An Ecologic Analysis of Congenital Anomalies and Agricultural Chemicals in Colorado, 1989-1991

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Abstract

Objectives — The purpose of this article is to describe the distribution of congenital anomalies in relation to pesticide application, crop type, and farming methods in Colorado.

Methods — Birth defects data, assigned to the county of residence of the mother, were obtained from Colorado's Registry for Children with Special Needs for the years 1989–1991. Counties were grouped by crop reporting districts; these crop reporting districts were classified as high, medium or low based on total acres of each agricultural activity as a ratio of the total acres in the district. Rates were calculated for high, medium, and low districts for 10 different farming practices.

Results — Rate ratios for Down syndrome and other chromosomal anomalies were elevated in areas high in herbicide application (3.02, 2.04), irrigated pastureland (2.83, 2.59), and fungicide application (2.39, 2.02). Rate ratios for patent ductus arteriosus were elevated in areas with irrigated pastureland (1.26) and irrigated cropland (1.22).

Conclusions — Districts in Colorado high in application of herbicides and fungicides, and areas using irrigation methods have elevated rates of certain birth defects, including chromosomal defects and heart anomalies. A more detailed evaluation of these relationships are needed.

Keywords. **Birth defects, Pesticides, Farming activities.**

Environmental contaminants, including pesticides, are not necessarily easily recognized; non-point source influences arise in water supplies, soil, and airborne particulate matter. For this reason, concerns about agricultural chemicals extend beyond the exposure of the agricultural work force into the entire population residing in both rural areas and metropolitan communities. Indeed, pesticides have become so ubiquitous in the environment that few persons remain unexposed.

The use of insecticides, herbicides, and fertilizers has increased dramatically since World War II (Schardein, 1993). Their importance to the economy and as an environmental agent cannot be underrated; the prevention of crop loss and control of

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disease vectors has dramatically improved crop production and diminished the occurrence of epidemics worldwide (Sharp et al., 1986). In the United States, approximately 11 million people have potential exposure to agricultural chemicals and the solvents used in their application (Weisenberger, 1993). The most common routes of exposure for occupationally exposed workers are through dermal contact and inhalation, based on application methods of agricultural chemicals (Cordier et al., 1992). However, farm families and residents of rural areas are particularly susceptible to contamination through undetected oral ingestion of affected water sources (Zierler et al., 1988).

The pesticide atrazine, found commonly in contaminated rural wells, has been the focus of two studies in Iowa and Nebraska (Munger et al., 1992; Weisenberger et al., 1992). Communities in southern Iowa surrounding Rathbun reservoir, which was found to be contaminated with elevated levels of atrazine, showed an increased number of birth defects compared to communities matched in size and known maternal risk factors to birth defects, such as smoking, education, and prenatal care (Munger et al., 1992). Cardiac defects, urogenital defects, and limb reduction defects were especially noted at increased levels in these studies.

In New Zealand, 2,4,5-T was sprayed between four and six months of the year by a predominantly male work force throughout the 1960s. In a study by Hanify et al., hospital records were used to identify all diagnosed malformations per live births, and this information was then categorized into areas in which high aerial spraying occurred compared to little spraying. An increase in talipes, hypospadias, and epispadias was reported (Hanify et al., 1981).

Direct, physical involvement in an agricultural occupation may be a less important factor than the county of residence of the mother (Schwartz and LoGerfo, 1988). In a case-control study, using California birth records, women who resided primarily in the high agricultural setting of Imperial County, California, were more likely to have infants with limb reduction defects than women who resided in areas with less agricultural activity (Schwartz and LoGerfo, 1988). Economic and medical factors associated with agricultural locations also were given as potential explanations for the increased incidence of limb reduction defects (Schwartz and LoGerfo, 1988).

Malathion, an aliphatic organophosphate insecticide and acaricide, is the ninth most commonly used pesticide in the United States (Schardein, 1993). During a 1981 Mediterranean fruit fly infestation in California's San Francisco Bay area, repeated rounds of aerial spraying over a 12-month period were used to control the pest (Thomas et al., 1992). Increased rates of gastrointestinal defects associated with second trimester exposure, and limb and orofacial anomalies associated with first trimester exposure were found (Thomas et al., 1992). However, studies repeated the following year when low doses of malathion were again sprayed in the Bay area did not corroborate these results; the only increased rate seen in 1982 was for tracheoesophageal fistulas (Grether et al., 1987).

Organochlorine chemicals of the DDT group have been associated with spontaneous abortion, stillbirths, and premature birth (Leoni et al., 1989). Hyperpigmentation of the skin is the only anomaly listed in human studies on this family of chemicals, although animal studies have shown a number of teratogenic malformations (Leoni et al., 1989). As with many of the chemicals applied as agricultural pesticides, the toxicologic laboratory studies and human data are not congruent.

Captan is a fungicide with many structural similarities to thalidomide, including a varied record of producing congenital anomalies in animal studies (Schardein, 1993). This chemical was heavily used in the floriculture industry in Colombia,

where a moderate increase in the prevalence of congenital malformations was detected among infants whose mothers were occupationally exposed to Captan and 126 other fungicides and pesticides (Restrepo et al., 1990a). Classification of malformations was a problem in this study, however, because 53% of the children reported by their parents as malformed were found to be normal upon examination, indicating significant misclassification. Additional studies on this population by Restrepo et al. (1990b) found elevated rates for spontaneous abortion, premature birth, and malformations among female workers and among the wives of male workers.

The hypothesis of this investigation is that certain types of birth defects are associated with different agricultural production activities. By describing the distribution of pesticide application patterns in Colorado and the distribution of congenital anomalies in Colorado through a birth defects registry, any change in the normal rates of congenital anomalies in association with these patterns may be detected. The state of Colorado is a unique environment for studying agricultural practices, due to the varied geography and agricultural activities. The rolling Eastern Plains, with acres of wheat and corn, are distinctly different from the ranches high in the Rocky Mountains, or the valleys left fertile by glacial debris. Virtually every type of farming operation can be found within Colorado, from llama breeding and more traditional feedlots to enormous acreage of croplands.

Materials and Methods

Four different data sources contributed information in this investigation: they were Colorado's Registry for Children with Special Needs, the Colorado Agricultural Statistics Service, the 1987 Census of Agriculture, and the Colorado Vital Statistics for 1989-1991.

Colorado's Registry for Children with Special Needs (CRCSN) became operational in late 1988 as a central registry for all children with birth defects or developmental disabilities that manifest themselves in children by the age of three years. This surveillance system is designed to characterize and monitor the occurrence of birth defects in Colorado with a specific purpose of assessing regulatory and reporting information. Children are identified from Colorado birth and death certificates, Colorado hospital discharge data, the Health Care Program for Children with Special Needs (a program serving children from birth to 21 years who meet specific medical and financial eligibility requirements), the Newborn Genetic Screening Program, the Mountain States Regional Genetic Screening Network, epidemiology reports, and voluntary physician reports. Duplicate reports of diagnoses for the same individuals help to increase the reliability of the provided data, and active medical review is conducted by the program's medical record information team. Classifications indicating typical conditions occurring in the postnatal periods were not pertinent to this report, and thus, were eliminated. Many children in the CRCSN had more than one congenital defect; all anomalies listed were utilized in this study.

The Colorado crop reporting districts, defined by the Colorado Agricultural Statistics Service, combine counties with distinct geographical features to form six separate groups: Northeast, East Central, Southeast, San Luis Valley, Southwest, and Northwest and Mountains.

Data obtained from the 1987 Census of Agriculture were used to determine the amount of county-wide activity of the 10 agricultural practices listed below. The data available from the Agricultural Census include specific acreage per county of

different agricultural activities. In certain categories in the Census, the exact amount of acreage was excluded to preserve anonymity; for this study, these designations were entered as zero. The 10 activities used in this study were: (1) the percent of insecticide use per crop acreage; (2) the percent of herbicide use per crop acreage; (3) the percent of fungicide use per crop acreage; (4) the percent of fertilizer use per crop acreage; (5) the percent of chemical use per crop acreage; (6) the percent of wheat production per crop acreage; (7) the percent of corn production per crop acreage within the district; (8) the percent of irrigated crop acres per farm acreage; (9) the percent of irrigated pastureland per farm acreage within each district; and (10) the percent of farm acres per total acreage within the district. The chemicals used on irrigated pastureland often are similar to those used elsewhere, however, they often are applied more heavily than on croplands.

The Health Statistics and Vital Records Division of the Colorado Department of Public Health and Environment reports on a variety of information about the health status of Coloradans by county. Of interest for this study was the number of live births per county per year. The number of births was used to calculate the rate of birth defects per number of live births for each crop reporting district, as well as the rates of specific birth defects occurring in the crop reporting districts.

High exposure, medium exposure, or low exposure was assigned based on the percent activity of the given variable within each crop reporting district. Each division was to contain two crop reporting districts. In cases where there was no clear distinction between groups (e.g., high and medium, or medium and low), chi-square analysis was used to assign the outlying district to the appropriate classification. The chi-square analysis had to indicate a significant difference between the two categories (medium to high, medium to low) for a district to be assigned in a manner that would yield more than two districts per group. After combining the crop reporting districts into the appropriate high, medium, or low exposure status for each of the 10 agricultural activities, the county-wide data from the 20 categories of birth defects data were aggregated and rate ratios and confidence intervals were calculated.

The rates for each category of birth defect were calculated by dividing the number of defects by the population at risk. Rate ratios represent the rate of birth defects within either the high or medium exposure groups compared to the low exposure classification:

$$RR_i = \frac{R_i}{R_L}$$

where

I = medium or high exposure groups

L = low exposure group

A 95% confidence interval was calculated to determine statistical significance of the rate ratio:

$$95\%\ \text{C.I.} = (\ln RR_i) \pm \sqrt[z]{\frac{1}{y_i} + \frac{1}{y_L}}$$

where

I = medium or high exposure group

L = low exposure group

To discern the potential impact of urban environments on the rates of the 20 selected congenital anomalies, Denver County was separated from the East Central district and the rates of birth defects were calculated for both areas. A Z-test for comparison of two proportions was used to determine if there was any difference between rates in the primarily rural section of the East Central district versus the urban county of Denver. Based on these calculations, anomalies that were statistically different in the two areas were reanalyzed with the rates for East Central excluding Denver County.

Results

Colorado's Registry for Children with Special Needs contained 29,218 eligible diagnoses and conditions for the period from 1989 to 1991, representing 17,784 children. Elimination of previously mentioned defects reduced the observations utilized in this study to 19,008 eligible diagnoses and conditions.

Each agricultural operation was evaluated to determine the extent of activity that occurred relative to overall acreage within each crop reporting district; these were expressed as a percent of activity per crop acres, farm acres or total acres in each region depending on the variable. An exposure of high, medium or low was assessed for each crop reporting district based on this percent, and the six districts were grouped to most accurately conform to these divisions. Within the different variables the percentages differed dramatically; for example, the variable percent chemical use per crop acres had low exposure percentages at approximately 34%, while the variable percent fungicide use per crop acres had a high exposure percentage at 18%.

Of the 400 rate ratios included in this study, a total of 173 rate ratios were elevated and 227 rate ratios were below 1.0. Seventy-five rate ratios had confidence intervals that excluded 1.00; 12 were significantly elevated (table 1), and 63 rate ratios were significantly low (table 2). Twenty of the 400 rate ratios would be likely to have statistically significant results based solely on chance.

Table 1. Congenital anomalies with rate ratios significantly elevated above 1.00

Agricultural Activity	Type of Congenital Anomaly	Level of Activity	Rate Ratio & 95% C.I.	Crop Districts within Level
Chemical acres/Crop acres	NSR*			
Corn acres/Crop acres	NSR			
Farm acres/Total acres	NSR			
Fertilizer/Crop acres	Cryptorchidism	High	1.50 (1.02,2.21)	NW
Fungicide/Crop acres	Down syndrome	High	2.39 (1.02,5.60)	SLV
	All chromosomal	High	2.02 (1.04,3.93)	SLV
Herbicide/Crop acres	Down syndrome	High	3.02 (1.29,7.11)	SLV
	All chromosomal	High	2.04 (1.06,3.92)	SLV
Insecticide/Crop acres	Cleft palate	Medium	1.52 (1.17,1.98)	EC and SW
Irrigation/Crop acres	Patent ductus	High	1.22 (1.08,1.39)	SLV and NE
	Patent ductus	Medium	1.33 (1.11,1.60)	SW and NW
	Heart anomalies	Medium	1.21 (1.03,1.42)	SW and NW
Irrigation/Pasture acres	Down syndrome	High	2.83 (1.32,6.05)	SLV
	All chromosomal	High	2.59 (1.42,4.76)	SLV
	Patent ductus	Medium	1.26 (1.13,1.42)	NE, NW and SW
Wheat acres/Crop acres	NSR			

* No Significant Results.

polydactyly and syndactyly, polydactyly and syndactyly, the category including all limb defects, and hypospadias, a urinary defect. While the rates of limb defects were significantly elevated in Denver compared to the rural section of the East Central district, the rate of hypospadias was lower in the urban area.

Discussion

The importance of ecologic investigations on the issue of congenital anomalies cannot be underestimated; thus far, clinical observations and population-based studies are the most accurate indications of teratogenic effects in human populations due to the lack of appropriate animal models. This study generated a substantial amount of information on the possible association between agricultural activities and the presence of elevated rates of certain types of congenital anomalies that differ from the state incidence rates. These results are not necessarily reflected only in elevated rate ratios; high rates of heart defects in the Southeast district resulted in low rate ratios due to the district's low exposure status.

Although most defects represented in this data base occurred in sufficient numbers to allow for reasonable statistical power, some results may have been due to small numbers. For example, as a consequence of the small population of the San Luis Valley, there were no anomalies in 10 categories, including cleft palate, neural defects, and urinary disorders. While this could be indicative of a strongly protective effect, it is more likely due to a smaller number of births in this sparsely populated region. The inclusion of additional years of data would be useful to alleviate this problem.

Major categories that showed statistically significant rate ratios below 1.00 were heart defects, especially septal defects, central nervous system disorders, chromosomal anomalies, and limb defects. Defects which are fatal to the fetus will be under represented in rates based on live births. Although some congenital anomalies are obvious and readily identified by the physician at the time of delivery, other types of malformations are less likely to be present in a birth defects registry due to their organ position, absence of overt symptoms, or lethality in utero. Spontaneous abortions are always a possible confounding factor in the analysis of birth defects. Many spontaneous abortions may be induced by certain defects, thus reducing the number of reported occurrences of these anomalies in the population even though the actual incidence rate could be quite high (Wilcox et al., 1988). This is particularly important with chromosomal anomalies and anomalies of the vital organs, both of which would be likely to result in fetal death. Spontaneous abortions occurring in the first month of pregnancy usually go undetected, yet this is the time of major development for the cardiovascular system and the nervous system, both of which could contribute to spontaneous abortion if malformations occurred.

While the crop reporting districts were designed to establish common geographic and agricultural perimeters, ethnic and socioeconomic separations also were created. Race and socioeconomic status have been reported to be factors in a number of congenital anomalies. For instance, Native American offspring are more likely to have cleft palate/lip, while neural tube disorders are more common in women of lower socioeconomic class (Persaud et al., 1985). The Spanish/White population of the San Luis Valley has a high incidence of diabetes, which may lead to difficulties in pregnancy and adverse reproductive outcomes (Burchfiel et al., 1990). These factors were not controlled for in this study, and thus, could be contributing to both positive and negative results.

Under reporting is always an issue with even the most complete surveillance system, and this source of bias may occur with the CRCSN. However, some of the major sources of information, for example, the birth certificate information, provid

statewide coverage. This foundation, complimented with the other specialty sources, lends strength to the belief that, although under reporting may occur, it is not necessarily contributing a significant bias to the study.

Exposure status can be very difficult to ascertain in any ecologic study, however, inquiries on reproductive outcomes have many complex elements that exacerbate the problem. It is estimated that 25% of all pregnant women relocate at some time during their pregnancy. Therefore establishing exposure, especially in conjunction with specific windows of developmental susceptibility, may be impossible Schulman et al., 1993).

The census sources used to measure exposure in this study supply a valuable gauge for exposure at a population level. The utilization of these data sources, which give county-wide agricultural activity, are not accurate for estimating an individual exposure. The assumption is that women are uniformly exposed at whatever measure was ascertained for the crop reporting district. However, this is not necessarily an accurate assumption.

The accuracy of measurement in an ecologic study contributes to the limitations outlined above, but it is nonetheless a useful tool for describing differences in populations. Although causality cannot be inferred from the rate ratios established in this study, they can be viewed as indicating hypotheses worthy of further investigation.

Overall, 400 rate ratios were generated from the exposures analyzed. Many rate ratios indicated no significant association between any of the 10 agricultural activities and the congenital anomalies that were reviewed. The major conclusions that can be drawn from the significantly elevated rate ratios observed in this study are:

1. Chromosomal defects were significantly elevated in areas with high fungicide use, high herbicide use, and high acreage of irrigated pastureland.
2. Heart defects were elevated in areas with high acreage of irrigated cropland and irrigated pastureland.
3. Further research is needed to establish the possible causal links between congenital anomalies, agricultural chemicals, and the activities associated with this chemical use.

Many of these findings are supported by other investigations and by possible explanations for the potentially teratogenic activity associated with different agricultural activities.

The epidemiologic studies on the possible role played by agricultural chemicals in the induction of congenital anomalies show great diversity. While many studies had positive associations between reproductive outcomes and pesticides and nitrates, other studies had weak, or negative associations. Many investigators in occupational studies hypothesized that the solvents mixed with many pesticides — not necessarily the pesticides themselves — may play an important role in the teratogenic activity seen in and around agricultural operations (Cordier et al., 1992; Deane et al., 1989; Holmberg et al., 1982).

Another potential cause of birth defects may be environmental factors, for they seem to function in an unknown, yet important, manner. Women who maintain residence in a given municipality after giving birth to a malformed infant were significantly more likely to have a baby with a defect in a later pregnancy than mothers who moved from that locale, implying that the environmental site was important (Lie and Skjaerven, 1994). Due to the many potential factors involved in teratology, the ability to identify a single cause-effect relationship is difficult. Yet, many of these studies indicate the need to continue to undertake the task of identifying environmental contributors to adverse reproductive outcomes.

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