Scand J Work Environ Health 2000;26(3):193—198

Maternal occupation in agriculture and risk of limb defects in Washington State, 1980—1993

by Lawrence S Engel, PhD,[1,2] Ellen S O'Meara, PhD,[1,3] Stephen M Schwartz, PhD[1,3]

Engel LS, O'Meara ES, Schwartz SM. Maternal occupation in agriculture and risk of limb defects in Washington State, 1980—1993. Scand J Work Environ Health 2000;26(3):193—198.

Objectives This study examined the association between maternal occupational exposure to agricultural chemicals and the risk of limb defects among offspring.

Methods A retrospective cohort study was conducted using Washington State birth records for the years 1980 through 1993. The exposed group, consisting of 4466 births to mothers employed in agriculture, was compared with 2 reference groups: (i) 23 512 births in which neither parent worked in agriculture ("nonagricultural" group) and (ii) 5994 births in which only the father worked in agriculture ("paternal agriculture" group). The outcome of interest was limb defects [syndactyly, polydactyly, adactyly, and "other limb reductions" (as listed in the birth record)].

Results An elevated risk of limb defects was observed for the exposed group in comparison with both the nonagricultural and paternal agriculture groups, with ethnicity-adjusted prevalence ratios of 2.6 [95% confidence interval (95% CI) 1.1—5.8] and 2.6 (95% CI 0.7—9.5), respectively.

Conclusions These results support the hypothesis that maternal occupational exposure to agricultural chemicals may increase the risk of giving birth to a child with limb defects.

Key terms agriculture, birth defects, epidemiologic study, limb defects, pesticides.

Over the past few decades, there has been growing concern about the possible role of pesticides and other agricultural chemicals in the etiology of birth defects. Over 100 pesticides have been shown to cause birth defects in one or more animal models (1). There is also epidemiologic evidence of an association between pesticides and birth defects, including limb defects, among humans (2—5). However, the evidence for humans is mixed, and several investigators report no association with limb defects (6—7). There has been very little research into the human reproductive or developmental effects of fertilizers. Kristensen et al (5) observed associations of exposure to fertilizers with polydactyly and syndactyly. Given the large number of people worldwide who are regularly exposed to agricultural chemicals, clarification of the developmental risks posed by these chemicals is of great importance.

In our study we have investigated the risk of limb defects for women likely to be occupationally exposed to pesticides and other agricultural chemicals. Data were obtained from Washington State birth certificates for the years 1980—1993. Limb defects were selected as an outcome on the basis of reports by other investigators, the likely identification of such defects at birth, and the presence of the necessary information on birth certificates. The availability of 14 years of statewide birth data allowed us to assemble a large cohort and enhanced our power to detect risks associated with such rare outcomes.

Material and methods

To examine the association between maternal exposure to agricultural chemicals and limb defects among

1 Department of Epidemiology, University of Washington, Seattle, Washington, United States.
2 Pacific Northwest Agricultural Safety and Health Center (PNASH), University of Washington, Seattle, Washington, United States.
3 Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington, United States.

Reprint requests to: Dr Lawrence Engel, Occupational Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd, EPS 8111, Rockville, MD 20892—7240, USA. [E-mail: engell@mail.nih.gov]

offspring, we analyzed computerized records of live singleton births in Washington State during the years 1980 through 1993. Occupation in agriculture, as coded on the birth certificates, served as a proxy measure of exposure to agricultural chemicals. These occupations included farmer, orchardist, horticulturist or nurseryman, wheat or grain farmer, farm manager, farm foreman, farm laborer, family farm worker, farm caretaker, farm worker (self-employed), migrant farm worker, and orchard laborer. Although exposure can vary widely between and within the listed job categories, the following occupations were excluded due to their small numbers and to their likely differences in type and degree of agricultural chemical exposure in comparison with crop workers: forester, cattle or sheep rancher, dairy farmer or worker, sheepherder, logger or lumberman, and pest control worker. The exposed group comprised all 4466 births to women employed in agriculture, according to the preceding definition of the groups, during the study period.

Two comparison groups were used. Each was selected from the statewide birth records during the same time period as the exposed group. The first comparison group consisted of a random sample of births to women who worked outside the home, in occupations other than those in the previously selected list and in which the birth record indicated that the father did not work in agriculture. This "nonagricultural" comparison group numbered 23 512 births. The second comparison group consisted of all births to women similarly working outside the home in occupations other than those in the previously selected list but in which the father was employed in agriculture. This "paternal agriculture" comparison group comprised 5994 births. Women who indicated their occupation as housewife, were unemployed, or whose occupation was missing in the birth record were excluded from both comparison groups in order to minimize potential biases related to the fact of employment or to employability (the "healthy worker effect"). The primary reason for creating the latter comparison group was to control for socioeconomic factors that could not be ascertained from the birth certificate data. In addition, births to fathers in agriculture may represent an intermediate dose group if the mothers received secondary exposure to agricultural chemicals. Alternatively, paternal exposure to agricultural chemicals may be independently related to fetal outcome. (The present study design did not allow us to distinguish between these alternatives.)

Limb defects are rare, occurring in about 0.1% of live births in Washington according to birth certificate data. Because of the rarity of these defects, related outcome categories were grouped. Thus the limb-defect group consisted of births with syndactyly, polydactyly, adactyly, and "other limb reductions" (as found in the musculoskeletal field of the birth record).

The use of agricultural chemicals varies with season and is generally the most intense during late spring and summer. Since the frequency of adverse birth outcomes might, therefore, also vary by season, we looked for seasonal trends in the frequency of limb defects.

Factors that might modify or confound the relation between maternal occupation in agriculture and the risk of giving birth to children with limb defects were examined. These factors included maternal age (examined continuously in years and dichotomized at <30;≥30 years old), marital status (married;unmarried), maternal residence (rural;urban), birthplace (rural;urban), smoking and

Table 1. Selected characteristics of the births.

	Characteristic[a]																				
	Maternal age (years) (%)			Maternal age (years)		Maternal race or ethnicity (%)			Married (%)	Rural maternal residence (%)	Parity (%)			Parity		Smoked during pregnancy[b]		Drank alcohol during pregnancy[c]		Late, or no, prenatal care	
	<20	20—34	≥35	Mean	SD	White	Hispanic	Other			0	1	≥2	Mean	SD	%	Missing (%)	%	Missing (%)	%	Missing (%)
Exposed[d] (N=4466)	10.5	80.9	8.5	26.1	5.6	34.5	62.1	3.3	73.4	53.9	26.7	25.7	45.0	1.8	1.9	8.3	4.7	1.0	3.7	16.2	5.8
Nonagricultural comparison group[e] (N=23 512)	6.5	85.2	8.2	26.8	5.2	59.1	35.5	5.2	80.9	41.9	45.1	31.1	21.3	0.9	1.1	14.5	4.6	3.6	6.6	5.5	2.7
Paternal agriculture comparison group[f] (N=5994)	5.5	86.5	8.0	26.9	5.0	78.1	18.8	2.9	90.5	66.8	40.8	31.2	25.4	1.0	1.2	12.3	3.5	2.6	3.8	4.9	1.8

[a] Missing data given when it exceeded 3% for any group.
[b] Data available 1984—1993 (exposed N=3296, nonagricultural comparison group N=18 081, paternal agriculture comparison group N=4188).
[c] Data available 1989—1993 (exposed N=1829, nonagricultural comparison group N=11 544, paternal agriculture comparison group N=2094).
[d] Maternal occupation in agriculture.
[e] Maternal and paternal occupation not in agriculture.
[f] Maternal occupation not in agriculture; paternal occupation in agriculture.

alcohol use during pregnancy (yes;no), prenatal care ("early" if care was sought before or during the fifth month of pregnancy; "late" otherwise), parity (continuous and dichotomized at 0;≥1 prior live births), maternal race or ethnicity (white;Hispanic;other), gestational length (continuous in weeks and dichotomized at <38;≥38 weeks), and gender of the baby. For analyses using the paternal agriculture comparison group, type of paternal employment was also considered ("farm worker" if occupation was listed as farm foreman, farm laborer, farm worker (self-employed), migrant farm worker, or orchard laborer; "farmer" otherwise). Reported gestation lengths of <15 or >44 weeks were assumed incorrect and treated as missing. Data on smoking during pregnancy were available since 1984, when this variable was added to the birth certificate. Data on alcohol use during pregnancy were available only since 1989. Analyses of these factors therefore included smaller sample sizes.

Prevalence ratios and 95% confidence intervals (95% CI) were estimated using unconditional logistic regression. Statistical interactions were assessed on a multiplicative scale.

Results

Characteristics of the subjects

Exposed mothers were similar in age to the mothers in either comparison group (mean = 26.1 years versus 26.8 years and 26.9 years) but were less likely to be married (73.4% versus 80.9% in the nonagricultural comparison group and 90.5% in the paternal agriculture group) (table 1). There was a much higher percentage of Hispanic mothers in the exposed group (62.1%) than in either comparison group (35.5% and 18.8% for the nonagricultural and paternal agriculture comparison groups, respectively). The percentage of non-Caucasian or non-Hispanic mothers in all 3 groups was very low, ranging from 2.9% to 5.2%. The exposed mothers were more likely to list a rural residence (53.9%) than the mothers in the nonagricultural group (41.9%), but they were less likely to do so than the mothers in the paternal agriculture group (66.8%). Parity was higher for mothers in the exposed group than in either comparison group (mean 1.8 versus 0.9 and 1.0 for the nonagricultural and paternal agriculture comparison groups, respectively).

For the years in which smoking and alcohol use information was available on the birth certificates, reported smoking was somewhat less common in the exposed group (8.3%) than in either of the comparison groups (14.5% and 12.3%). Reported alcohol use was low in all 3 groups, ranging from 1.0% in the exposed group to 3.6% in the nonagricultural group.

Limb defects

The number of limb defects in our sample was small (table 2). There were 9 (0.20%) among the exposed births, 19 (0.08%) among the nonagricultural comparison births, and 4 (0.07%) among the paternal agriculture comparison births. The proportion of births with missing birth certificate information on the presence or absence of birth defects was similar across the groups, ranging from 6.0% in the exposed group to 7.7% and 8.2% in the comparison groups.

Maternal employment in agriculture was associated with an elevated risk of limb defects in the offspring (table 3). The crude prevalence ratio (PR) was 2.5 (95% CI 1.1—5.4] relative to the nonagricultural group and 3.0 (95% CI 0.9—9.6) relative to the paternal agriculture group. These relationships were not substantially altered by adjustment for maternal age, marital status, alcohol use, smoking, parity, level of prenatal care, residence, gestation length, or gender of baby. Adjusting for maternal ethnicity (Hispanic versus non-Hispanic) made little difference; the adjusted prevalence ratio was 2.6 (95% CI 1.1—5.8) relative to the nonagricultural group and 2.6 (95% CI 0.7—9.5) relative to the paternal agriculture group. Adjusting for type of paternal agricultural employment (farm worker versus farmer) had a similar impact

Table 2. Distribution of limb defects by exposure group.[a]

	Exposed (N=4466)		Nonagricultural comparison group (N=23 512)		Paternal agriculture comparison group (N=5994)	
	N	%	N	%	N	%
Limb defects	9	0.2	19	0.1	4	0.1

[a] Missing data were 267 (6.0%) for the exposed group, 1816 (7.7%) for the nonagricultural comparison group, and 490 (8.2%) for the paternal agriculture comparison group.

Table 3. Risks of limb defects in association with maternal occupation in agriculture.

Adjustment[a]	Nonagricultural comparison group		Paternal agriculture comparison group	
	Prevalence ratio[b]	95% CI	Prevalence ratio[b]	95% CI
None	2.5	1.1—5.4	3.0	0.9—9.6
Maternal ethnicity	2.6	1.1—5.8	2.6	0.7—9.5
Maternal age	2.4	1.1—5.3	2.8	0.8—9.1
Parity	2.8	1.2—6.3	3.0	0.9—10.1
Paternal occupation	-	.	2.6	0.8—8.9

[a] Maternal race or ethnicity was coded as Hispanic versus non-Hispanic; paternal occupation was coded as farm worker or laborer versus farmer. Adjustments for maternal age (in years) and parity were continuous.

[b] Number of limb defects: 9 for the exposed group, 19 for the nonagricultural comparison group, and 4 for the paternal agriculture comparison group.

on the estimated risk, the adjusted prevalence ratio being 2.6 (95% CI 0.8—8.9) relative to the paternal agriculture group. Due to the small number of cases in our exposed group, we were unable to adjust for more than 1 factor at a time. The small numbers also precluded consideration of risk estimates separately by ethnicity or other factors. We did not observe any effect modification.

We did not observe a seasonal trend in the risk of limb defects for the exposed group relative to either comparison group (data not shown). The prevalence ratios varied widely between the estimated calendar months of conception, but showed no clear pattern. Confidence intervals were wide and overlapping, with no statistically significant differences.

Discussion

The present study investigated the risk of limb defects among offspring of women employed in agriculture and, therefore, likely to be exposed to agricultural chemicals. Our results indicate that agriculturally employed women in Washington State were at increased risk of giving birth to children with limb defects. The adjusted prevalence ratios for limb defects were similar with the use of either the nonagricultural or the paternal agriculture comparison groups, although only the nonagricultural comparison group produced a significant result.

These findings are consistent with the results from several studies of likely pesticide exposure and limb defects. Kristensen et al (5) reported an odds ratio of 2.50 for limb defects among children of farmers in a cohort study involving almost 200 000 births in Norway. Schwartz et al (3) found an increased risk of limb reduction defects among children of agricultural workers (relative risk 2.3) in a review of more than 2400 birth records from an agricultural county in southern California. This study was followed by a case-referent study of limb reduction defects (4), which found no increased risk among children of agricultural workers but did observe elevated risks among children whose mothers resided in counties of high versus minimal agricultural productivity (relative risk 1.7, 95% CI 1.1—2.7) and high versus minimal pesticide use (relative risk 1.9, 95% CI 1.2—3.1). Risks were further elevated among children with additional birth anomalies. Kricker et al (2), in a case-referent study of congenital limb reduction defects in Australia, found a relative risk of 3.4 for women reporting pesticide exposure in a workplace or garden. Further analyses examining 2 levels of exposure (1 versus ≥1 "incident" of exposure to pesticides) showed an exposure-response relationship.

Other studies report little or no evidence of a relationship between pesticide exposure and limb defects. A case-referent study of birth defects in Colombia (6) found no increase in risk associated with pesticide exposure. Nurminen et al (8) found no association between maternal agricultural employment and skeletal defects in a Finnish case-referent study, although this difference from the findings of the present study may be due to differences in case definition. Lin et al (7) found that neither parental pesticide exposure nor farming occupation was related to a risk of total limb reduction defects. However, they did observe that limb reduction defects with additional malformations showed a weak but consistent association with parental occupational pesticide exposure. We observed no such relationship for cases of limb defects with associated malformations; however, the total number of such cases was small (N=12) and the power to detect an association was low.

We are aware of only one study addressing specifically the human developmental risks of exposure to commercial fertilizers. Kristensen et al (5) observed odds ratios of 1.54 (95% CI 0.98—2.42) and 1.85 (95% CI 1.15—2.99) for polydactyly in association with exposure to medium (5—24 kg/hectare) and high (≥25 kg/hectare) levels, respectively, of phosphorus from commercial fertilizers. In addition, they reported an odds ratio of 1.60 (95% CI 1.04—2.46) for syndactyly in association with the use of certain fertilizer regimens.

Numerous pesticides have been shown to cause limb defects in animal models, although effects vary widely between species and routes of exposure. Pesticides causing limb defects in at least one test species include the fungicides captafol, captan, cycloheximide, ethylene oxide, and the maneb degradation product imidazolidinethione; the herbicide dicotex; the insecticides aldrin, apholate, carbaryl, demeton, dialifor, dieldrin, dimethoate, diazinon, and endrin; chlormequat; and cyhexatin (1). Most of these pesticides were available during at least part of our study period.

In the present study, we evaluated the possibility of a seasonal trend in limb defects. We found no apparent association between estimated month of conception and risk of limb defects in the exposed group. However, given the small number of limb defects in this group (N=9), the power to detect a trend for this outcome was very low. Research by Gibson et al (9) has indicated a strong relationship between time of exposure and adverse birth outcomes, including musculoskeletal abnormalities. Specifically, the period of greatest risk was observed to be in the first 6 weeks of gestation. Kristensen et al (5) found the highest prevalence of limb reduction defects among farmers' offspring conceived in April through June.

One limitation of this study is potential misclassification of occupation. A study by Marshall et al (10) found reasonable accuracy of occupation information recorded on birth certificates. However, most agricultural work is seasonal and Washington State birth certificates

since 1983 record only the mother's most recent employment. Women engaged in farm work during their first trimester of pregnancy, when the fetus is most susceptible to teratogens, are likely to give birth during the nonagricultural season. If they have engaged in other, nonagricultural, employment since that time, their recorded occupation will not reflect that agricultural exposure. The opposite effect would be expected for women who engage in agricultural work only late in their pregnancy, when the fetus is less susceptible to teratogenesis. The likely effect of such exposure misclassification is to attenuate any observed exposure-disease relationship. This possibility would suggest that the observed risks may be underestimates of the true risk.

An additional limitation is the use of job title as a surrogate for the actual exposure of interest – agricultural chemicals. Some agricultural workers have little or no contact with pesticides and other agricultural chemicals, while some nonagricultural workers do receive such exposures. This misclassification of our true exposure of interest is unlikely to be related to birth outcome and thus is expected to attenuate our risk estimates.

Missing data are unlikely to have had an appreciable effect on our results. The proportions of missing data related to limb defects were similar across the exposure groups and were relatively small, the greatest being 8.2%.

Last, we were limited in our ability to control for potential confounding factors, due, in part, to the nature of the data recorded on birth certificates. In particular, information on smoking and alcohol use during pregnancy was not recorded on birth certificates in the early years of the study. Even for more recent years, such information provided only a crude measure of actual exposure. Data on other potential confounding factors such as socioeconomic status and occupational or behavioral risk factors were either not available on the birth certificates or were missing for a large proportion of the subjects.

We observed only 9 limb defects among the exposed subjects, and this result further limited our ability to adjust for confounders. Limb defects are rare, occurring in approximately 0.1% of live births in Washington State. This situation precluded simultaneous adjustment for multiple confounders. However, none of the individual potential confounders examined had an appreciable effect on risk estimates.

We used a comparison group consisting of births to fathers who worked in agriculture in addition to a comparison group of births in which neither parent worked in agriculture in an attempt to control for factors such as socioeconomic status, for which the birth record does not provide sufficient data. However, most fathers in the exposed group were farm workers [N=2485 (58.6%)], while most fathers in the paternal agriculture comparison group were farmers [N=3025 (50.5%)]; this finding indicates that our strategy probably did not result in groups with similar socioeconomic backgrounds. Nonetheless, the interpretation of risk estimates was not affected by adjustment for type of paternal agricultural employment. Furthermore, any effects in the paternal agriculture comparison group from indirect pesticide exposure of the mothers or from direct exposure of the fathers were apparently small, since all the risk estimates were similar using either comparison group.

In conclusion, the results of our study suggest that occupational exposure to agricultural chemicals may increase a woman's risk of giving birth to children with limb defects. These results add to a growing body of evidence of the harmful effects of pesticide or fertilizer exposure during pregnancy. Given the vast number of people employed in agriculture or otherwise exposed to agricultural chemicals in the United States and worldwide, we believe that this issue has important public health implications and warrants further attention. Future research would benefit from improved assessment of exposure to agricultural chemicals. Objective markers of exposure such as employers' agricultural chemical application records, personnel records, or biomarkers would strengthen studies. Self-reporting of factors that influence an individual's exposure, such as job tasks performed, use of protective equipment, and exposure outside the workplace, would also contribute. Prospective studies of birth outcomes — likely feasible due to the relatively short human gestation period — should prove especially valuable.

Acknowledgments

The authors wish to thank Lowell Sever for his thoughtful comments and suggestions concerning an earlier version of this manuscript. We are also indebted to Bill O'Brien for providing the necessary data.

References

1. Schardein JL. Pesticides. In: Schardein JL, editor. Chemically induced birth defects. 2nd ed. New York (NY): Marcel Decker, 1993:675—721.
2. Kricker A, McCredie J, Elliott J, Forrest J. Women and the environment: a study of congenital limb anomalies. Community Health Stud 1986;10:1—11.
3. Schwartz DA, Newsum LA, Heifetz RM. Parental occupation and birth outcome in an agricultural community. Scand J Work Environ Health 1986;12:51—4.
4. Schwartz DA, LoGerfo JP. Congenital limb reduction defects in the agricultural setting. Am J Public Health 1988;78:654—8.
5. Kristensen P, Irgens LM, Andersen A, Bye AS, Sundheim L. Birth defects among offspring of Norwegian farmers, 1967—

1991. Epidemiology 1997;8:537—44.
6. Restrepo M, Munoz N, Day N, Parra JE, Hernandez C, Blettner M, et al. Birth defects among children born to a population occupationally exposed to pesticides in Colombia. Scand J Work Environ Health 1990;18:239—48.
7. Lin S, Marshall EG, Davidson GK. Potential parental exposure to pesticides and limb reduction defects. Scand J Work Environ Health 1994;20:166—79.
8. Nurminen T, Rantala K, Kurppa K, Holmberg PC. Agricultural work during pregnancy and selected structural malformations in Finland. Epidemiology 1995;6:23—30.
9. Gibson, GT, Colley DP, Baghurst PA. Maternal exposure to environmental chemicals and the aetiology of teratogenesis. Aust N Z J Obstet Gynaec 1983;23:170—4.
10. Marshall EG, Gensburg LJ, Roth GB, Davidson GK, Dlugosz LJ. Comparison of mother's occupation and industry from the birth certificate and a self-administered questionnaire. J Occup Med 1992;34:1090—6.

Received for publication: 18 March 1999