageal fistula	0.214	0.257
Hirschsprung's disease	0.270	0.150
Hydrocephalus	0.352	0.057
Hypoplastic left heart syndrome	0.389	0.034
Hypospadias & epispadias	0.310	0.096
Microcephaly	0.044	0.818
Obstructive genitourinary defect	0.220	0.244
Patent ductus arteriosis	0.088	0.645
Pulmonary valve atresia/stenosis	-0.142	0.453
Pyloric stenosis	0.341	0.065
Rectal and large intestinal atresia/stenosis	0.042	0.824
Limb reduction defect, lower	0.003	0.986
Limb reduction defect, upper	0.065	0.733
Renal agenesis/hypoplasia	0.210	0.265
Spina Bifida	0.259	0.167
Tetralogy of Fallot	0.031	0.870
Transposition of great vessels	0.252	0.178
Tricuspid valve atresia/stenosis	-0.041	0.830
Trisomy 13	0.066	0.730
Trisomy 18	0.020	0.915
Ventricular septal defect	0.139	0.465

Table 9: Pearson correlations between proportions of state land area treated with teratogenic pesticides (*Tera97*) and rates of individual birth defects, grouped by common ontogeny. Note that a very high proportion (13 of 15) of specific birth defects are positively correlated with *Tera97*.

Birth defect grouping	**Correlation coefficient with *Tera97***	**P value**
Central Nervous System	0.354	0.055
Chromosomal Anomaly	0.083	0.664
Cleft Lip/Palate	-0.021	0.911
Conotruncal Heart Defects	0.170	0.370
Face and Neck	0.148	0.436
Gastrointestinal – Lower	0.150	0.430
Gastrointestinal – Upper	0.391	0.033
Genitourinary – Male	0.301	0.106
Heart – Other Defects	0.091	0.631
Limb Reduction Defects	0.046	0.808
Musculoskeletal – Other	0.079	0.678
Obstructive Heart Defects – Left side	0.185	0.329
Obstructive Heart Defects –Right side	-0.151	0.425
Other Circulatory System	0.088	0.645
Renal and Urinary System	0.222	0.239

Table 10: Pearson correlations between all pesticides included in *Tera97* (N = 220) and rates of infant mortality due to birth defects. Note that a very high proportion (142 / 220) of the relationships between rates of use of individual pesticides and *BDmort* were positive.

Pesticide	Correlation coefficient with *BDmort*	P value
ABAMECTIN	-0.134	0.363
ACEPHATE	0.184	0.209
ACETOCHLOR	0.081	0.583
ACIFLUORFEN	0.303	0.037
ALACHLOR	0.017	0.908
ALDICARB	0.235	0.108
AMETRYN	0.004	0.981
AMITRAZ	0.118	0.423
ASULAM	0.101	0.494
ATRAZINE	0.076	0.606
AZADIRACHTIN	-0.049	0.743
AZINPHOS-METHYL	-0.194	0.187
AZOXYSTROBIN	0.252	0.084
BENEFIN	0.155	0.294
BENOMYL	-0.031	0.832
BENSULFURON	0.215	0.142
BENSULIDE	-0.297	0.041
BENTAZON	0.230	0.116
BENZYLADENINE	-0.128	0.385
BIFENTHRIN	0.190	0.196
BROMACIL	-0.083	0.575
BROMOXYNIL	0.348	0.015
BT	0.038	0.796
BUPROFEZIN	0.096	0.515
BUTENOIC-ACID	-0.093	0.528
BUTYLATE	0.024	0.874
CACODYLIC-ACID	-0.008	0.954
CAPTAN	-0.497	0.000
CARBARYL	0.138	0.351
CARBOFURAN	0.252	0.083
CHLORETHOXYFOS	0.095	0.520
CHLORIMURON	-0.002	0.988
CHLOROPICRIN	0.026	0.863
CHLOROTHALONIL	-0.136	0.356
CHLORPYRIFOS	0.137	0.354
CHLORSULFURON	0.222	0.129
CLETHODIM	0.296	0.041
FENPROPATHRIN	0.059	0.690

FERBAM	-0.475	0.001
FLUAZIFOP	0.187	0.202
FLUMETRALIN	0.107	0.468
FLUMETSULAM	0.136	0.358
FLUMICLORAC	0.077	0.605
FLUOMETURON	0.311	0.031
FLUTOLANIL	0.063	0.672
FOMESAFEN	0.240	0.100
FONOFOS	0.071	0.633
FORMETANATE-HCL	-0.170	0.247
FOSETYL-AL	-0.125	0.397
GIBBERELLIC-ACID	-0.135	0.361
GLYPHOSATE	0.382	0.007
HALOSULFURON	0.016	0.912
HEXAZINONE	-0.181	0.218
HEXYTHIAZOX	-0.431	0.002
IMAZAMETHABENZ	0.393	0.006
IMAZAPIC	0.049	0.743
IMAZAQUIN	0.189	0.199
IMAZETHAPYR	0.087	0.556
IMIDACLOPRID	-0.069	0.641
IPRODIONE	-0.103	0.484
LACTOFEN	0.193	0.190
LAMBDACYHALOTHRIN	0.162	0.271
LINDANE	0.106	0.473
LINURON	-0.222	0.129
MALATHION	0.299	0.039
MALEIC-HYDRAZIDE	0.087	0.555
MANCOZEB	0.082	0.580
MANEB	-0.041	0.783
MCPA	0.413	0.004
MCPB	-0.134	0.362
MCPP	-0.338	0.019
MEFENOXAM	0.043	0.771
MEPIQUAT-CHLORIDE	0.239	0.101
METALAXYL	0.151	0.305
METALDEHYDE	-0.099	0.502
METAM-SODIUM	0.050	0.736
METHAMIDOPHOS	0.074	0.616
METHIDATHION	-0.092	0.534
METHOMYL	-0.113	0.443
METHOXYCHLOR	-0.069	0.642
METHYL-BROMIDE	-0.089	0.549
METHYL-PARATHION	0.413	0.004
METIRAM	-0.140	0.342
METOLACHLOR	-0.017	0.908
METRIBUZIN	0.001	0.996
METSULFURON	0.191	0.193
MOLINATE	0.262	0.072
MSMA	0.273	0.060

MYCLOBUTANIL	-0.176	0.230
NAA	-0.249	0.088
NAD	-0.050	0.735
NALED	-0.069	0.641
NAPROPAMIDE	-0.368	0.010
NAPTALAM	-0.235	0.108
NICOSULFURON	0.126	0.394
NORFLURAZON	0.234	0.109
OIL	-0.148	0.315
ORYZALIN	-0.084	0.571
OXAMYL	0.249	0.087
OXYDEMETON-METHYL	-0.088	0.553
OXYFLUORFEN	0.108	0.467
OXYTETRACYCLINE	-0.222	0.129
OXYTHIOQUINOX	-0.091	0.538
PARAQUAT	0.070	0.635
PCNB	0.321	0.026
PEBULATE	-0.048	0.748
PENDIMETHALIN	0.164	0.265
PERMETHRIN	-0.012	0.937
PHENMEDIPHAM	0.284	0.051
PHORATE	0.284	0.050
PHOSMET	-0.153	0.298
PICLORAM	0.150	0.310
PRIMISULFURON	0.136	0.358
PROFENOFOS	0.286	0.048
PROMETRYN	0.303	0.036
PRONAMIDE	-0.089	0.548
PROPACHLOR	0.187	0.204
PROPAMOCARB	0.021	0.888
PROPANIL	0.218	0.137
PROPARGITE	-0.022	0.883
PROPICONAZOLE	-0.009	0.953
PROSULFURON	0.181	0.217
PYRAZON	-0.054	0.716
PYRIDABEN	-0.354	0.014
PYRIDATE	0.158	0.283
PYRIPROXYFEN	0.081	0.583
PYRITHIOBAC	0.342	0.017
QUINCLORAC	0.226	0.123
QUIZALOFOP	0.258	0.077
RIMSULFURON	0.158	0.283
SETHOXYDIM	0.260	0.074
SIMAZINE	-0.182	0.217
SODIUM-CHLORATE	0.284	0.050
SPINOSAD	0.323	0.025
STREPTOMYCIN	-0.302	0.037
SULFENTRAZONE	0.117	0.429
SULFUR	-0.138	0.351

SULFURIC-ACID	0.226	0.122
SULPROFOS	0.334	0.020
TEBUCONAZOLE	0.376	0.008
TEBUFENOZIDE	0.245	0.094
TEBUPIRIMPHOS	0.157	0.287
TEBUTHIURON	0.108	0.466
TEFLUTHRIN	-0.104	0.480
TERBACIL	-0.091	0.539
TERBUFOS	0.078	0.600
THIDIAZURON	0.339	0.018
THIFENSULFURON	0.094	0.526
THIOBENCARB	0.164	0.266
THIODICARB	0.239	0.102
THIOPHANATE-METHYL	0.191	0.193
THIRAM	-0.202	0.169
TRALOMETHRIN	0.311	0.031
TRIADIMEFON	-0.086	0.563
TRIALLATE	0.307	0.034
TRIASULFURON	0.164	0.265
TRIBENURON	0.263	0.071
TRIBUFOS	0.292	0.044
TRICLOPYR	0.059	0.689
TRIFLUMIZOLE	-0.080	0.588
TRIFLURALIN	0.410	0.004
TRIFLUSULFURON	0.276	0.057
TRIFORINE	-0.190	0.195
TRIPHENYLTIN-HYD	0.266	0.067
1-3-D	0.083	0.575
2-4-D	0.443	0.002
2-4-DB	-0.005	0.974
VERNOLATE	0.065	0.659
VINCLOZOLIN	-0.307	0.034
ZIRAM	-0.338	0.019

Table 11: Pearson correlations between proportions of state land area treated with teratogenic pesticides (*Tera97*) and rates of individual birth defects. Only 25 of the 49 suspected teratogens showed a positive relationship.

Teratogen	Correlation coefficient with BDmort	P value
ABAMECTIN	-0.134	0.363
ALACHLOR	0.017	0.908
AMITRAZ	0.118	0.423
BENOMYL	-0.031	0.832
BIFENTHRIN	0.190	0.196
BROMOXYNIL	0.348	0.015
CHLORSULFURON	0.222	0.129
CYANAZINE	0.124	0.400
CYCLOATE	0.236	0.107
DIAZINON	-0.331	0.021
DICAMBA	0.285	0.050
DICLOFOP	0.254	0.081
DIMETHOATE	0.203	0.165
DIURON	0.089	0.549
EPTC	0.179	0.223
FENBUTATIN OXIDE	-0.115	0.435
FENOXAPROP	0.425	0.003
FLUAZIFOP	0.187	0.202
LINURON	-0.222	0.129
MANCOZEB	0.082	0.580
MANEB	-0.041	0.783
METAMSODIUM	0.050	0.736
METHYLBROMIDE	-0.089	0.549
METIRAM	-0.140	0.342
METRIBUZIN	0.001	0.996
MOLINATE	0.262	0.072
MYCLOBUTANIL	-0.176	0.230
NALED	-0.069	0.641
OXYDEMETON-METHYL	-0.088	0.553
OXYTETRACYCLINE	-0.222	0.129
OXYTHIOQUINOX	-0.091	0.538
PROMETRYN	0.303	0.036
PROPACHLOR	0.187	0.204
PROPARGITE	-0.022	0.883
PROPICONAZOLE	-0.009	0.953
QUIZALOFOP	0.258	0.077
SIMAZINE	-0.182	0.217
STREPTOMYCIN	-0.302	0.037
SULPROFOS	0.334	0.020
TEBUTHIURON	0.108	0.466
TERBACIL	-0.091	0.539

THIOPHANATE	0.191	0.193
THIRAM	-0.202	0.169
TRIADIMEFON	-0.086	0.563
TRIFORINE	-0.190	0.195
TRIPHENYLTIN	0.266	0.067
V24DB	-0.005	0.974
VINCLOZOLIN	-0.307	0.034
ZIRAM	-0.338	0.019

Table 12: Pearson correlations between measures of pesticide use intensity. Note that all variables are highly collinear with Tera97 except %Farmland. In all cases N = 48 and $p < 0.00001$.

	Tera97	%Cropland	%Harvested Cropland	%Farmland	%Cropland treated w/ pesticides
Tera97	1.00				
%Cropland	0.90	1.00			
%Harvested Cropland	0.93	0.98	1.00		
%Farmland	0.65	0.80	0.73	1.00	
%Cropland treated w/ pesticides	0.96	0.92	0.94	0.66	1.00

Tera97 = 1995-1998 average state acreage treated with teratogenic pesticides as a proportion of the total land area of the state (third root transformed to better satisfy normality).

%Cropland = 1997-2002 average state percentage of land area used for cropland (third root transformed to better satisfy normality).

%Harvested Cropland = 1997-2002 average state percentage of harvested cropland (third root transformed to better satisfy normality).

%Farmland = 1997-2002 average state percentage of land area used for farmland (third root transformed to better satisfy normality).

%Cropland treated w/ pesticides = 1997-2002 average state percentage of cropland treated with pesticides (third root transformed to better satisfy normality).

Appendix 1: Pesticides included in the 1990-1993 NCFAP database (N=220) and 1995-1998 NCFAP database (N=235).

1-3-D	CRYOLITE	FENBUTATIN-OXIDE	METHOXYCHLOR	**PYRIPROXYFEN**
2-4-D	CYANAZINE	FENOXAPROP	METHYL-BROMIDE	**PYRITHIOBAC**
2-4-DB	**CYCLANILIDE**	FENPROPATHRIN	METHYL-PARATHION	QUINCLORAC
ABAMECTIN	CYCLOATE	***FENVALERATE***	METIRAM	QUIZALOFOP
ACEPHATE	CYFLUTHRIN	FERBAM	METOLACHLOR	**RIMSULFURON**
ACETOCHLOR	**CYMOXANIL**	FLUAZIFOP	METRIBUZIN	SETHOXYDIM
ACIFLUORFEN	CYPERMETHRIN	**FLUMETRALIN**	METSULFURON	***SIDURON***
ALACHLOR	CYROMAZINE	**FLUMETSULAM**	***MEVINPHOS***	SIMAZINE
ALDICARB	CYTOKININS	**FLUMICLORAC**	MOLINATE	SODIUM-CHLORATE
AMETRYN	DCNA	FLUOMETURON	MSMA	**SPINOSAD**
AMITRAZ	DCPA	**FLUTOLANIL**	MYCLOBUTANIL	STREPTOMYCIN
ANILAZINE	**DELTAMETHRIN**	FOMESAFEN	NAA	**SULFENTRAZONE**
ASULAM	DESMEDIPHAM	FONOFOS	NAD	SULFUR
ATRAZINE	DIAZINON	FORMETANATE-HCL	NALED	SULFURIC-ACID
AZADIRACHTIN	DICAMBA	FOSETYL-AL	NAPROPAMIDE	SULPROFOS
AZINPHOS-METHYL	DICHLOBENIL	GIBBERELLIC-ACID	NAPTALAM	**TEBUCONAZOLE**
AZOXYSTROBIN	DICLOFOP	GLYPHOSATE	NICOSULFURON	**TEBUFENOZIDE**
BENEFIN	DICOFOL	**HALOSULFURON**	NORFLURAZON	**TEBUPIRIMPHOS**
BENOMYL	DICROTOPHOS	HEXAZINONE	OIL	TEBUTHIURON
BENSULFURON	***DIETHATYL ETHYL***	**HEXYTHIAZOX**	ORYZALIN	TEFLUTHRIN
BENSULIDE	DIFENZOQUAT	IMAZAMETHABENZ	OXAMYL	TERBACIL
BENTAZON	DIFLUBENZURON	**IMAZAPIC**	OXYDEMETON-METHYL	TERBUFOS
BENZYLADENINE	**DIMETHENAMID**	IMAZAQUIN	OXYFLUORFEN	***THIABENDAZOLE***
BIFENTHRIN	DIMETHIPIN	IMAZETHAPYR	OXYTETRACYCLINE	THIDIAZURON
BROMACIL	DIMETHOATE	**IMIDACLOPRID**	OXYTHIOQUINOX	THIFENSULFURON
BROMOXYNIL	**DIMETHOMORPH**	IPRODIONE	PARAQUAT	THIOBENCARB
BT	***DINOCAP***	***ISOPROPALIN***	PCNB	THIODICARB
BUPROFEZIN	***DIPHENAMID***	LACTOFEN	PEBULATE	THIOPHANATE-METHYL
BUTENOIC-ACID	DIQUAT	LAMBDACYHALOTHRIN	PENDIMETHALIN	THIRAM
BUTYLATE	DISULFOTON	LINDANE	PERMETHRIN	TRALOMETHRIN
CACODYLIC-ACID	DIURON	LINURON	PHENMEDIPHAM	TRIADIMEFON
CAPTAN	DODINE	MALATHION	PHORATE	TRIALLATE
CARBARYL	DSMA	MALEIC-HYDRAZIDE	PHOSMET	TRIASULFURON
CARBOFURAN	ENDOSULFAN	MANCOZEB	PICLORAM	TRIBENURON
CARBOXIN	ENDOTHALL	MANEB	PRIMISULFURON	TRIBUFOS
CHLORAMBEN	EPTC	MCPA	PROFENOFOS	***TRICHLORFON***
CHLORETHOXYFOS	ESFENVALERATE	MCPB	PROMETRYN	TRICLOPYR
CHLORIMURON	ETHALFLURALIN	MCPP	PRONAMIDE	***TRIDIPHANE***
CHLOROPICRIN	ETHEPHON	**MEFENOXAM**	PROPACHLOR	**TRIFLUMIZOLE**
CHLOROTHALONIL	ETHION	MEPIQUAT-CHLORIDE	**PROPAMOCARB**	TRIFLURALIN
CHLORPYRIFOS	ETHOFUMESATE	METALAXYL	PROPANIL	**TRIFLUSULFURON**
CHLORSULFURON	ETHOPROP	METALDEHYDE	PROPARGITE	TRIFORINE
CLETHODIM	ETHYL-	METAM-SODIUM	PROPICONAZOLE	***TRIMETHACARB***

	PARATHION			
CLOFENTEZINE	ETRIDIAZOLE	METHAMIDOPHOS	**PROSULFURON**	TRIPHENYLTIN-HYD
CLOMAZONE	FENAMIPHOS	***METHAZOLE***	PYRAZON	VERNOLATE
CLOPYRALID	FENARIMOL	METHIDATHION	**PYRIDABEN**	VINCLOZOLIN
COPPER	**FENBUCONAZOLE**	METHOMYL	PYRIDATE	ZIRAM

Bold compounds were used in '97 but not '92, ***bold italics*** were used in '92 but not '97. All others were used in both years.

Appendix 2: Pesticides from the 1990-1993 NCFAP database classified as Suspected Teratogens (N=54).

2-4-DB	CYCLOATE	LINURON	OXYDEMETON-METHYL	TEBUTHIURON
ABAMECTIN	DIAZINON	MANCOZEB	OXYTETRACYCLINE	TERBACIL
ALACHLOR	DICAMBA	MANEB	OXYTHIOQUINOX	THIABENDAZOLE
AMITRAZ	DICLOFOP	METAM-SODIUM	PROMETRYN	THIOPHANATE-METHYL
ANILAZINE	DIMETHOATE	METHAZOLE	PROPACHLOR	THIRAM
BENOMYL	DINOCAP	METHYL-BROMIDE	PROPARGITE	TRIADIMEFON
BIFENTHRIN	DIURON	METIRAM	PROPICONAZOLE	TRIFORINE
BROMOXYNIL	EPTC	METRIBUZIN	QUIZALOFOP	TRIPHENYLTIN-HYD
CARBOXIN	FENBUTATIN-OXIDE	MOLINATE	SIMAZINE	VINCLOZOLIN
CHLORSULFURON	FENOXAPROP	MYCLOBUTANIL	STREPTOMYCIN	ZIRAM
CYANAZINE	FLUAZIFOP	NALED	SULPROFOS	

Appendix 3: Pesticides from the 1995-1998 NCFAP database classified as Suspected Teratogens (N=49).

2-4-DB	DIAZINON	MANCOZEB	OXYTETRACYCLINE	TEBUTHIURON
ABAMECTIN	DICAMBA	MANEB	OXYTHIOQUINOX	TERBACIL
ALACHLOR	DICLOFOP	METAM-SODIUM	PROMETRYN	THIOPHANATE-METHYL
AMITRAZ	DIMETHOATE	METHYL-BROMIDE	PROPACHLOR	THIRAM
BENOMYL	DIURON	METIRAM	PROPARGITE	TRIADIMEFON
BIFENTHRIN	EPTC	METRIBUZIN	PROPICONAZOLE	TRIFORINE
BROMOXYNIL	FENBUTATIN-OXIDE	MOLINATE	QUIZALOFOP	TRIPHENYLTIN-HYD
CHLORSULFURON	FENOXAPROP	MYCLOBUTANIL	SIMAZINE	VINCLOZOLIN
CYANAZINE	FLUAZIFOP	NALED	STREPTOMYCIN	ZIRAM
CYCLOATE	LINURON	OXYDEMETON-METHYL	SULPROFOS	

Appendix 4: Pesticides from the 1990-1993 NCFAP database classified as Suspected Endocrine Disruptors (N=45).

2-4-D	CYANAZINE	FENVALERATE	METHOMYL	SIMAZINE
ALACHLOR	CYFLUTHRIN	IPRODIONE	METHOXYCHLOR	TEFLUTHRIN
ALDICARB	CYPERMETHRIN	LAMBDACYHALOTHRIN	METHYL-PARATHION	THIRAM
ATRAZINE	DICOFOL	LINDANE	METIRAM	TRALOMETHRIN
BENOMYL	ENDOSULFAN	LINURON	METOLACHLOR	TRIADIMEFON
BIFENTHRIN	ESFENVALERATE	MALATHION	METRIBUZIN	TRIFLURALIN
CARBARYL	ETHYL-PARATHION	MALEIC-HYDRAZIDE	PCNB	TRIPHENYLTIN-HYD
CHLORPYRIFOS	FENARIMOL	MANCOZEB	PENDIMETHALIN	VINCLOZOLIN
CLOFENTEZINE	FENPROPATHRIN	MANEB	PERMETHRIN	ZIRAM

Appendix 5: Pesticides from the 1995-1998 NCFAP database classified as Suspected Teratogens (N=47).

2-4-D	CYANAZINE	FENPROPATHRIN	METHOXYCHLOR	THIRAM
ACETOCHLOR	CYFLUTHRIN	IPRODIONE	METHYL-PARATHION	TRALOMETHRIN
ALACHLOR	CYPERMETHRIN	LAMBDACYHALOTHRIN	METIRAM	TRIADIMEFON
ALDICARB	DELTAMETHRIN	LINDANE	METOLACHLOR	TRIFLURALIN
ATRAZINE	DICOFOL	LINURON	METRIBUZIN	TRIPHENYLTIN-HYD
BENOMYL	ENDOSULFAN	MALATHION	PCNB	VINCLOZOLIN
BIFENTHRIN	ESFENVALERATE	MALEIC-HYDRAZIDE	PENDIMETHALIN	ZIRAM
CARBARYL	ETHYL-PARATHION	MANCOZEB	PERMETHRIN	
CHLORPYRIFOS	FENARIMOL	MANEB	SIMAZINE	
CLOFENTEZINE	FENBUCONAZOLE	METHOMYL	TEFLUTHRIN	

Appendix 6: Information on socioeconomic and demographic variables used in the regression models:

%CRPLNDRT3 represents the 1997-2002 average state percentage of land area used for cropland, third root transformed to better satisfy normality. Accessed online May 25, 2005 from the National Agricultural Statistics Service census query website @ http://www.nass.usda.gov/Census_of_Agriculture/index.asp

%FRMLNDRT3 represents the 1997-2002 average state percentage of land area used for farmland, third root transformed to better satisfy normality. Accessed online May 25, 2005 from the National Agricultural Statistics Service census query website @ http://www.nass.usda.gov/Census_of_Agriculture/index.asp

%F1844SMOKE9903 represents the 1999-2003 average state percentage of females aged 18-44 having ever smoked 100 cigarettes in a lifetime and currently smoking everyday or some days. Obtained online May 24, 2005 from www.marchofdimes.com/peristats.

%HRVCPLDRT3 represents the 1997-2002 average state percentage of harvested cropland, third root transformed to better satisfy normality. Accessed online May 25, 2005 from the National Agricultural Statistics Service census query website @ http://www.nass.usda.gov/Census_of_Agriculture/index.asp

%5FRUITVEG represents the 2003 average state percentage of persons consuming 5+ servings of fruits of vegetables per day. Obtained online May 24, 2005 from http://apps.nccd.cdc.gov/brfss/

ABORT9600 represents the averaged state abortion rate per 1000 women for years 1996 and 2000. Obtained online March 3, 2007 @ www.abortiontv.com/Misc/AbortionStatistics.htm#United%20States and http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5212a1.htm

DRCVRGINV represents the state number of doctors per 100000 resident population in 2001, inverse transformed to better satisfy normality. Obtained online March 17, 2005 @ http://factfinder.census.gov/home/saff/main.html?_lang=en

HSHLDINC represents the state average median household income in 1999. Obtained online March 17, 2005 @ http://factfinder.census.gov/home/saff/main.html?_lang=en

PCNTBACH represents the state percentage of persons aged 25+ years having obtained a bachelor's degree or higher. Obtained online March 17, 2005 @ http://factfinder.census.gov/home/saff/main.html?_lang=en

PCTWYTARCSIN represents the percentage of a state's total population of non-Hispanic white origin in 2003, arcsine transformed to better satisfy normality. Obtained online March 17, 2005 @ http://www.census.gov/popest/race.html

PNC9296RT represents the 1992-1996 average state percentage of mothers delivering live infants who did not receive care during the first trimester of pregnancy, square root transformed to better satisfy normality. Obtained online May 24, 2005 @ http://www.cdc.gov/nchs/fastats/prenatal.htm

PREGSMOKE9602 represents an average of the percentage of mothers who smoked during pregnancy as detailed from surveys taken in 1996 and 2002. Data was taken from Smoking During Pregnancy --- United States, 1990—2002, Morbidity and Mortality Weekly Report, October 8, 2004 / 53(39);911-915. Obtained online February 9, 2005 @ http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5339a1.htm.

PRIMEMATAGE represents the average state percentage of live births to mothers between ages 20 to 39 for the years 2000-2002. Obtained online May 24, 2005 from www.marchofdimes.com/peristats.

UNEMPLYMT represents the state unemployment rate in 2002. Obtained online March 17, 2005 @ http://factfinder.census.gov/home/saff/main.html?_lang=en

Appendix 7: Calculations and data used to determine relative risk. Values were calculated by inserting the values for the states with lowest and highest pesticide use into the equation of the regression model in Table 6. Relative risk is equal to the ratio of the rate of infant mortality due to birth defects in the state with the highest pesticide use to the state with the lowest.

Data:

	TERA97RT3	*HSHLDINC*	*%F1844SMOKE9903*	*ABORT9600*
Minimum	0.10471			
Maximum	0.71005			
Mean		40983	25.95	13.81

Calculations:

BDmort = 19.90 + 2.82(*Tera97*) – 0.000135(avg state rate of *HSHLDINC*) -0.09269(avg state value of *%F1844SMOKE9903*) – 0.0446(avg state abortion rate)

(Highest BDmort)$^{0.5}$ = 19.90 + 2.82(.71005) – 0.000135(40982.6) – 0.09269(25.95) – 0.0446(13.81) = 178 deaths /10,000 live births in state with highest pesticide use

(Lowest BDmort)$^{0.5}$ = 19.90 + 2.82(.10471) – 0.000135(40982.6) – 0.09269(25.95) – 0.0446(13.81) = 135.5 deaths /10,000 live births in state with lowest pesticide use

Relative Risk = Ratio highest:lowest = 182.9/140.8 = **1.31**