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Male Pesticide Exposure and Pregnancy Outcome

David A. Savitz,[1,2] Tye Arbuckle,[1,3] Diane Kaczor,[2] and Kathryn M. Curtis[1,2]

Potential health effects of agricultural pesticide use include reproductive outcomes. For the Ontario Farm Family Health Study, the authors sampled Ontario farms from the 1986 Canadian Census of Agriculture, identified farm couples, and obtained questionnaire data concerning farm activities, reproductive health experience, and chemical applications. Male farm activities in the period from 3 months before conception through the month of conception were evaluated in relation to miscarriage, preterm delivery, and small-for-gestational-age births. Among the 1,898 couples with complete data (64% response), 3,984 eligible pregnancies were identified. Miscarriage was not associated with chemical activities overall but was increased in combination with reported use of thiocarbamates, carbaryl, and unclassified pesticides on the farm. Preterm delivery was also not strongly associated with farm chemical activities overall, except for mixing or applying yard herbicides (odds ratio = 2.1, 95% confidence interval 1.0–4.4). Combinations of activities with a variety of chemicals (atrazine, glyphosate, organophosphates, 4-[2,4-dichlorophenoxy] butyric acid, and insecticides) generated odds ratios of two or greater. No associations were found between farm chemicals and small-for-gestational-age births or altered sex ratio. Based on these data, despite limitations in exposure assessment, the authors encourage continued evaluation of male exposures, particularly in relation to miscarriage and preterm delivery. *Am J Epidemiol* 1997;146:1025–36.

abortion; fathers; herbicides; infant, premature; infant, small for gestational age; insecticides; pesticides; sex ratio

Despite the generally favorable health experience of farmers, potential adverse health effects associated with exposure to pesticides have been of concern. Most of the focus has been on cancer (1, 2), generally but not always (3) among men. Reproductive health has been of secondary interest, with studies of both maternal and paternal pesticide exposure in relation to such endpoints as infertility, miscarriage, stillbirth, preterm delivery, low birth weight, and birth defects (4).

Male exposures, in isolation from female or fetal exposures, have been shown in experimental studies to be capable of affecting the entire spectrum of reproductive health endpoints (5) through mechanisms involving the sperm. Such effects are most likely to occur from exposures in the 3 months before conception (6). Nonetheless, we do not yet have firm evidence of a causal relation between paternal exposure in humans and a reproductive health endpoint other than infertility.

The Ontario Farm Family Health Study incorporates many of the necessary features for a study of male pesticide exposure and pregnancy outcome. This large survey acquired data from several thousand farm couples, with women reporting on their reproductive history and health behaviors, men describing their farm activities, including sufficient detail to identify the timing of exposure by year and by month and use of protective equipment, and farm operators reporting on the specific pesticides used on the farm.

MATERIALS AND METHODS

Overview of Ontario Farm Family Health Study

The 1986 Canadian Census of Agriculture served as the sampling frame for the selection of farms for the study, as described in detail elsewhere (7). Ontario was chosen for the study because of the number and diversity of farm operations in this province. Farms were restricted to those most likely to be full-time family-operated holdings. Attempts were made to con-

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Abbreviations: CI, confidence interval; 2,4-DB, 4-[2,4-dichlorophenoxy] butyric acid; OR, odds ratio; SGA, small for gestational age.

[1] Department of Epidemiology, School of Public Health, University of North Carolina, Chapel Hill, NC.
[2] Carolina Population Center, University of North Carolina, Chapel Hill, NC.
[3] Bureau of Reproductive and Child Health, Laboratory Centre for Disease Control, Health Canada, Ottawa, Ontario, Canada.
Reprint requests to Dr. David A. Savitz, Department of Epidemiology, CB 7400, University of North Carolina, Chapel Hill, NC 27599.

tact the farm operator for all farms that met the selection criteria to determine their eligibility for the study. Farm couples were eligible if they were living year-round on the farm and the woman was age 44 years or younger at the time of the interview. Couples and farm operators eligible for the study were mailed detailed questionnaires, and nonrespondents were sought for telephone interviews.

Pregnancy outcomes

All pregnancies reported by farm couples were classified based on outcome, with current pregnancies also included. Pregnancies were excluded if we could not determine the time interval of the pregnancy with certainty (incompatible or missing dates of conception and delivery), if the pregnancy did not occur while the woman was living on the study farm (conception occurred before April in the year the woman first moved to the farm), or if it was unlikely that the husband who completed the questionnaire was the father of the conception (for women married more than once, the conception had to be within 9 months before the marriage date).

Outcomes were classified as singleton live births, multiple gestations (twins, triplets), miscarriage (recognized pregnancy loss before 20 weeks of completed gestation), stillbirth (pregnancy loss at 20 or more weeks of completed gestation), medically induced abortion, currently pregnant, or other (ectopic pregnancy, hydatidiform mole, unknown). Singleton live births were classified as preterm if they occurred before the completion of 37 weeks of gestation and small for gestational age (SGA) if they fell below the 10th percentile of birth weight for gestational age based on Canadian percentiles (8). Sex ratio was defined as the proportion of males among singleton live births. We analyzed the risk of miscarriage, preterm delivery, and SGA births, as well as sex ratio, not addressing stillbirths and other more rare outcomes due to insufficient numbers for analysis.

In each instance, the denominator included pregnancies with at least some period at risk for the event. For miscarriages, this included pregnancies ending in miscarriages, singleton live births, induced abortions, and stillbirths, as well as current pregnancies of 20 or more weeks of gestation. For preterm delivery, all live births and current pregnancies of 37 or more weeks of gestational age were included in the denominator. For analysis of SGA births, all live births of known weight and gestational age were included, and for sex ratio, all live births of known sex.

Farm exposures

Using a checklist, we asked men directly about their farm activities over the past 5 years. For each reported activity, they were asked the months of the year in which it was done. We assumed that the applicable time period for their reported activities extended beyond the 5-year interval back to the time they first worked on the farm. We also assumed that the following activities did not involve direct pesticide exposure: milking cows, plowing, harrowing or discing, cultivating, planting, applying fertilizer or manure, harvesting, working with livestock, working in the family garden, working in dusty areas, heavy lifting, or filling, servicing, or unloading a silo. Incidental exposure may occur in several of these activities, e.g., milking cows, harvesting, or working in the family garden, if done in close temporal proximity to the time of spraying; however, the frequency of such exposure and absolute levels should be far less than that associated with mixing and applying the pesticides. Five activities were presumed to involve direct pesticide exposure: mixing or applying crop herbicides, crop insecticides and fungicides, livestock chemicals, yard herbicides, and building pesticides.

We classified the man's exposure based on his experiences in the time window of 3 months before conception to the time of conception, consistent with potential sperm-mediated effects. During that time window, specific to each pregnancy, we first determined whether he had engaged in any activities associated with direct pesticide exposure for 1 or more months. If he had, the pregnancy was classified as exposed, both to the specific type of exposure (e.g., "mix/apply livestock chemicals") as well as to the broader group, "chemical activity." If the pregnancy was not classified as having direct pesticide exposure, we determined whether any months in the time window involved farm activities that were not associated with direct chemical exposure (e.g., milking cows, cultivating crops). If so, we classified the pregnancy as "nonchemical activity" but did not consider which specific nonchemical activity had occurred. Finally, if the man had engaged in no activities at all during the time window of interest, then the pregnancy was classified as "no activity." For the purposes of analysis, we created a referent group consisting initially of those pregnancies with no activity; however, because of the small numbers of men who reported no activity and the similarity of pregnancy outcomes among those with no activity and those with no chemical activity, we combined these two groups to serve as the referent. We examined exposed groups defined by any chemical activity and defined by each of the five individual chemical activities listed above.

Two refinements to the activity-based exposure assessment were included. We elicited information on the use of protective equipment, but it was not specific to each of the chemical activities and indicated only a date of initial use. Nonetheless, the use of any protective equipment should convey a general tendency toward care in working with pesticides. We created a dichotomous indicator of protective equipment use based on whether the man reported regularly using any of the following in the year of conception or earlier: tractor with a cab; plastic, rubber, or vinyl gloves; face shield or goggles; plastic apron; respirator or mask with pesticide filters; pressurized helmets; charcoal filters; disposable coveralls; and plastic/rubber suit.

A second refinement incorporated information provided by the farm operator (who may or may not have been the male partner) regarding the application of specific pesticides on the farm in the time period of interest, as described in detail elsewhere (9). We analyzed subsets of men defined by the combination of chemical activity reported by the husband and use of specific chemicals reported to have occurred on the farm. The combination of engaging in a chemical exposure activity and reported use of an agent on the farm does not guarantee that this was the agent used in the specific activity, however, since there is no way to directly link a specific farm activity and chemical agent to determine exactly which pesticide was mixed or applied. Also, although the exposures are defined based on male activities on the farm, these exposures may reach their wives through general environmental contamination around the home and farm and through laundering pesticide-contaminated clothing.

Data analysis

We examined a number of potential determinants of pregnancy outcome as potential confounders. The initial list included mother's and father's age, education, jobs outside the farm (classified as potentially hazardous or nonhazardous), tobacco use, alcohol use, caffeine use, mother's language, ethnicity, religion, parity, per capita income, child's sex, interval between conception and the survey, and the month of conception.

Unadjusted risk ratios between the potential confounders and each of the four outcomes (miscarriage, preterm delivery, SGA, and sex ratio) were calculated, starting with finely stratified exposure variables. Based on the pattern of crude results, variables were eliminated and categories of variables were collapsed to retain only those variables and strata that yielded risk ratios of less than 0.8 or greater than 1.2. For each of the pregnancy outcomes, a logistic regression model was constructed that used the reduced set of variables and category levels. Additional variables were eliminated from the logistic regression models, and categories were collapsed or converted to continuous variables as appropriate. Footnotes to the tables indicate which of the potential confounders were included in the final models.

For each of the four outcomes, we generated risks and relative risks, contrasting exposed to unexposed groups. Men with no activity or no chemical activity served as the referent, with various subsets of men defined by activity, use of protective equipment, and farm chemical use constituting the exposed groups. Adjusted odds ratios were calculated using logistic regression models with all the predictors of each outcome described above along with the exposure of interest.

Because we included multiple pregnancies per woman, the variance estimates from the logistic regression are expected to be slightly underestimated on average. We conducted several logistic regression analyses based on generalized estimating equations, which account for the within-woman correlation across pregnancies (10). The influence on the width of the confidence intervals was quite modest for both the pesticide exposure indicators and potential confounders. All confidence intervals were within 20 percent of their original width, and 83 percent were within 10 percent. Surprisingly, approximately 40 percent of the confidence intervals were slightly narrower rather than wider, so that the overall impact of failure to account for correlations among pregnancies is minimal.

RESULTS

Starting with 7,379 farms selected from the Canadian Census of Agriculture, screening identified 2,693 eligible farms, with most of the attrition due to ineligibility based on absence of eligible couples based on age or marital status or disqualifying farm characteristics. Only a small proportion (7 percent) were lost due to refusal to provide the necessary information (table 1). In the screening telephone call, 2,946 couples were identified who met the criterion of living on or near the farm, among whom 1,898 (64 percent) provided forms for the farm operator, husband, and wife. Responding couples identified 5,853 pregnancies, of which 3,984 were included in the analysis. Among the 1,548 live births, 417 women contributed one only, 595 contributed two, 354 contributed three, 152 contributed four, and 30 contributed five.

Women who had live births were most often between the ages of 20 and 34, with at least 12 years of education (table 2). Smoking occurred in 17 percent of pregnancies resulting in live births. Income was modest, with the majority earning less than $10,000 per

TABLE 1. Response and eligible pregnancies, Ontario Farm Family Health Study, 1991-1992

	Farms		Couples		Pregnancies	
	No.	%	No.	%	No.	%
Selected from census	7,379	100				
Telephone screen						
No longer a farm	296	4				
Duplicate farm	13	0				
New farm operator	197	3				
Unable to contact	533	7				
Refusal	491	7				
Ineligible	3,156	43				
Eligible	2,693	36	2,946	100		
Study interview						
Eligible			2,946	100		
Unable to contact			23	1		
Determined ineligible			98	3		
Refusal			545	18		
Missing one or two forms			382	13		
Completed all three forms			1,898	64	5,853	100
Total pregnancies					5,853	100
Pregnancy not on farm					1,759	30
Pregnancy >1 year before marriage					27	0
Multiple gestation					42	1
Ectopic, hydatidiform mole, other					41	1
Pregnancy included in analysis					3,984	68

person in the household. Parity for eligible pregnancies was relatively high, with 40 percent of live births three or more. The recall interval was mostly in the range of 5–15 years. Women who had miscarriages were more often older than 35 years, were more highly educated, tended to have higher income and parity, and had shorter recall intervals. SGA births were associated with less education, smoking during pregnancy, and lower parity. Preterm delivery was weakly related to mother's smoking but otherwise was similar to total live births.

Miscarriage risk was not associated overall with participation in farm activities involving chemicals, with adjusted odds ratios of 1.0 or 1.1 for all types of chemical applications (table 3). Failure to use protective equipment among those who engaged in chemical activities was associated with slightly elevated odds ratios (1.2–1.4) for crop herbicides, yard herbicides, and building pesticides.

The combination of engaging in pesticide activities and reported use of specific chemicals on the farm produced a number of more substantially elevated adjusted odds ratios for miscarriage. (Note that the alignment reflects which agents are subsets of other categories, e.g., triazines are a subset of herbicides, atrazine is a subset of triazines.) Odds ratios (ORs) greater than 1.5 were found for crop herbicide application combined with use of thiocarbamates (OR = 1.9, 95 percent confidence interval (CI) 1.1–3.3) and carbaryl (OR = 1.9, 95 percent CI 1.1–3.1), with atrazine, glyphosate, and other (unclassified) pesticides yielding adjusted odds ratios of 1.5. There was some overlap among pregnancies in which there was male exposure to thiocarbamates and carbaryl, with 126 exposed to thiocarbamates, 156 exposed to carbaryl, and 67 exposed to both.

Application of crop insecticides and fungicides combined with reported use of carbaryl yielded an odds ratio of 2.1 (95 percent CI 1.1–4.1) and combined with reported use of insecticides, a broader category that includes all those exposed to carbaryl, produced an odds ratio of 1.6 (95 percent CI 1.1–2.4). Yard herbicide activity combined with thiocarbamates was more strongly associated with miscarriage (OR = 1.9, 95 percent CI 0.9–3.9) as well as yard herbicides plus other pesticides (OR = 2.0, 95 percent CI 0.8–5.2), with virtually no overlap among the pregnancies assigned exposure to thiocarbamates and other pesticides. None of the combinations with livestock chemicals yielded elevated risks, and only building pesticides combined with other pesticides generated an increased odds ratio of 1.8 (95 percent CI 0.6–5.1). Focusing on specific agents across chemical activities provides some replicated evidence implicating thiocarbamates, carbaryl, and other pesticides.

Analysis of preterm delivery yielded adjusted odds ratios of 1.2 or less for chemical activities in the aggregate, as well as for crop herbicides, crop insec-

TABLE 2. Characteristics of pregnancies, Ontario Farm Family Health Study, 1991-1992

	Live births		Preterm births		SGA* births		Miscarriages	
	No.	%	No.	%	No.	%	No.	%
Total	3,427	100	128	100	276	100	395	100
Mother's age (years)								
<20	96	3	4	3	9	3	5	1
20–34	3,236	94	120	94	262	95	360	91
≥35	95	3	4	3	5	2	30	8
Mother's education (years)								
<8	137	4	7	5	16	6	18	5
8–11	342	10	16	13	29	11	34	9
12	1,281	37	44	34	116	42	128	32
≥13	1,664	49	60	47	115	42	212	54
Mother's smoking during pregnancy (cigarettes/day)								
None	2,711	79	93	73	182	66	299	76
>0–<10	134	4	8	6	20	7	21	5
10–<20	239	7	10	8	31	11	26	7
≥20	211	6	11	9	33	12	32	8
Per capita income (dollars/year)								
<5,000	731	21	26	20	63	23	79	20
5,000–<10,000	1,181	34	36	28	83	30	120	30
10,000–<15,000	424	12	15	12	28	10	50	13
≥15,000	576	17	26	20	61	22	94	24
Parity								
1	966	28	38	30	117	42	91	23
2	1,078	31	35	27	83	30	116	29
≥3	1,383	40	55	43	76	28	188	48
Interval from conception to survey (years)								
<2	281	8	11	9	25	9	59	15
2–<5	682	20	28	22	34	12	80	20
5–<10	1,096	32	38	30	79	29	115	29
10–<15	804	23	25	20	66	24	84	21
≥15	525	15	22	17	71	26	49	12

* SGA, small for gestational age.

ticides, and fungicides (table 4). However, livestock chemicals and building pesticides were associated with slightly more elevated risks (ORs = 1.6) and yard herbicides, especially, indicated a stronger association (OR = 2.1, 95 percent CI 1.0–4.4). Failure to use protective equipment not only did not confer increased risks but was actually associated with a lower risk in most instances, most notably for yard herbicides (ORs = 2.5 and 1.1 for those who used and did not use protective equipment, respectively).

Analysis of specific chemicals combined with farm activities in relation to preterm delivery generated a number of markedly elevated odds ratios, most of which are imprecise. Crop herbicide activity combined with atrazine or glyphosate yielded odds ratios of 2.4 based on 10 and five exposed cases, respectively, and minimal overlap of the two exposures. Livestock chemical activity plus use of organophosphates on the farm was associated with preterm delivery (OR = 2.7, 95 percent CI 0.7–11.0). All categories of chemicals combined with yard herbicide activity yielded adjusted odds ratios of 2.3 or greater, most notably for atrazine (OR = 4.9, 95 percent CI 1.6–14.5) and 4-[2,4-dichlorophenoxy] butyric acid (2,4-DB) (OR = 3.5, 95 percent CI 1.2–9.9). Among the 136 pregnancies assigned atrazine exposure and 45 assigned 2,4-DB exposure, 21 pregnancies were assigned exposure to both. Building pesticide activity combined with insecticide use on the farm was also associated with nearly a twofold increased risk of preterm delivery (OR = 1.9, 95 percent CI 0.6–5.7).

Risk of SGA deliveries was not increased in relation to chemical activities, individually or in the aggregate (table 5), with a tendency toward slightly reduced risks associated with use of livestock chemicals and building pesticides. Use of protective equipment did not affect estimated relative risks. A combination of chemical activities with reported use of specific types

TABLE 3. Male farm activities and miscarriage, Ontario Farm Family Health Study, 1991–1992

Activity	Miscarriage cases	Risk (per 100)	Unadjusted risk ratio	Adjusted odds ratio*	95% CI†
None/nonchemical	102	9.5			
Any chemical	244	10.4	1.1	1.1	0.8–1.3
Crop herbicides	133	10.4	1.1	1.0	0.7–1.4
Used protective equipment	85	9.5	1.0	1.0	0.7–1.3
No protective equipment	28	13.8	1.5	1.4	0.9–2.4
Chemicals on farm‡					
Herbicides	86	13.1	1.4	1.4	1.0–2.0
Triazines	42	12.8	1.4	1.4	0.9–2.2
Atrazine	28	12.5	1.3	1.5	0.9–2.4
Phenoxy herbicides	50	12.4	1.3	1.3	0.9–1.9
2,4-DB	7	9.0	0.9	0.7	0.3–1.8
2,4-D	27	12.0	1.3	1.3	0.8–2.1
MCPA†	21	10.4	1.1	1.1	0.6–1.8
Thiocarbamates§	18	14.8	1.6	1.9	1.1–3.3
Dicamba	16	12.2	1.3	1.1	0.6–2.1
Carbaryl	23	15.2	1.6	1.9	1.1–3.1
Glyphosates	17	13.7	1.5	1.5	0.8–2.7
Other pesticides	8	18.2	1.9	1.5	0.5–4.0
Crop insecticides or fungicides	82	10.9	1.1	1.1	0.8–1.6
Used protective equipment	62	10.5	1.1	1.2	0.8–1.7
No protective equipment	9	10.7	1.1	1.0	0.4–2.3
Chemicals on farm					
Insecticides	45	14.2	1.5	1.6	1.1–2.4
Organophosphates	18	11.0	1.2	1.3	0.7–2.3
Carbaryl	13	17.6	1.9	2.1	1.1–4.1
Fungicides	24	11.4	1.2	1.2	0.7–2.1
Other pesticides	11	12.1	1.3	1.4	0.7–2.8
Livestock chemicals	112	10.4	1.1	1.1	0.8–1.5
Used protective equipment	54	10.5	1.1	1.0	0.7–1.5
No protective equipment	22	9.5	1.0	1.0	0.6–1.7
Chemicals on farm					
Insecticides	27	12.0	1.3	1.2	0.7–2.0
Organophosphates	7	11.1	1.2	0.9	0.3–2.4
Other pesticides	7	11.3	1.2	1.0	0.4–2.6

Table 3 continues

of chemicals on the farm generally yielded odds ratios slightly less than 1.0, with crop herbicide activity combined with atrazine, cyanazine, and dicamba generating odds ratios of 0.5 or 0.6. The only odds ratio greater than 1.5 was found for livestock chemical activity plus reported use of other pesticides on the farm (OR = 1.7, 95 percent CI 0.6–4.7).

Sex ratio was generally not associated with farm chemical activities (table 6). In fact, each of the types of farm activities was associated with odds ratios of 1.0, but there was a consistent observation of reduced sex ratio (OR = 0.8) for men who did not report using protective equipment. Analysis of specific chemicals (not shown) did not yield any odds ratios notably different from the null.

DISCUSSION

Our results provide some indication that male farm activities may influence risk of preterm delivery, particularly when occurring in combination with reported applications of specific chemicals on the farm. The pattern for miscarriage also suggested some potential effect of male activities combined with reported chemical use, although to a lesser extent than for preterm delivery. We found virtually no evidence of associations with SGA births or altered sex ratio in the offspring.

For miscarriage, there is clear experimental evidence of a paternal effect (5), and the epidemiologic literature offers at least some replicated indications of an environmental contribution, most strongly for mercury and anesthetic gases (11). Preterm delivery has not been assessed as a consequence of male exposures in experimental studies, and very limited epidemiologic research has been generated on this issue (12). Maternal characteristics, particularly reproductive and medical, are most strongly associated with preterm delivery (13).

TABLE 3. Continued

Activity	Miscarriage cases	Risk (per 100)	Unadjusted risk ratio	Adjusted odds ratio*	95% CI†
Yard herbicides	82	10.8	1.1	1.0	0.7–1.5
Used protective equipment	45	9.9	1.0	1.0	0.7–1.5
No protective equipment	19	12.3	1.3	1.2	0.6–2.1
Chemicals on farm					
Herbicides	50	12.3	1.3	1.3	0.8–1.9
Triazines	26	13.3	1.4	1.4	0.8–2.3
Atrazine	14	10.9	1.2	1.2	0.6–2.3
Phenoxy herbicides	28	11.3	1.2	1.2	0.7–1.9
2,4-DB	19	11.6	1.2	1.2	0.7–2.1
MCPA	9	9.4	1.0	0.9	0.4–2.0
Thiocarbamates§	12	15.8	1.7	1.9	0.9–3.9
Dicamba	13	13.2	1.4	1.2	0.6–2.4
Carbaryl	11	11.3	1.2	1.3	0.6–2.5
Glyphosates	13	13.4	1.4	1.4	0.7–2.8
Other pesticides	7	19.4	2.1	2.0	0.8–5.2
Building pesticides					
Used protective equipment	66	10.9	1.2	1.1	0.8–1.6
No protective equipment	31	10.2	1.1	1.0	0.6–1.6
Chemicals on farm	17	12.5	1.3	1.3	0.7–2.4
Insecticides	22	12.6	1.3	1.4	0.8–2.4
Organophosphates	7	13.0	1.4	1.3	0.5–3.1
Other pesticides	8	21.6	2.3	1.8	0.6–5.1

*Adjusted for mother's age (continuous), parity (continuous), mother's education (≥9, <9 years), father's education (high school or less, post-high school), per capita income (≥$15,000/year, <$15,000/year), mother's off-farm job (none, nonhazardous, hazardous), father's off-farm job (none, nonhazardous, hazardous), mother's smoking during pregnancy (no, yes), mother's alcohol use during pregnancy (no, yes), and conception to interview interval (<5, ≥5 years).

† CI, confidence interval; MCPA, 2-methyl-4-chlorophenoxyacetic acid.

‡ Chemicals reported on farm; only those with five or more exposed cases are included.

§ Thiocarbamate applications are approximately 70% as fungicides, 30% as herbicides.

Combining male farm activities and reported use of specific chemicals on the farm, as reported by the farm operator, provided some suggestion regarding which pesticide classes and individual pesticides might be harmful. For miscarriage, thiocarbamates, carbaryl, and the nonspecific category "other pesticides" were most strongly implicated, whereas for preterm delivery, triazines (particularly atrazine) and 2,4-DB were most suggestively associated with increased risk.

A number of epidemiologic studies (14–17) have reported mixed results concerning the relation to miscarriage of male exposure to Agent Orange in the Vietnam War. The agent of interest is dioxin, which is also a contaminant of 2,4,5-trichlorophenoxyacetic acid; however, studies of sprayers (18, 19) and factory workers (20) have not found increased risk of miscarriage associated with paternal exposure. Dioxin is not likely to be present to any significant extent in the pesticides we considered.

Several studies have addressed dibromochloropropane, a proven cause of male infertility, with one report (21) suggesting a threefold increased risk of miscarriage in the offspring and another (22), which has not been replicated (23), indicating a decrease in the proportion of male offspring. Dibromochloropropane exerts its effects through direct testicular toxicity, which is not known to occur from other more commonly used pesticides. A study of workers in the floriculture industry of Colombia (24) is of limited value due to severe nonresponse and the use of agents different from those used in Canadian farming.

More analogous to our results are studies of father's occupation and pregnancy outcome in Quebec (25), Scotland (26), and the United States (27). However, these surveys of diverse occupations provided very little information on agricultural workers and no information on specific pesticides. Within that constraint, McDonald et al. (25) found no association between male work in the agriculture/horticulture sector and risk of spontaneous abortion. Male employment in agriculture was not associated with risk of preterm delivery or SGA births in the United States or Scotland (26, 27). However, using data from the same national survey in the United States, father's self-reported exposure to pesticides was associated with a small increased risk of SGA births but not preterm

TABLE 4. Male farm activities and preterm delivery, Ontario Farm Family Health Study, 1991–1992

Activity	Preterm cases	Risk (per 100)	Unadjusted risk ratio	Adjusted odds ratio*	95% CI†
None/nonchemical	31	3.2			
Any chemical	80	3.9	1.2	1.2	0.7–1.9
Crop herbicides	44	4.0	1.2	1.2	0.6–2.3
Used protective equipment	32	4.1	1.3	1.4	0.7–2.7
No protective equipment	6	3.5	1.1	1.1	0.3–3.7
Chemicals on farm‡					
Herbicides	23	4.3	1.3	1.4	0.6–2.0
Triazines	11	4.1	1.3	1.5	0.6–3.8
Atrazine	10	5.4	1.7	2.4	0.8–7.0
Phenoxy herbicides	13	3.9	1.2	1.4	0.5–3.6
2,4-DB	8	4.3	1.3	1.7	0.6–4.8
Glyphosates	5	5.1	1.6	2.4	0.8–7.9
Crop insecticides or fungicides	19	3.0	0.9	1.1	0.6–2.4
Used protective equipment	17	3.4	1.0	1.4	0.7–2.9
No protective equipment	1				
Chemicals on farm					
Insecticides	9	3.5	1.1	1.3	0.5–3.5
Organophosphates	6	4.4	1.4	1.7	0.5–5.2
Triazines	5	3.9	1.2	2.4	0.6–8.5
Livestock chemicals	43	4.6	1.4	1.4	0.8–2.5
Used protective equipment	22	5.0	1.5	1.6	0.8–3.1
No protective equipment	7	3.5	1.1	1.2	0.5–3.2
Chemicals on farm					
Insecticides	9	4.9	1.5	1.4	0.5–3.8
Organophosphates	5	10.0	3.1	2.7	0.7–11
Yard herbicides	30	4.6	1.4	2.1	1.0–4.4
Used protective equipment	20	5.1	1.6	2.5	1.1–5.8
No protective equipment	5	3.8	1.2	1.1	0.3–4.5
Chemicals on farm‡					
Herbicides	18	5.4	1.7	2.3	0.9–5.8
Triazines	10	6.2	1.9	3.2	1.2–8.9
Atrazine	9	8.3	2.6	4.9	1.6–15
Phenoxy herbicides	11	5.3	1.6	2.5	0.9–7.3
2,4-DB	10	7.2	2.2	3.5	1.2–9.9
Building pesticides	27	5.2	1.6	1.6	0.8–3.2
Used protective equipment	14	5.4	1.7	2.0	0.9–4.6
No protective equipment	7	6.1	1.9	1.5	0.5–4.9
Chemicals on farm					
Insecticides	6	4.2	1.3	1.9	0.6–5.7

*Adjusted for mother's age (20–34, <20, ≥35 years), mother's education (high school or more, <high school), father's education (≥9, <9 years), per capita income (≥$15,000/year, <$15,000/year), mother's off-farm job (none, nonhazardous, hazardous), mother's ethnicity (European, non-European), mother's smoking during pregnancy (no, yes), mother's caffeine use during pregnancy (no, yes), primary language (English, French), and month of conception (December through May, June through August, September through November).

† CI, confidence interval.

‡ Chemicals reported on farm; only those with five or more exposed cases are included.

deliveries (28). Most relevant to the present report, men who reported exposure to pesticides in their job had an adjusted odds ratio of 1.1 for preterm delivery (95 percent CI 0.7–1.8) and 1.4 for SGA births (95 percent CI 0.9–2.3) (28).

Evidence linking paternal pesticide use and pregnancy outcome also comes from a study of cotton field workers in India (29), thought to be exposed to a range of chlorinated pesticides such as dichlorodiphenyltrichloroethane (DDT), organophosphates such as malathion, and other agents. More than 1,000 exposed and an equal number of unexposed men were considered, with a calculated relative risk of 1.7 (95 percent CI 1.6–1.9) contrasting miscarriage risk among exposed versus unexposed men. Methodological details were missing, however; and the data on exposure, outcome, and potential confounders are of limited or uncertain quality.

TABLE 5. Male farm activities and SGA* births, Ontario Farm Family Health Study, 1991–1992

Activity	SGA cases	Risk (per 100)	Unadjusted risk ratio	Adjusted odds ratio*	95% CI*
None/nonchemical	69	7.3			
Any chemical	164	8.1	1.1	1.0	0.6–1.3
Crop herbicides	91	8.3	1.1	1.1	0.7–1.5
Protective equipment used	65	8.4	1.2	1.1	0.7–1.6
No protective equipment	14	8.3	1.1	1.0	0.5–2.1
Chemicals on farm‡					
Herbicides	33	6.1	0.8	0.6	0.5–1.3
Triazines	16	6.0	0.8	0.8	0.4–1.5
Atrazine	8	4.3	0.6	0.5	0.2–1.3
Cyanazine	5	10.4	1.4	0.6	0.2–2.0
Phenoxy herbicides	19	5.7	0.8	0.7	0.4–1.2
2,4-DB	12	6.4	0.9	0.7	0.3–1.4
MCPA*	11	6.4	0.9	1.0	0.5–2.0
Thiocarbamates§	7	7.2	1.0	1.0	0.4–2.8
Dicamba	5	4.8	0.7	0.6	0.2–1.7
Carbaryl	6	4.9	0.7	0.7	0.3–1.8
Glyphosates	5	5.2	0.7	0.8	0.2–2.3
Crop insecticides or fungicides	46	7.2	1.0	0.9	0.5–1.3
Protective equipment used	37	7.3	1.0	0.9	0.5–1.4
No protective equipment	5	7.1	1.0	0.8	0.3–2.3
Chemicals on farm					
Insecticides	14	5.4	0.7	0.9	0.5–1.7
Organophosphates	7	5.2	0.7	0.8	0.3–2.0
Fungicides	10	5.6	0.8	0.9	0.4–1.9
Thiocarbamates	5	6.5	0.9	0.8	0.2–2.8
Livestock chemicals	69	7.4	1.0	0.9	0.6–1.3
Protective equipment used	33	7.5	1.0	0.8	0.5–1.4
No protective equipment	12	6.0	0.8	0.7	0.4–1.5
Chemicals on farm					
Insecticides	9	4.9	0.7	0.8	0.4–1.8
Other pesticides	6	11.1	1.5	1.7	0.6–4.7
Yard herbicides	54	8.3	1.1	1.0	0.6–1.5
Protective equipment used	27	6.9	1.0	0.8	0.5–1.4
No protective equipment	18	14.0	1.9	1.8	0.9–3.4
Chemicals on farm					
Herbicides	21	6.3	0.9	0.8	0.4–1.4
Triazines	9	5.6	0.8	0.7	0.3–1.5
Atrazine	5	4.7	0.6	0.5	0.2–1.5
Phenoxy herbicides	14	6.7	0.9	0.8	0.4–1.6
2,4-DB	10	7.2	1.0	0.8	0.4–1.8
MCPA	8	9.5	1.3	1.6	0.7–3.6
Building pesticides	38	7.4	1.0	0.8	0.5–1.3
Protective equipment used	18	6.9	1.0	0.7	0.4–1.3
No protective equipment	9	7.9	1.1	1.0	0.4–2.3
Chemicals on farm					
Insecticides	7	4.9	0.7	0.8	0.3–1.8

* SGA, small for gestational age; CI, confidence interval; MCPA, 2-methyl-4-chlorophenoxyacetic acid.

† Adjusted for mother's age (continuous), father's age (<30, ≥30 years), parity (1, ≥2), father's education (<high school, ≥high school), per capita income (≥$15,000/year, <$15,000/year), father's off-farm job (none, hazardous, nonhazardous), mother's smoking during pregnancy (no, yes), father's cigarette smoking during pregnancy (<20/day, ≥20/day), mother's alcohol use during pregnancy (no, yes), father's alcohol use during pregnancy, ≤3 oz/day, >3 oz/day), child's sex (male, female), conception to interview interval (<5, 5–<15, ≥15 years), primary language (English, French), and month of conception (December through August, September through November).

‡ Chemicals reported on farm; only those with five or more exposed cases are included.

§ Thiocarbamate applications are approximately 70% as fungicides, 30% as herbicides.

TABLE 6. Male farm activities and proportion of male births, Ontario Farm Family Health Study, 1991–1992

Activity	Male births	Risk (per 100)	Unadjusted risk ratio	Adjusted odds ratio*	95% CI†
None/nonchemical	479	50.3			
Any chemical	1,021	50.3	1.0	1.0	0.8–1.1
Crop herbicides	550	50.0	1.0	1.0	0.8–1.2
Protective equipment used	394	51.0	1.0	1.0	0.8–1.2
No protective equipment	76	45.0	0.9	0.8	0.6–1.1
Crop insecticides or fungicides	325	50.9	1.0	1.0	0.8–1.2
Protective equipment used	258	51.2	1.0	1.0	0.8–1.3
No protective equipment	32	45.7	0.9	0.8	0.5–1.4
Livestock chemicals	462	49.8	1.0	1.0	0.8–1.2
Protective equipment used	224	50.7	1.0	1.0	0.8–1.3
No protective equipment	92	46.0	0.9	0.8	0.6–1.1
Yard herbicides	331	51.0	1.0	1.0	0.8–1.2
Protective equipment used	204	52.3	1.0	1.1	0.8–1.3
No protective equipment	58	45.0	0.9	0.8	0.6–1.2
Building pesticides	254	49.2	1.0	1.0	0.8–1.2
Protective equipment used	127	48.8	1.0	0.9	0.7–1.2
No protective equipment	53	46.5	0.9	0.8	0.6–1.3

* Adjusted for mother's age (≥20, <20 years), father's age (≥20, <20 years), and father's off-farm job (none or nonhazardous, hazardous).

† CI, confidence interval.

The greatest strength of the present study relative to previous efforts is the detailed exposure assessment, integrating self-reported farm activities, use of protective equipment, and farm operator-reported use of chemicals. Compared with previous research, the breadth and depth of our evaluation of exposure are notable. Nonetheless, exposure assessment remains the most important limitation. Although a chemical activity was reported by the father and a specific agent or class of agents was thought to be in use on the farm at that time, there is no guarantee that the chemical activity involved the use of that agent. In addition, there was some overlap among exposures that we were not able to adjust for, leaving uncertainty regarding which, if any, chemicals account for observed associations.

We were not able to quantify the amount of time spent mixing and applying pesticides or to examine the work practices and exposure circumstances in detail. The group designated as "unexposed" still lived on the farm and may have engaged in farm activities that involved some level beyond background exposure. The assignment of exposure is probabilistic, with men who engaged in specific activities more likely to be truly exposed than men who did not; however, more quantitative inferences regarding dose are not attainable. In fact, we cannot be certain that any associations reported are not actually due to maternal exposure in the course of general environmental contamination through pesticide use or through household contamination from clothing worn by the man and brought into the home.

The information on pregnancy outcomes has the advantage of having been maternally reported, which is likely to be superior to paternally reported information. Detailed information on gestational age, part of the definition of preterm delivery and SGA births, is of uncertain quality from this source, although errors are not likely to differ in relation to exposure status. Miscarriage reporting should be reasonably complete as well, and even if suspected to be related to pesticide exposure, the algorithm for assigning exposure that links dates of reported farm activities of men and reported chemical use by farm operators makes correlation between errors in reporting pregnancy outcome and chemical exposures unlikely. Assuming that the errors are not correlated, we would generally expect bias toward the null, if bias is present (30).

Imprecision is a limitation, even in this large survey. Pregnancy itself is a relatively rare event, and adverse outcomes are rarer still, so that the linkage with chemical activities, particularly those involving individual agents, leads to imprecise risk estimates. There is a trade-off between the larger numbers and more precise estimates for broad categories like "application of crop herbicides" and the smaller numbers for more refined, biologically specific categories like "application of crop herbicides on farms where atrazine was reported to have been used."

Finally, the lengthy recall interval may have reduced the quality of information on both exposure and health outcome. Most pregnancies of interest occurred more than 5 years before questionnaire completion, and many occurred 10–15 years before. Miscarriage reporting has been found to deteriorate after approximately 10 years (31), and it might be that the inferences about farm activities and reports of chemical use might do the same. The limited numbers of events precluded conducting analyses restricted to recent pregnancies.

The overall implication of these results is to add to the interest in a possible role of male pesticide exposure in adverse pregnancy outcome and to direct attention to both preterm delivery and miscarriage. We may have gone as far as possible in a survey of this type, which obtains information on exposure and outcome in a large, diverse population of farm families. Replication of these findings in other geographic settings in a study of similar quality would be of value; however, to improve on our strategy, the availability of some unusually detailed source of historical exposure data would be necessary. Alternatively, other research strategies may be applicable. Detailed consideration of male pesticide exposure in relation to sperm function and genetic alterations would help to bridge experimental studies (with their refined measures of exposure and outcome) and epidemiologic studies (with the species and exposure as conditions of interest). Extrapolating from biologically defined endpoints to the clinical outcomes of ultimate concern would remain a challenge, but such research would complement the strengths and limitations in the methods of the present study.

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