Published in final edited form as:

J Agromedicine. 2010 April ; 15(2): 127–136. doi:10.1080/10599241003622699.

Maternal Pesticide Use and Birth Weight in the Agricultural Health Study

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Abstract

Objective—Studies examining the association between maternal pesticide exposure and low birth weight yield conflicting results. We examined the association between maternal pesticide use and birth weight among women in the Agricultural Health Study, a large study of pesticide applicators and their spouses in Iowa and North Carolina.

Methods—We evaluated self-reported pesticide use of 27 individual pesticides in relation to birth weight among 2246 farm women whose most recent singleton birth occurred within 5 years of enrollment (1993–97). We used linear regression models adjusted for site, preterm birth, medical parity, maternal body mass index, height, and smoking.

Results—Mean infant birth weight was 3586 g (± 546 g), and 3% of the infants were low birth weight (< 2500 g). First-trimester pesticide-related tasks were not associated with birth weight. Ever use of the pesticide carbaryl was associated with decreased birth weight (-82 g, 95% CI = -132 , -31).

Conclusions—This study provides limited evidence about pesticide use as a modulator of birth weight. Overall, we observed no associations between birth weight and pesticide-related activities during early pregnancy; however, we have no data on temporal specificity of individual pesticide exposures prior to or during pregnancy and therefore cannot draw conclusions related to these exposure windows. Given the widespread exposure to pesticide products, additional evaluation of maternal pregnancy exposures at specific time windows and subsequent birth outcomes is warranted.

INTRODUCTION

Over 700 million pounds of pesticides are used annually in agriculture in the US ¹, and several studies document increased exposures for farmers, farm workers, and families living in agricultural regions compared with non-farming populations ^{2–5}. The Agricultural Health

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Human Subjects Approval: The Agricultural Health Study (AHS) complies with all applicable requirements of the USA including institutional review boards of the National Institutes of Health and its contractors and the University of Washington.

All authors have no competing financial interests to disclose.

Study (AHS) is a study of pesticide applicators and their spouses – a population at high risk for pesticide exposure. Results of studies examining the association between maternal occupational and environmental pesticide exposure and birth weight have yielded inconsistent findings, potentially due to different characterization of exposure, different biomarkers of exposure, and the time window during pregnancy that was investigated ^{6–9}.

Organophosphate pesticide exposures during pregnancy have been associated with decreased birth weight in Dominican and African American populations in an urban US area ¹⁰, but not in a farmworker population in central California ⁶. Similarly, studies examining maternal herbicide exposure yield conflicting results regarding potential effects on fetal growth ^{11,12}. In an ecological study, communities with drinking water contaminated by the herbicides atrazine, metolachlor, and cyanazine had significantly increased risk of giving birth to babies who were small-for-gestation compared with adjacent communities without water contamination ¹¹. However, Villanueva et al. reported no association between atrazine in drinking water and low birth weight or small-for-gestation births in a district in France ¹². Organochlorine pesticides were used extensively in the past and, for the most part, have been removed from the market in the US, although their persistence in the environment and biological tissues is well-described. Organochlorine exposure has been associated with both inverse associations and lack of association with birth weight ^{13–15}.

Very few animal studies have examined the impact of pre-conception pesticide exposure on reproduction and birth weight, but it is possible that these exposures may play a role in fetal growth and development. In a study of endosulfan, early life pre-conception exposures, short-term exposures at environmentally relevant concentrations lead to long term effects on growth and reproduction in medaka fish ¹⁶. In addition, Fei et al. reported lower birthweight in relation to perfluorinated compounds measured in blood at 4–14 weeks gestation ¹⁷. Given that these compounds have long biological half-lives, it is likely that these exposures preceded conception and may have a long term impact on in-utero development. To further address the issue of pesticide use and birth weight, we used data from the Agricultural Health Study to examine the association between participation in prenatal pesticide-related tasks and mother's specific pesticide use history with birth weight.

METHODS

Study Population

The AHS is a large study of private pesticide applicators (primarily farmers), their spouses, and commercial pesticide applicators in Iowa and North Carolina. Applicators were enrolled between 1993 and 1997, when they received their pesticide license training ¹⁸. Spouses enrolled by completing a questionnaire brought home by the applicator. The spouse questionnaire asked about demographic and lifestyle characteristics as well as use of specific pesticides. A separate female and family health questionnaire (FFH) was completed and included questions about health conditions and pregnancy history. Female spouses completed the spouse and FFH questionnaire within one month of their husband's enrollment. In the FFH, specific information was collected for the most recent pregnancy, including pesticide-related activities during the first three months of pregnancy, pregnancy complications, and pregnancy outcome.

A total of 32,172 female spouses enrolled in the study, representing 75% of the married pesticide applicators. Of those who enrolled, 81% returned the spouse questionnaire in the mail, while 19% completed this questionnaire over the phone. Of the enrolled female spouses, 61% (19,623) completed the FFH survey. Within the survey, women reported up to 6 pregnancies including their most recent pregnancy with 17,948 reporting at least one pregnancy. In addition, women reported information, including birth weight, on up to 4 live born children, including the most recent live born child. Thus, our sample began with 9,202

women whose most recent pregnancy ended as a live birth and was between 1975 and date of enrollment. This population was further restricted to births occurring within five years of enrollment (N = 2598). Given that the spouse questionnaire did not provide specific time periods associated with individual pesticide use, we restricted to births that occurred within five years of enrollment to increase the probability that exposure to specific pesticides had occurred before the birth. We further dropped all pregnancies that resulted in a multiple birth (N=58) or where the multiple status was unknown (N=12) leaving 2528 pregnancies that resulted in a single live born child. We additionally excluded births from women who were missing birth weight or length of gestation (N=161). After these exclusions, 2367 births remained for analysis. We further limited to the sample to 2246 births with complete information on all base model covariates.

Exposure classification

Pesticide exposure related task information for the first three months of the most recent pregnancy was classified into four ordered exposure categories, previously defined by Saldana et. al., based on combining activities with similar potential for pesticide exposure¹⁹. The four categories, ranging from the lowest to the highest exposure potential were: 1. No exposure - women who responded negatively to all exposure questions, 2. Indirect exposure (planting, pruning, weeding, picking or harvesting), 3. Residential exposure (applying pesticides to garden or inside the house). and 4. Agricultural exposure (mixing, or applying pesticides to crops or repairing pesticide application equipment). Women who reported activities pertaining to more than one category were classified according to the category with the highest potential for exposure. We did not have data on specific pesticides used during the most recent pregnancy and therefore could not further characterize exposure during the first trimester of pregnancy.

We also examined data on the women's ever use of pesticides. The information was based on the following question, "Have you ever personally mixed or applied this (pesticide)?" which was asked for 50 individual pesticides. This question was not specific to any particular time period during the woman's life. We limited our analysis to those exposures for which at least 20 women reported being exposed, which resulted in 27 individual pesticides for analysis.

Outcome definition

Women were asked to report the birth weight in pounds and ounces for each most recent birth. We converted this to grams and used birth weight as a continuous dependent variable in this analysis.

Statistical analysis

We used linear regression to estimate the change in birth weight related to reported pesticide use. Women were asked about pregnancy duration as two categories: 20–36 weeks and 37 or more weeks. Preterm birth was defined as less than 37 weeks of gestation and was included in the model, as it is an important predictor of birth weight. All presented models additionally included mother's body mass index (BMI, kg/m²) (modeled as BMI and BMI squared) and height, parity (number of births the woman had, including stillbirths), preterm status (<37 weeks, 37 weeks or more), state (Iowa or North Carolina), and maternal smoking during pregnancy (ever smoked anytime during pregnancy). We used BMI at enrollment in lieu of pre-pregnancy BMI, because the latter was not available. Mother's age at most recent pregnancy and infant sex were not significantly predictive of birth weight in the final models and were thus omitted, as was mother's education. Maternal age, maternal education, and infant sex did not change either the point estimates or the standard errors in our models. All statistical analyses were performed using STATA, version 9.0²⁰. This analysis used the PIREL0506 release of the AHS Phase I dataset. The AHS study complies with all applicable requirements of the USA including institutional review boards of the National Institutes of Health and its

contractors and the University of Washington. All questionnaires are available at <http://aghealth.nci.gov.nih.gov/questionnaires.html>.²¹

RESULTS

The majority (79%) of the 2246 live births within five years of enrollment occurred among mothers from Iowa. Sixty-six percent of the women were educated beyond high school. Almost all mothers were white (98%), and few reported smoking during pregnancy (7%). The proportions of preterm birth (<37 weeks gestation) and low birth weight (<2500 g) were 7% and 3%, respectively (Table 1). Figure 1 shows the distribution of birth weight among all infants, with a mean birth weight of 3586 g and median of 3608 g. Table 2 shows birth weight in relation to several of the predictors examined in this study. Infants born in North Carolina, preterm, females, infants of mothers with low BMI, and infants of smokers had lower birth weight compared with their counterparts.

We did not see any association between any pesticide-related activity during pregnancy and birth weight or preterm birth, although there was a slight, non-significant decrease in birth weight in relation to agricultural exposure during pregnancy (−72 g change, 95% Confidence Interval (CI) = −222, 79), however only 2% of women reported this level of exposure during pregnancy (Table 3). Among the 27 individual pesticides that we evaluated, only carbaryl appeared to be significantly associated with a reduction in birth weight (−82 grams, 95% Confidence Interval (CI) = −132, −31) (Table 4). Preterm delivery, a strong predictor of birth weight, was included in the linear models to increase the precision of the estimates. In models that did not include preterm birth, more pesticides yielded estimates with confidence intervals that did not include 0. However, none of the examined pesticides was associated with preterm birth (data not shown).

DISCUSSION

In this well-educated population of women living on farms, we found that out of 27 individual pesticides examined, only a history of carbaryl use, a cholinesterase-inhibiting insecticide, was associated with lower birth weight. Previous studies on carbamates or carbaryl in particular are limited. Among pregnant women in NY, residential prenatal exposures to the carbamate pesticide, proxopur, was not associated with changes in birth weight⁸. One animal study examining pre-conception and post-conception carbaryl and malathion exposures in rats and mice found a significant decrease in birth weight in relation to high dose exposures²².

Birth weight was slightly lower among women who reported agricultural exposures during pregnancy in our analysis, but the exposed group was small and the exposure measure was not pesticide-specific. While limited information exists on carbamates, more data are available on organophosphate insecticide exposures during pregnancy. In a cohort of inner city women, Whyatt et al. found that chlorpyrifos concentrations in cord blood were inversely related to birth weight⁸. In another cohort of New York women whose homes were sprayed with insecticides, organophosphate exposure during pregnancy (as measured by urine metabolites) was associated with decreased head circumference only among women with slow activity of paraoxonase 1, an enzyme involved in the metabolism of organophosphate pesticides⁹. This finding suggests that this group of women may have longer time periods of detoxification and thus potentially higher organophosphate concentrations in the body over a long period of time, which could impact fetal growth⁹. However, in the CHAMACOS (the Center for the Health Assessment of Mothers and Children of Salinas) birth cohort, Eskenazi and colleagues did not find a significant relationship between prenatal organophosphate exposure as measured with biological markers and fetal growth⁶.

Studies examining pre-conceptional exposure to cholinesterase-inhibiting pesticides and potential long term impacts on reproduction are lacking. Organochlorine insecticides can persist in the body over long periods of time, and some may have genotoxic effects leading to long term health impact. The organochlorine endosulfan, is known to be genotoxic with mutagenic effects leading to decreased apoptosis and potential for mutant cell growth²³. In a study of medaka fish, early life endosulfan exposure had long term impacts on growth and reproduction¹⁶. In addition, DDT, a persistent organochlorine pesticide, has long term, generational effects on female reproduction and development²⁴. Because the half-life of cholinesterase-inhibiting pesticides is usually much shorter, their long term toxic effects are more difficult to study in humans. Future animal and human research should focus on such impacts of these chemicals.

We relied on self-reported information on exposures and outcomes in this analysis. Because our analysis was cross-sectional, it is possible that exposure misclassification and recall bias may have influenced our results. However, the quality of self-reported birth weight and pesticide data are generally regarded as accurate. Two studies examining the validity of self-reported birth weight in relation to medical records document excellent correlations between the two among cases with cancer and age/year matched controls (correlation coefficients of 0.84 – 0.99)^{25,26}. Rates of preterm delivery and low birth weight in our study population (primarily white) were lower than that of the non-Hispanic white US population in 2005 (12% and 5%, respectively) according to the Centers for Disease Control and Prevention National Vital Statistics Report²⁷. These low rates may indicate that this is an overall healthier population compared with the US white population as a whole.

In utero pesticide exposure may be related to preterm birth, itself a major cause of low birth weight, and thus inclusion of preterm birth in the regression models may mask an effect. However, we saw no indication that pesticide exposure was associated with preterm birth, and we included preterm birth in the model to increase the precision of the estimates. For the pregnancy-related exposures, point estimates showed a greater effect for indirect and residential exposures, but confidence intervals remained large when preterm birth was not controlled for in the model. The point estimates for several individual pesticides showed approximately a 10% change when preterm birth was taken out of the model, and some results became statistically significant. For example, the point estimate for terbufos changed from 150g (95% CI= -5, 319) to 180g (95% CI= 5, 355). For malathion, the point estimate changed from -59g (95% CI= -118, 0.5) to -67g (95% CI= -131, -3). Among term births only (93% of the cohort), the results are very similar to those for the entire cohort. For carbaryl, the point estimate for birth weight was slightly attenuated but with a similar confidence interval, -65g (95% CI -113, -17). The only other association that was statistically significant in this subset was for the use of terbufos, 163g (95% Confidence Interval 10, 317).

Other studies within the US report an association between high rates of farm work and pesticide use among farmer's wives^{28,29}. In the AHS, an analysis examining the reliability of self-reported pesticide use by applicators showed 70–90% agreement between repeated self-administered questionnaires³⁰. For pregnancy-related exposures, we aggregated questions based on potential magnitude of exposure and created a hierarchical structure for these data. Exposures may have differed within each level, but we believe that the exposures within each group are of the same relative magnitude. We could not account for other pesticide exposure pathways, including diet, which may depend on residential use as well as take-home exposures from the spouse (such as contaminated clothes, shoes, etc). Our analysis of pesticide exposure during pregnancy was limited by small numbers of women reporting agricultural exposures, the estimated highest exposure category. This may have limited our ability to see an effect if one existed. In addition, we only had data on first trimester exposures. While the velocity of weight gain is highest in the third trimester, the fetus is growing throughout pregnancy. It is unclear when the primary window of susceptibility might be for a potential impact of pesticides

on fetal weight gain but current studies point to the third trimester as the most important time period. Recently, the first trimester has been recognized as an important period of vulnerability in relation to adverse birth outcomes including low birth weight³¹. The entire pregnancy may present different windows of susceptibility for environmental exposures to impact growth. There is little evidence suggesting that paternal pesticide use may be related to changes in birth weight. We conducted an analysis examining paternal individual pesticide use in relation to birth weight which resulted in null findings for all exposures examined. Given the lack of evidence in the scientific literature and the lack of temporal specificity of paternal exposures we did not proceed further with this analysis.

While we did not see an association between birth weight and pesticide-exposure related activities during pregnancy, we did observe an inverse association with the women's use of carbaryl. Temporality of exposure in relation to outcome is a major limitation of our study. We restricted our analysis to the most recent birth that occurred within five years of enrollment to maximize the probability that the exposure occurred before the birth of the child, although we have no data to verify that this was indeed the case. However, a previous analysis from the AHS suggested that women with small children were less involved with farm work³², and it is thus likely that, in the time window examined, the pesticide exposure preceded birth. As an additional analysis, we included all pregnancies (not restricting to those within five years of enrollment) and saw similar results: maternal report of carbaryl use was inversely associated with birth weight, even though in this case the temporal relation between exposure and birth may be more likely to go in either direction. Our exposure data are unfortunately limited in that we do not have measures on either intensity or duration and timing of exposure. Other studies have generally relied upon biological markers of exposure, which provide a better measure of dose, but with the trade-off of a smaller sample size compared to our study. We explored 27 individual pesticide compounds, and this resulted in 27 comparisons, and the one significant finding for carbaryl may well be a result of chance. With a Bonferroni correction, this result would not achieve statistical significance.

While the overall response rate for spouses was high (75%), only 61% of these women returned the female and family health questionnaire. Among all enrolled women younger than 50 years whose husband reported having at least one child in the home the response rate to the FFH questionnaire was 57%. Women who did not complete the questionnaire did not differ by age, race, BMI, education level, or the number of children in the home compared with those who returned the FFH questionnaire. Current smokers were less likely to return the FFH. Women who reported use of any individual pesticide were slightly more likely to have completed the FFH compared to women who did not complete FFH (56% vs. 53%) and women who reported carbaryl use were slightly more likely to return the FFH compared to women who did not report carbaryl use (27% vs. 25%). While the differences in proportions are not large, we did see that more exposed women were likely to be included in this analysis, potentially giving us more power to detect an association. Given the small proportion of low birth weight babies in this group, it is unlikely that women who completed the FFH had worse outcomes than those who did not return the questionnaire.

Our results provide information regarding pesticide exposure as a modulator of birth weight. Only one pesticide, carbaryl, use was associated with reduced birth weight among children of farm women in the AHS. Carbaryl is widely used for agricultural and residential purposes in the US, and was used by 21% of the women in the AHS. Our limited findings support the possibility that carbaryl use may affect birth weight. Additional research is needed, with biomarker and temporal characterization of exposure, to examine maternal pesticide exposure in relation to later health outcomes.

Acknowledgments

We would like to thank Stuart Long of Westat for help in data management and Tina Saldana for her help in project conception. This work was supported by the Intramural Research Program of the NIH, National Institute of Environmental Health Sciences (Z01-ES049030) and National Cancer Institute (Z01-CP010119).

Funding: This work was supported by the Intramural Research Program of the NIH, National Institute of Environmental Health Sciences (Z01-ES049030) and National Cancer Institute (Z01-CP010119).

List of Abbreviations

AHS	Agricultural Health Study
BMI	Body mass index
CI	Confidence interval
FFH	Female and family health questionnaire
SD	Standard deviation
US	United States

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Mean	3586 g
Standard Deviation of Mean	545 g
Median	3608 g

FIGURE 1.
Distribution of Birth Weight (g) for 2246 Live Births in the Agricultural Health Study within
5 Years of Enrollment (1993–1997)

Table 1

Maternal Characteristics of 2246 Live Births in the Agricultural Health Study within 5 Years of Enrollment (1993– 1997)

	N	%
Site		
Iowa	1784	79
North Carolina	462	21
Infant Sex		
Male	1159	52
Female	1060	47
Race		
Caucasian	2205	98
Black	11	0
Native American	7	0
Asian American	5	0
Other	7	0
Smoking during pregnancy		
Yes	161	7
No	2085	93
Maternal age at most recent pregnancy		
18 – 25	206	9
25 – 29	628	28
30 – 34	917	41
35 – 45	495	22
Mother's Education Level		
Less than high school	30	1
High School	508	23
>High School	1490	66
Height (inches)		
58 – 65	1134	50
>65 – 74	1112	50
BMI at enrollment (kilograms/meters ²)		
16 – 18.5	56	2
18.5 – 24.9	1311	58
25 – 29.9	564	25
≥30 – 56	315	14
Parity		
1	500	22
2	823	37
3	588	26
≥4	335	15
Preterm Birth		

	N	%
Yes	150	7
No	2096	93
Pesticide Activities During First Trimester of Pregnancy		
None	1162	52
Indirect	764	34
Residential	278	12
Agricultural	42	2
Birthweight (grams)		
540 – 1500	12	1
>1500 – 2500	54	2
>2500 – 4090	1817	81
>4090 – 5256	363	16

Table 2

Association between Maternal Factors and Birth Weight Among 2246 Live Births within the Agricultural Health Study

Variable	N	%	Mean Birth Weight (g)	Linear Regression Coefficient (g)	95% CI (g)
Site					
Iowa	1784	79	3609	Referent	
North Carolina	462	21	3498	-111	-167, -55
Infant Sex					
Male	1159	52	3636	Referent	
Female	1060	47	3533	-103	-148, -58
Maternal Race					
White	2205	98	3589	Referent	
Other	30	1	3467	-24	-100, 53
Smoking During Pregnancy					
No	2085	93	3603	Referent	
Yes	161	7	3358	-246	-333, -159
Maternal Age Category (years)					
18 - 25	206	9	3535	Referent	
25 - 29	628	28	3566	32	-54, 117
30 - 34	917	41	3603	69	-14, 151
35 - 45	495	22	3600	65	-24, 153
Mother's Education					
Less than high school	30	1	3437	-140	-339, 60
High School	508	23	3576	Referent	
>High School	1490	66	3594	18	-37, 72
Maternal Height (inches)					
58 - 65	1134	50	3530	Referent	
>65 - 74	1112	50	3642	112	67, 157
BMI at enrollment (kilograms/meters ²)					
16 - 18.5	56	2	3257	-306	-451, -161

Variable		N	%	Mean Birth Weight (g)	Linear Regression Coefficient (g)	95% CI (g)
Parity	18.5 – 24.9	1311	58	3563	Referent	
	25 – 29.9	564	25	3653	90	36, 144
	>30 – 56	315	14	3618	55	–12, 121
	1	500	22	3445	Referent	
	2	823	37	3597	151	91, 212
Preterm (≤ 36 weeks)	3	588	26	3655	210	145, 274
	>=4	335	15	3647	202	127, 277
	No	2096	93	3642	Referent	
	Yes	150	7	2805	–837	–921, –754

Table 3

Multiple Regression Estimates of Change in Birth Weight (grams) in Relation to First Trimester of Pregnancy Self-Reported Pesticide Use by Category in the Agricultural Health Study (N=2246) *

Prenatal Pesticide Exposure Category	Number of Women	%	Coefficient (g)	95% CI (g)
No Exposure	1162	52	referent	n/a
Indirect	764	34	9	−36, 53
Residential	278	12	−5	−69, 60
Agricultural	42	2	−72	−222, 79

* All analyses controlled for site, BMI, BMI squared, parity, maternal height, preterm status, smoking

Table 4

Multiple Regression Estimates of Change in Birth Weight (grams) in Relation to Maternal Self-reported Individual Pesticide Use for 2246 Births in the Agricultural Health Study *

Individual Pesticides	Total Number of Women	Number of Women Reporting Ever Use	%	Coefficient (g)	95% CI (g)
Herbicides					
Alachlor	2201	46	2	-53	-196, 91
Atrazine	2203	55	2	-39	-171, 92
Chlorimuron-ethyl	2200	20	1	76	-140, 292
Cyanazine	2201	36	2	-71	-232, 91
Dicamba	2200	50	2	-24	-162, 114
Glyphosate	2220	700	32	4	-40, 48
Imazethapyr	2201	42	2	-22	-172, 128
Metolachlor	2201	47	2	-8	-149, 134
Paraquat	2202	21	1	-0.2	-212, 212
Petroleum Oil	2205	58	3	-112	-239, 16
Pendimethalin	2203	32	1	-22	-193, 149
Trifluralin	2204	64	3	-19	-141, 103
2,4-D	2205	253	11	-38	-103, 27
Fungicides					
Captan	2201	33	1	-68	-236, 100
Metaxyl	2198	26	1	-63	-255, 129
Insecticides					
Carbaryl	2207	471	21	-82	-132, -31
Chlordane	2177	21	1	22	-190, 233
Chlorpyrifos	2193	61	3	-51	-176, 73
Coumaphos	2182	21	1	51	-160, 262
Diazinon	2197	177	8	-63	-139, 13
Dichlorvos	2184	40	2	-50	-203, 104
Fonofos	2193	20	1	17	-200, 233
Malathion	2211	307	14	-59	-118, 0.5
Permethrin on crops	2197	38	2	61	-96, 218

Individual Pesticides	Total Number of Women	Number of Women Reporting Ever Use	%	Coefficient (g)	95% CI (g)
Permethrin on animals	2184	77	4	64	-47, 176
Phorate	2193	30	1	-37	-215, 140
Terbufos	2195	36	2	157	-5, 319

* All analyses controlled for site, BMI, BMI squared, parity, maternal height, preterm status, smoking