Chlorophenoxy herbicides are widely used in the United States and Western Europe for broadleaf weed control in grain farming and park maintenance. Most of the spring and durum wheat produced in the United States is grown in Minnesota, Montana, North Dakota, and South Dakota, with more than 85% of the acreage treated with chlorophenoxy herbicides such as 2,4-dichlorophenoxyacetic acid (2,4-D) and 4-chloro-2-methylphenoxyacetic acid (MCPA). Rates of adverse birth outcomes in rural, agricultural counties of these states during 1995–1997 were studied by comparing counties with a high proportion of wheat acreage and those with a lower proportion. Information routinely collected and made available by federal agencies was used for this ecologic study. Significant increases in birth malformations were observed for the circulatory/respiratory category for combined sexes [odds ratio (OR) = 1.65; 95% confidence interval (CI), 1.07–2.55]. A stronger effect was observed for the subcategory, which excluded heart malformations (OR = 2.03; 95% CI, 1.14–3.59). In addition, infants conceived during April–June—the time of herbicide application—had an increased chance of being diagnosed with circulatory/respiratory (excluding heart) malformations compared with births conceived during other months of the year (OR = 1.75; 95% CI, 1.09–2.80). Musculoskeletal/integumental anomalies increased for combined sexes in the high-wheat counties (OR = 1.50; 95% CI, 1.06–2.12). Infant death from congenital anomalies significantly increased in high-wheat counties for males (OR = 2.66; 95% CI, 1.52–4.65) but not for females (OR = 0.48; 95% CI, 0.20–1.15). These results are especially of concern because of widespread use of chlorophenoxy herbicides.

Key words: birth malformations, chlorophenoxy herbicides, congenital anomalies, ecologic studies, endocrine disruption. Environ Health Perspect 111:1259–1264 (2003). doi:10.1289/ehp.5830 available via http://dx.doi.org/
and cancer mortality—in counties where wheat is the major crop and exposure of residents to chlorophenoxy herbicides is likely (Garry et al. 1996; Schreinemachers 2000). Birth malformations among 1995–1997 births in agricultural, rural counties of Minnesota, Montana, North Dakota, and South Dakota were investigated, comparing high-wheat to low-wheat counties. The purpose of this exploratory study is to identify a potential, regional health hazard. Results should be viewed in this light.

Materials and Methods

Information on newborns and infants for 1995–1997 births was obtained from the Linked Birth and Infant Death files, National Center for Health Statistics (NCHS 1995, 1996, 1997). Agricultural information on crop acreage by state and county and herbicide use by state was obtained from the U.S. Department of Agriculture 1992 census (USDA 1992a, 1992b).

To reflect populations more likely exposed to agricultural pesticides than urban populations, counties in Minnesota, Montana, North Dakota, and South Dakota were selected if at least 50% of the county’s population was rural and if at least 20% of the county’s land was dedicated to cropland. By selecting counties from these four states, a wide range for the percentage of land dedicated to wheat was obtained. A county was assigned to either the low-wheat or high-wheat group depending on its percentage of wheat acreage with respect to the median of all selected counties. Wheat acreage was used as a surrogate measure for exposure to chlorophenoxy herbicides.

White, singleton births to mothers 18 or more years old were selected if the birth’s county of residence was included in the study. The assumption was that county of birth would be the same as the county where the newborn was conceived and the parents lived during pregnancy. Only white, singleton births were included, thereby preventing unreliable results for race (only 18% of all births were to nonwhite parents) and excluding malformed or preterm births due to multiple gestations. The proportion of the following outcome variables in combined high-wheat counties was studied with low-wheat counties. The following covariates were used: maternal age (≥35 vs. <35 years); maternal education (less than high school vs. at least high school); marital status (not married vs. married); parity (first birth vs. second or higher birth); prenatal care (prenatal care in second or third trimester or no prenatal care vs. prenatal care in first trimester); previous preterm or SGA birth (yes vs. no); tobacco use during pregnancy (yes vs. no); alcohol use during pregnancy (yes vs. no); sex of child (male vs. female); time of conception [conception during April through June (time of herbicide application) vs. conception during other months]. Models were run only if at least five observations per covariate were available in each exposure group. A covariate with a p-value ≤0.1 for either the male, female, or combined male–female analyses was retained for the final set of covariates for all three analyses, male, female, and combined male–female.

Results

From among the 262 counties in Minnesota, Montana, North Dakota, and South Dakota, 147 agricultural counties with a mostly rural population were selected for the low-wheat (n = 73) and high-wheat (n = 74) groups (Table 1). The major field crops spring and durum wheat, corn, and soybeans were heavily treated with herbicides (USDA 1992b). Chlorophenoxy herbicides (2,4-D and MCPA) were applied predominantly to spring and durum wheat (88% of acreage) but also to some of the corn acreage (13%) and soybean acreage (4%).
parity, 0.2%; prenatal care, 2.0%; previous preterm, 1.9%; smoking or alcohol use during pregnancy, 15%. Covariate information specific to the low-wheat and high-wheat counties is presented in Table 2.

ORs comparing birth malformations and other prenatal outcomes in high-wheat counties with those in low-wheat counties are presented in Table 3. Anomalies available from birth records were analyzed as single categories, provided enough data were available, and as aggregate categories. Based on the 1989 revision of the U.S. Standard Certificate of Live Birth classification scheme (NCHS 1998), the following categories were included: all central nervous system anomalies—aneurysm, spina bifida/meningocele, hydrocephalus, microcephalus, other central nervous system anomalies; all circulatory/respiratory anomalies—heart malformations, other circulatory/respiratory anomalies; all digestive system anomalies—hernia, other musculoskeletal/integumental anomalies, poly-/syn-/adactyly, clubfoot, diaphragmatic hernia, other musculoskeletal/integumental anomalies; all chromosomal anomalies—Down syndrome, other chromosomal anomalies; all other congenital anomalies.

Significant increases were observed for circulatory/respiratory and musculoskeletal/integumental anomalies among combined male and female births, and for infant death from congenital anomalies among boys. Among births with circulatory/respiratory anomalies [International Classification of Diseases, 9th rev. (ICD-9 1989) 745–748], adjustment for the significant covariates (maternal age and conception during April–June, peak time of herbicide application) did not result in a change for the effect of high-wheat counties, as shown by the following adjusted ORs: combined male–female, OR = 1.64 (95% CI, 1.06–2.53); males, OR = 1.81 (95% CI, 1.05–3.11); females, OR = 1.65 (95% CI, 0.89–3.04). Further analysis of the circulatory/respiratory category showed that the strongest effects were observed for the “other” subcategory (ICD-9 747–748), which excludes heart malformations (ICD-9 745–746) but includes anomalies of the aorta, patent ductus arteriosus, other anomalies of the circulatory system, and all anomalies of the respiratory system. Among births with these “other” circulatory/respiratory malformations, the only significant covariate was conception during April–June. Adjustment for this covariate did not change the high-wheat effects presented in Table 3, as shown by the following adjusted ORs: combined male–female, OR = 1.99 (95% CI, 1.12–3.53); males, OR = 2.02 (95% CI, 1.01–4.02); females, OR = 2.06 (95% CI, 0.92–4.61). ORs for the effect of conception during April–June were as follows: combined male–female, OR = 1.75 (95% CI, 1.09–2.80); males, OR = 2.42 (95% CI, 1.42–4.15); females, OR = 1.02 (95% CI, 0.45–2.34). Given both wheat production and month of conception, boys conceived during April–June and born in high-wheat counties were almost five times more likely to be diagnosed with a birth anomaly coded as ICD-9 747–748 than were boys in low-wheat counties conceived during other months of the year. The difference of the seasonality effect between boys and girls was confirmed by a statistical test for interaction between the high-wheat county group and sex (p = 0.002).

The male–female ratios of births with any congenital anomaly were 1.67 and 1.60 in the low- and high-wheat counties, respectively, whereas these ratios for all births were 1.07 and 1.03 for low- and high-wheat counties, respectively, suggesting that males may be more susceptible to congenital anomalies than are girls. Similar observations about the sex ratios have been made previously (Francannet et al. 1993; Garry et al. 1996, 2002; Imaizumi et al. 1991).

Additional congenital anomalies, not diagnosed at birth, were identified from death certificates for 24 infants, including 20 infants with circulatory/respiratory anomalies. Combining these additional cases with those obtained from birth records, the OR for births with any anomaly (combined boys and girls) did not change (OR = 1.07; 95% CI, 0.87–1.30), whereas the OR for births with circulatory/respiratory anomalies decreased slightly (OR = 1.55; 95% CI, 1.04–2.32).

Discussion

Results from this study indicate that in rural, agricultural counties where wheat acreage occupies a larger percentage of the land and where use of chlorophenoxy herbicides is higher, anomalies of the circulatory/respiratory and musculoskeletal/integumental system significantly increased. To interpret these results, one should bear in mind the choice of reference group. The advantage of selecting rural, agricultural, low-wheat counties as

Table 2. Characteristics of 1995–1997 live births.

| Characteristic | Low wheat | High wheat |
|---------------|------------|------------|
| Number of births | 33,380 | 10,254 |
| Sex (%) | | |
| Male | 51.6 | 50.7 |
| Female | 48.4 | 49.3 |
| Maternal age (%) | | |
| ≥ 35 | 11.5 | 12.6 |
| < 35 | 88.5 | 87.4 |
| Maternal education (%) | | |
| ≤ High school | 6.8 | 7.6 |
| High school graduate | 92.6 | 92.0 |
| Unknown | 0.6 | 0.4 |
| Marital status (%) | | |
| Unmarried | 13.7 | 10.7 |
| Married | 86.3 | 89.3 |
| Parity (%) | | |
| 1 | 27.5 | 27.1 |
| ≥ 2 | 72.3 | 72.9 |
| Unknown | 0.2 | 0.0 |
| Prenatal care (%) | | |
| None or started after first trimester | 12.7 | 16.3 |
| Started first trimester | 84.8 | 83.1 |
| Unknown | 2.5 | 0.5 |
| Previous preterm or SGA (%) | | |
| Yes | 2.1 | 1.8 |
| No | 95.9 | 96.9 |
| Unknown | 2.1 | 1.2 |
| Tobacco use during pregnancy (%) | | |
| Yes | 11.6 | 9.9 |
| No | 75.3 | 69.6 |
| Unknown | 13.1 | 20.5 |
| Alcohol use during pregnancy (%) | | |
| Yes | 0.6 | 0.7 |
| No | 86.0 | 78.7 |
| Unknown | 13.4 | 20.6 |
| Season of conception (%) | | |
| April–June (spring) | 24.3 | 24.2 |
| Other months | 74.7 | 75.6 |
| Unknown | 1.0 | 0.2 |
| Births with missing information (%) | | |
| Malformation | 2.1 | 1.2 |
| Gestational age | 1.0 | 0.2 |
| SGA | 1.0 | 0.2 |
referred was that counties included in the study would be more alike, except for wheat acreage, the factor under investigation. The disadvantage was that the reference group was not a null-data referent. If, for example, a specific anomaly had been associated with both chlorophenoxy herbicides in high-wheat counties and other herbicides applied to corn and soy beans in low-wheat counties, no effect might have been observed for this anomaly in high-wheat counties. In other words, use of low-wheat counties as the referent may have produced an underestimate of effects in association with high-wheat counties. Although selection of urban counties as referent would have had the advantage of little or no exposure to agricultural herbicides, the disadvantage would have been that other, nonagricultural factors might also be involved in causing a lower level of birth malformations in urban counties. For example, easier access to prenatal care may be associated with elective abortion prior to prenatal diagnosis of an anomaly (Cragan and Khooury 2000). Underreporting may be more frequent in urban than in rural counties, because in large hospitals information on birth malformations is provided by obstetricians, in contrast to small hospitals, where pediatricians are the source of information (Hexter and Harris 1991). Therefore, selection of urban counties as referent would likely have overestimated the effects in high-wheat counties. The contribution of this study is that by selecting rural, agricultural, low-wheat counties as referent, effect estimates, although conservative, could be more specifically tied to chlorophenoxy herbicides and/or contaminants.

Several limitations of this study need to be considered. Data for this study were based on birth certificates and therefore subject to significant underreporting (Snell et al. 1992). For example, only 28% of malformations recognizable at birth among 1989–1990 Georgia births, reported by the Metropolitan Atlanta Congenital Defects Program, were also reported by Georgia birth certificates (Watkins et al. 1996). In the present study, fewer than 2% of birth certificates were not marked for presence or absence of malformations, in contrast to at least 8% in urban counties. This supported the notion that reporting by small hospitals probably was more complete than reporting by larger hospitals in urban counties. Malformations not recognizable at birth, especially the occurrence of heart malformations among newborns discharged earlier from the hospital, could have contributed significantly to underreporting (Gadow et al. 1996; Watkins et al. 1996). Various birth malformations based on organ system classification may have resulted in risk estimates of malformations that do not share the same causal agents (Koger and Sala 1998). Wheat acreage per county, an indirect measure of use of chlorophenoxy herbicides, would be appropriate if the amount applied was in direct proportion to wheat acreage, which may or may not have been the case in the selected counties. Results from this ecologic study were designed to estimate regional differences. Conclusions drawn at the population level are not necessarily valid at the individual level (Morgenstern 1995).

It is remarkable that given the data limitations, the results of the present hazard-identification study are consistent with a previous birth malformation study (Garry et al. 1996). A Norwegian agricultural study reported increased rates for central nervous system anomalies, cryptorchism, hypospadias, urinary system anomalies, and limb reduction in association with grain agriculture and pesticide purchase or grain agriculture and use of spray equipment (Kristensen et al. 1997). Conceptions in spring showed an increase in birth malformations, in association with grain farming. A New Zealand study compared incidence of congenital anomalies in specific regions during years of spraying with 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) (1972–1976) with that in years of no spraying (1959–1965). 2,4,5-T is chemically related to 2,4-D and MCPA. Births with any malformation, heart malformations, hypospadias, or clubfoot were significantly increased in births during the years of 2,4,5-T application (Hanfert et al. 1981).

Other studies have reported increased levels of birth malformations in association with less specific pesticide exposures. An increase in transposition of the great arteries was reported among newborns, especially males, whose mother had been exposed to any pesticides during the first trimester (Loftrodo et al. 2001). An increased risk for neural tube malformations, oral clefts, and multiple anomalies was

| Table 3. Developmental outcomes in low-wheat and high-wheat counties for 1995–1997 live births. |
|--------------------------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Perinatal effect                   | Male + female | Male          | Female         | Male + female | Male          | Female         |
|                                  | \( N_{LW} \) | \( N_{NW} \) | OR (95% CI)    | \( N_{LW} \) | \( N_{NW} \) | OR (95% CI)    |
| Births with any anomaly           | 596          | 213          | 1.07 (0.87–1.31) | 373          | 131          | 1.04 (0.81–1.33) |
| Central nervous system anomalies  | 50           | 12           | 0.81 (0.46–1.42) | 25           | 7            | 0.97 (0.45–2.07) |
| Other central nervous system anomalies | 20           | 5            | 0.79 (0.30–2.11) | NA           | NA           | NA             |
| Circulatory/respiratory anomalies  | 74           | 39           | 1.65 (1.07–2.55) | 42           | 24           | 1.83 (1.06–3.14) |
| Heart malformations               | 40           | 15           | 1.23 (0.70–2.17) | NA           | NA           | NA             |
| Other circulatory/respiratory anomalies | 42           | 27           | 2.03 (1.14–3.59) | 25           | 16           | 2.05 (1.02–4.03) |
| Digestive system anomalies        | 87           | 24           | 1.39 (0.55–3.12) | 47           | 11           | 0.74 (0.37–1.48) |
| Cleft lip/palate                  | 46           | 16           | 1.12 (0.62–2.01) | 28           | 10           | 1.17 (0.55–2.47) |
| Urogenital anomalies              | 123          | 44           | 1.04 (0.71–1.52) | 112          | 37           | 0.97 (0.65–1.44) |
| Malformed genitalia               | NA           | NA           | NA             | 25           | 8            | 1.03 (0.51–2.09) |
| Other urogenital anomalies        | 100          | 35           | 1.01 (0.65–1.55) | 91           | 29           | 0.91 (0.57–1.44) |
| Musculoskeletal/integumental anomalies | 142         | 70           | 1.50 (1.06–2.12) | 78           | 37           | 1.45 (0.96–2.18) |
| Poly-/syn-/adactyly               | 19           | 14           | 2.43 (1.26–4.71) | 12           | 7            | 1.88 (0.86–4.10) |
| Club foot                         | 33           | 9            | 0.84 (0.39–1.80) | NA           | NA           | NA             |
| Other musculoskeletal/integumental anomalies | 84           | 47           | 1.70 (1.10–2.62) | 41           | 20           | 1.53 (0.87–2.66) |
| Chromosomal abnormalities         | 60           | 17           | 0.93 (0.55–1.58) | 36           | 11           | 1.07 (0.54–2.13) |
| Down syndrome                     | 32           | 10           | 1.02 (0.52–2.01) | NA           | NA           | NA             |
| Other chromosomal abnormalities   | 28           | 7            | 0.80 (0.33–1.96) | NA           | NA           | NA             |
| Other congenital anomalies        | 189          | 42           | 0.69 (0.49–0.98) | 113          | 29           | 0.80 (0.53–1.22) |
| Gestational age < 37 weeks        | 2,304         | 748         | 1.05 (0.95–1.16) | 1,277         | 416          | 1.08 (0.94–1.24) |
| Small for gestational age         | 1,552         | 503          | 1.05 (0.94–1.17) | 836          | 258          | 1.02 (0.90–1.16) |
| Infant death from congenital anomalies | 55          | 22           | 1.27 (0.80–2.00) | 23           | 17           | 2.66 (1.52–4.65) |

Abbreviations: NA, data not analyzed due to low number of observations; \( N_{LW} \), number of births in low-wheat counties; \( N_{NW} \), number of births in high-wheat counties; OR, unadjusted odds ratio. The following birth anomalies were included in the combined categories, based on organ system classification, but were not analyzed as single categories due to low number of observations: anencephalus, spina bifida/meningocele, hydrocephalus, microcephalus, rectal atresia/stenosis, tracheo-esophageal fistula, omphalocoele, other gastrointestinal anomalies, renal agenesis, diaphragmatic hernia. The following birth totals were used in the calculation of odds ratios and confidence intervals: Birth malformations: low-wheat, 32,674 (male, 16,859; female, 15,815); high-wheat, 10,233 (male, 5,182; female, 5,051). SGA: low-wheat, 33,047 (male, 17,073; female, 15,974); high-wheat, 10,233 (male, 5,183; female, 5,050). Infant death: low-wheat, 33,380 (male, 17,227; female, 16,153); high-wheat, 10,254 (male, 5,194; female, 5,060).
reported among offspring of mothers involved in agricultural activities during 1 month before and 3 months after conception, with presumably low levels of pesticide exposure (García et al. 1999). An association was observed between orchidopexy rates and level of pesticide use in agricultural regions in Spain (García-Rodríguez et al. 1996).

Other abnormalities reported in association with chlorophenoxy herbicide exposure may contribute to adverse developmental or reproductive effects: for example, increased risk of abortion at less than 12 weeks of gestation for preconception exposure (Arbuckle et al. 1999a, 2001); or increased levels of asthenospermia, necrospermia, and teratospermia in farm sprayers who applied 2,4-D (Lerda and Rizzi 1991).

Toxicologic studies have reported adverse developmental outcomes in rodent models. 2,4-D is teratogenic (Schardein 1993). Pure 2,4-D has been shown to be maternally toxic, embryolethal, and a potential inducer of kidney and urogenital malformations in rats (Fofana et al. 2000). Supernumerary ribs were observed in rat litters treated with 2,4-D (Chernoff et al. 1990). A review article on 2,4-D safety concluded that reproductive and developmental effects occur in toxicologic studies, but mostly at maternally toxic doses, and that no effects were expected at the low levels humans were exposed to (Munro et al. 1992). However, recent studies indicate that chlorophenoxy herbicides at low doses do have biologic effects, although not necessarily teratogenic effects. Reduced litter size was observed in pregnant mice exposed to low and environmentally relevant doses (0.01 mg/kg/day) in their drinking water of a commercial formulation of herbicides consisting of 2,4-D, mecoprop, dicamba, and inactive ingredients (Cavieres et al. 2002). An increase of the lymphocyte replicative index was observed for in vitro tests at a low dose (0.005 mM) of commercial 2,4-D (Holland et al. 2002). Exposure to 2,4-D may involve endocrine disruption due to interference of 2,4-D with thyroid hormone transport carriers (Van den Berg et al. 1991).

Toxicity of chlorophenoxy herbicides is usually tested on pure or reagent-grade compounds. Biologic responses to these herbicides in presence of contaminants, adjuvants, and fertilizer may be higher. Contaminants present in technical grade 2,4-D depend on the purity of the chemicals used to produce 2,4-D, and on the production process (IARC 1986). Occasionally, 2,3,7,8-tetrachlorodibenzo-p-dioxin may be present in technical grade 2,4-D (Johnson et al. 1992). Adjuvants may contribute to adverse health effects (Garry et al. 1999).

**REFERENCES**

Arbuckle TE, Lin Z, Mery LS. 2001. An exploratory analysis of the effect of pesticide exposure in the risk of spontaneous abortion in an Ontario farm population. Environ Health Perspect 109:851–857.

Arbuckle TE, Savitz DA, Mery LS, Curtis KM. 1999a. Exposure to phenoxyherbicides and the risk of spontaneous abortion. Epidemiology 10:752–760.

Arbuckle TE, Schrader SM, Cole D, Hale JC, Bancej CM, Turner LA, et al. 1999b. 2,4-Dichlorophenoxyacetic acid residues in semen of Ontario farmers. Reprod Toxicol 13:421–429.

Axelson O, Sundell L, Berg NO, Miller T, Axelson D. 1981. Soft-tissue sarcomas and exposure to chemical substances: a case-referent study. Br J Ind Med 38:227–232.

Feustlin A, Settini L, Pacirolli R, Fano V, Zuccaro P, Forastiere F. 1996. Immunological changes among farmers exposed to phenoxy herbicides: preliminary observations. Occup Environ Med 53:583–585.

Fofana D, Kobabe H, Odo S, Nishi J, Miyata K. 2000. Prenatal developmental effects of pure 2,4-dichlorophenoxyacetic acid (2,4-D) on the rat. Congenit Anom 40:287–296.

Francannet C, Lancaster PA, Pradat P, Cocchi G, Stoll C. 1993. The epidemiology of three serious cardiac defects. A joint study between five centres. Eur J Epidemiol 9:675–676.

Gadew EC, Otalio L, Lippold SE. 1996. Congenital malformations. Curr Opin Obstet Gynecol 8:412–418.

García AM, Fletcher T, Benavides FG, Orto E. 1999. Parental agricultural work and selected congenital malformations. Am J Epidemiol 149:64–74.

García-Rodríguez J, García-Martín M, Nogueras-Ocaña M, de Dios Luna-del-Castillo J, Espigares García M, Díez N, et al. 1996. Exposure to pesticides and cryopreservation: geographical evidence of a possible association. Environ Health Perspect 104:1090–1095.

Garry VF, Burroughs B, Tomarese R, Kesner JS. 1999. Herbicides and adjuvants: an evolving view. Toxicol Ind Health 15:159–167.

Garry VF, Harkins ME, Erickson LL, Long-Simpson LK, Holland SE, Burroughs BL. 2002. Birth defects, season of conception, and sex of children born to pesticide applicators living in the Red River Valley of Minnesota, USA. Environ Health Perspect 110(suppl 3):441–448.

Garry VF, Schreinemachers D, Harkins ME, Griffith J. 1996. Pesticide applicators, biocides, and birth defects in rural Minnesota. Environ Health Perspect 104:394–399.

Hanify JA, Metcalf P, Nobbs CL, Worsley KJ. 1981. Aerial spraying of 2,4,5-T and human birth malformations: an epidemiological investigation. Science 212:349–351.

Hardell L. 1981. Relation of soft-tissue sarcoma, malignant lymphoma and colo cancer to phenyoxo acids, chlorophenols and other agents. Scand J Work Environ Health 7:119–130.

Hardell L, Eriksson M, Lenner P, Lundgren E. 1981. Soft-tissue sarcomas and exposure to phenoxyacetic acids. A new case-referent study. Cancer 62:652–656.

Hardell L, Eriksson M, Lenner P, Lundgren E. 1981. Malignant lymphoma and exposure to organic solvents, chlorophenols and phenoxy acids: a case-control study. Br J Cancer 43:169–176.

Hardell L, Sandström A. 1978. Case-control study: soft-tissue sarcomas and exposure to phenoxyacetic acids or chlorophenoxy compounds. Br J Cancer 39:711–717.

Harris SA, Solomon KR. 1992. Human exposure to 2,4-D following controlled activities on recently sprayed turf. J Environ Sci Health B27(1):9–22.

Hextor AC, Harris JA. 1991. Bias in congenital malformations information from the birth certificate. Teratology 44:177–180.

Hill RT, To T, Holler JS, Fast DM, Smith SJ, Needham LL, et al. 1989. Residues of chlorinated phenols and phenoxy acid herbicides in the urine of Arkansas children. Arch Environ Contam Toxicol 18:469–474.

Hoar SK, Blair A, Holmes FF, Boysen CD, Robel RJ, Hoover R, et al. 1991. Bias in congenital malformations information from the birth certificate. Teratology 44:177–180.

IARC. 1986. Some halogenated hydrocarbons and pesticide exposures. IARC Monogr Eval Carcinog Risk Chem Hum 41:357–406.

Imazumi Y, Yamamura H, Nishikawa M, Matsuoka M, Moriyama I. 1991. The prevalence at birth of congenital malformations at a maternity hospital in Osaka City, 1948–1980. Jpn J Hum Genet 36:275–287.
Johnson ES, Parsons W, Weinberg CR, Shore DL, Mathews J, Patterson DG, et al. 1992. Current serum levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin in phenoxy acid herbicide applicators and characterization of historical levels. J Natl Cancer Inst 84:1648–1653.

Kogevinas M, Sala M. 1998. Pesticides and congenital malformations—how many studies will it take to reach a conclusion? Scand J Work Environ Health 24:445–447.

Kristensen P, Ingens LM, Andersen A, Bye AS, Sundheim L. 1997. Birth defects among offspring of Norwegian farmers, 1967–1991. Epidemiology 8:537–544.

Larney FJ, Cressa AJ, Bullock MS. 1999. Herbicide transport on wind-eroded sediment. J Environ Qual 28:1412–1421.

Lerda D, Rizzi R. 1991. Study of reproductive function in persons with maternal exposures to 2,4-dichlorophenoxyacetic acid (2,4-D). Mutat Res 262:47–50.

Loffredo CA, Silberfeld EK, Ferencz C, Zhang J. 2001. Interactions of halogenated industrial chemicals with transcytosis and effects on thyroid hormone levels in vivo. Arch Toxicol 65:15–19.

McDuffie HH, Pahwa P, McLaughlin JR, Spinelli JJ, Fincham S, Dosman JA, et al. 2002. Non-Hodgkin’s lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. Am J Epidemiol 153:529–536.

McMichael AJ. 2002. Population, environment, disease, and principles, and methods. Annu Rev Public Health 16:61–81.

McDonald JF, Aleson A, Gillis P, Griffiths R, Kogevinas M, Sala M. 1998. Pesticides and congenital malformations. Scand J Work Environ Health 24:445–447.

Nishioka MG, Burkholler HM, Brinkman MC, Gordon SM, Lewis RG. 1996. Measuring transport of lawn-applied herbicide acids from turf to home: correlation of dislodgable 2,4-D turf residues with carpet dust and carpet surface residues. Environ Health Perspect 103:3133–3130.

Nishioka MG, Lewis RG, Brinkman MC, Burkholler HM, Hines CE, Menkedick JR. 2001. Distribution of 2,4-D in air and on surfaces inside residences after lawn applications: comparing exposure estimates from various media for young children. Environ Health Perspect 109:1185–1191.

Pekkanen J, Pearce N. 2001. Environmental epidemiology: challenges and opportunities. Environ Health Perspect 109:1–5.

Persson B, Dahlander AM, Fredriksson M, Noorlind Brage H, Ohlson CD, Axelson O. 1989. Malignant lymphomas and occupational exposures. Br J Ind Med 46:516–520.

Renne DS, Wolf MA. 1979. Experimental studies of 2,4-D herbicide drift characteristics. Agric Meteorol 20:7–24.

SAS Institute. 2001. SAS/STAT Guide for Personal Computers, Version 8. Cary, NC: SAS Institute, Inc.

Schardein JL. 1993. Chemically Induced Birth Defects. 2nd ed. New York: Marcel Dekker, Inc.

Shy CM. 1997. The failure of academic epidemiology: witness for the prosecution. Am J Epidemiol 145:479–484.

Short P, Colborn T. 1999. Pesticide use in the U.S. and policy implications: a focus on herbicides. Toxicol Ind Health 15:240–275.

Slom LA, Polissar L, Severson RK, Heuser LS, Kulander BG, Vines P, Terraccini B, Cicone G, Cignetti A, Colombo E, et al. 1998. Phenoxy herbicides and soft-tissue sarcomas in female rice weaders. Scand J Work Environ Health 13:9–17.

Sterling TD, Arundel AV. 1986. Health effects of phenoxy herbicides. A review. Scand J Work Environ Health 12:161–173.

Susser M. 1998. Does risk factor epidemiology put epidemiology in vivo? J Epidemiol Community Health 52:608–611.

USGS. 1997. Pesticides in the Atmosphere. Factsheet FS-152-95. Sacramento, CA: U.S. Geological Survey. Available: http://water.usgs.gov/pubs/circ/circ1225 [accessed 25 February 2003].

Van den Berg KJ, van Raaij JAGM, Braga PC, Notten WRF. 1991. Herbicide transport on wind-eroded sediment. J Environ Qual 28:1412–1421.

Vineis P, Terraccini B, Cicone G, Cignetti A, Colombo E, et al. 1986. Phenoxy herbicides and soft-tissue sarcomas in female rice weiders. Scand J Work Environ Health 13:9–17.

Wolfe DT, Cressa AJ, Grover R, Kerr LA, Sihurra AD. 2002. Environmental concentrations of agricultural herbicides: 2,4-D and triallate. J Environ Qual 31:129–144.

Wright BS, Polissar L, Severson RK, Heuser LS, Kulander BG, Woods JS, Polissar L, Severson RK, Heuser LS, Kulander BG. 1989. Mortality study of Canadian male farm operators: non-Hodgkin’s lymphoma mortality and agricultural practices in Saskatchewan. J Natl Cancer Inst 82:575–582.

Williams DL, Creasy RK, Cunningham GC, Hawes WE, Norris FD, Tashiro M. 1982. Fetal growth and perinatal viability in California. Obstet Gynecol 59:624–632.

Menkedick JR. 2001. Distribution of 2,4-D in air and on surfaces inside residences after lawn applications: comparing exposure estimates from various media for young children. Environ Health Perspect 109:1185–1191.

Pekkanen J, Pearce N. 2001. Environmental epidemiology: challenges and opportunities. Environ Health Perspect 109:1–5.

Persson B, Dahlander AM, Fredriksson M, Noorlind Brage H, Ohlson CD, Axelson O. 1989. Malignant lymphomas and occupational exposures. Br J Ind Med 46:516–520.

Renne DS, Wolf MA. 1979. Experimental studies of 2,4-D herbicide drift characteristics. Agric Meteorol 20:7–24.

SAS Institute. 2001. SAS/STAT Guide for Personal Computers, Version 8. Cary, NC: SAS Institute, Inc.

Schardein JL. 1993. Chemically Induced Birth Defects. 2nd ed. New York: Marcel Dekker, Inc.

Shy CM. 1997. The failure of academic epidemiology: witness for the prosecution. Am J Epidemiol 145:479–484.

Snell LM, Little BB, Knoll KA, Johnston WL, Rosenfeld CR, Gant NF. 1992. Reliability of birth certificate reporting of congenital anomalies. Am J Perinatol 9:219–222.

Sterling TD, Arundel AV. 1986. Health effects of phenoxy herbicides. A review. Scand J Work Environ Health 12:161–173.

Susser M. 1988. Does risk factor epidemiology put epidemiology at risk? Peering into the future. J Epidemiol Community Health 52:608–611.

USDA. 1992a. Agricultural Chemical Usage, Field Crop Summary 1992. Washington, DC: U.S. Department of Agriculture. Available: http://usda.mannlib.cornell.edu/reports/nass/other/pnu-bbl [accessed 15 March 2002].

USGS. 1997. Pesticides in the Atmosphere. Factsheet FS-152-95. Sacramento, CA: U.S. Geological Survey. Available: http://water.usgs.gov/pubs/circ/circ1225 [accessed 25 February 2003].