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Biomonitoring for farm families in the Farm Family Exposure Study

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Objectives The Farm Family Exposure Study was conducted to evaluate real-world pesticide exposure for farmers, spouses, and children.

Methods Eligible farm families from Minnesota and South Carolina were randomly selected from a roster of licensed private pesticide applicators. Eligibility required that the family include a farmer, spouse, and at least one child between the ages of 4 and 17 years, that the family live on the farm, that the farmer planned to apply one of the target pesticides [glyphosate, chlorpyrifos, 2,4-dichlorophenoxy acetic acid (2,4-D)] to at least 10 acres (4.1 hectares) of land within 1 mile (1.6 kilometers) of the house. For each family member, geometric means were calculated for 24-hour composite urinary samples, with a 1 ppb (part per billion) limit of detection, the day before, the day of, and for 3 days after the application.

Results For the farmers, the peak geometric mean concentrations were 3 ppb for glyphosate, 64 ppb for 2,4-D, and 19 ppb for the primary chlorpyrifos metabolite. For the spouses and children, the percentage with detectable values varied by chemical, although the average values for each chemical did not vary during the study period. The applicators had the highest urine pesticide concentrations, children had much lower values, and spouses had the lowest values. Exposure to family members was largely, though not exclusively, determined by the degree of direct contact with the application process. The exposure profile varied for the three chemicals for each family member.

Conclusions The data of this study indicate the importance of chemical-specific considerations when exposure assessments are planned in epidemiologic studies.

Key terms agriculture; children; chlorpyridos; glyphosate; pesticides; spouse; 2,4-dichlorophenoxyacetic acid.

The Farm Family Exposure Study was designed to characterize real-world pesticide exposures among farm families around the time of pesticide application by measuring urinary pesticide levels of the applicator and his or her spouse and children. Specific goals were to quantify pesticide exposure among farmers and their family members through biomonitoring, determine the relationship between urinary pesticide levels and self-reported and observed measures of exposure, and identify work or home practices that may be associated with increased urinary pesticide levels.

Concern has been expressed about chronic health effects from pesticides, especially for lymphohematopoietic cancers, and research in this area is expanding rapidly. Exposure assessment is a challenging methodological issue in epidemiologic studies of pesticides and chronic diseases because pesticide practices vary widely. Such studies have generally relied on self-reported use of pesticides from questionnaires, information from proxy respondents, or other surrogate measures of exposure (1–11); however, characterizing the validity of these exposure metrics has been difficult. Some studies have attempted to verify self-reported pesticide exposure information using information from employers and other sources, such as sales records, but the extent of the misclassification and attendant effects on risk estimates are not clear (12–16).

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Misclassification of self-reported exposures obtained from persons, next-of-kin, or other proxy respondents, particularly for specific exposures, can contribute to discrepant risk estimates (8, 9, 14, 17–20). Job title has also been used as a surrogate for exposure, but such use does not discriminate the type and magnitude of exposure well (11, 21, 22). Exposure assessment studies at the time of pesticide application can provide precise quantitative exposure estimates, but they have provided limited information about the validity of self-reported exposure and do not characterize a health effect (23, 24). By contrast, the measurement of cholinesterase levels and the levels of urinary metabolites of organophosphate pesticide in Israel detected some correlation between the number of acute symptoms and the urinary levels of dimethylphosphate or diethyl phosphate (23).

Living on a farm has been used as a proxy of pesticide exposure, but farm residence does not assure direct exposure for a particular individual. The applicator probably receives most exposure from occupational contact, but the amount is uncertain. The spouse and children, if exposed, may be exposed through contaminated clothing, household surfaces, playing in fields following an application, and drift through agricultural use or the use of pesticides in gardens or homes or on lawns. However, the prevalence and amount of exposure are uncertain.

Various quantitative methods, such as dermal patches, handwipes, air sampling, soil samples, and dust samples, have been used to estimate pesticide exposure. Urine pesticide levels can be a biomarker for pesticide exposure when pesticide-specific metabolism and excretion are understood, and they more accurately reflect the internally absorbed dose of pesticide. Studies of urinary pesticide levels have relied on either spot or 24-hour urine pesticide levels, but the two methods have not been routinely compared.

Misclassification of exposure can lead to over- or underestimates of risk (1, 7, 8, 14, 15, 17, 18, 25). Quantifying the magnitude of potential misclassification will help to evaluate and interpret the results of epidemiologic studies that rely on self-reported pesticide exposure or surrogate information. In this report, we present a summary of the initial results of the Farm Family Exposure Study, describing the exposure prevalence for three chemicals, the ranges of exposures, and some observations on potential determinants of exposure that will be further evaluated in the future.

Study population and methods

Farm families were randomly selected from Minnesota and South Carolina from a roster obtained for licensed private pesticide applicators from the respective departments of agriculture. The applicators' addresses and telephone numbers were retrieved and confirmed from electronic telephone directories and randomly ordered, and the applicators were contacted initially by letter and subsequently by telephone.

After a letter of introduction was sent explaining the study, a staff member contacted the potential participants by telephone to assess eligibility and invite the family to participate. Eligibility to participate required that the family included a farmer, spouse, and at least one child between the ages of 4 and 17 years, that the family lived on the farm, that the farmer was to personally apply pesticides to at least 10 acres (4.1 hectares) of land within one mile (1.6 kilometers) of the house, and that the farmer planned to apply at least one of the target pesticides [2,4-dichlorophenoxyacetic acid (2,4-D), glyphosate, or chlorpyrifos] as part of the routine operation during the study period. In addition, the farmer, spouse, and eligible children had to be willing to collect all their urine in containers for five consecutive days, and the farmer and spouse had to be willing to complete the pre- and postapplication questionnaires.

Families were enrolled in the study when an eligible application was made. Our target was to enroll approximately 100 farm families equally distributed among the three study chemicals. We enrolled 95 farm families, a small, but hopefully representative fraction of all the eligible families from Minnesota and South Carolina. To the extent possible, the random order in which the families were initially contacted was preserved when the families were enrolled and, thereby, reduced the potential for a substantial selection bias. Some eligible families were passed over if weather or other circumstances (eg, children temporarily away from farm) prevented them from making the application or completing all the study requirements. All the children who met the age requirements were included in the study. A signed consent form was obtained from all the participating family members before the urine collection began. The study protocol was approved by the University of Minnesota Human Subjects Research Committee.

As an incentive for participation, up to USD 1000 was provided for the pesticide applied during the study, and the family received USD 300 if they completed the study requirements.

The farmer and spouse completed a questionnaire before the pesticide application and at the end of the study period. The farmer's enrollment questionnaire included questions on demographic characteristics, farm practices, household practices, use of personal protective equipment, local site conditions, and specific facts about pesticide applications, including the number of pesticide applications in the past year, number of crops or growing seasons in the last year, when the last pesticide application was done prior to the study, and what pesticide was used for this most recent application. The spouse's enrollment questionnaire included questions about demographic and lifestyle characteristics, household information, and recent use of the study pesticide. Both parents were asked the same questions about their children's demographic characteristics and recent pesticide exposures.

The farmer completed a follow-up questionnaire to assess specifics about the pesticide application, amount and type of pesticide used, type of application, use of personal protective equipment, details of mixing, loading and application, weather and local site conditions, personal hygiene and work practices, and their assessment of the exposure of the participating children. The spouses' follow-up questionnaire was used to assess their exposure and that of the participating children during the week of the study, including the dates, whether the children played in the field or around the mixing area or worked in the field or around the mixing area and if the child was present in the field or near the field at the time of application.

The family members were asked to collect all urine voids into separate containers from 1 day prior to the application through 3 days following the application, a total of 5 days. A composite 24-hour urine sample was made for each day of the study period using an amount of urine from each sample that was proportional to the sample weight and the total weight of urine collected that day. The composite samples were timed with respect to the handling of chemicals for the start of the pesticide application.

Field staff observed the pesticide applications, collected urine samples each day, and monitored compliance with the urine collection. If compliance was below expectation, the field staff discussed ways to improve compliance with the applicator or spouse.

Information recorded about the application included the formulation, batch or lot number, manufacturer, expiration date, number of containers, total amount received, condition of product upon arrival, concentration of active ingredient, storage location of pesticide, unusual occurrences or spills during mixing-loading and application, mixing and transferring to application container, and distance of the location of mixing and application from the home (a map was made of the mixing-loading area and the sprayed field and their relationship to and distance from the home), method of pesticide application and assessment of conditions of operation (weather conditions including relative humidity, wind speed and direction, air temperature, etc), personal protective clothing or equipment worn, open or closed mixing and transfer system, amount of pesticide applied, number of acres to which the pesticide was applied, and the number of loads. The presence of the spouse or child during the time of mixing or application and whether they assisted was recorded; however, additional detail about their use of personal protective equipment was not.

A standard protocol was used to review forms, reconcile discrepant information, and compile missing data. Data retrieval was used to complete missing information and clarify blank or inconsistent responses.

The composite urine samples were analyzed for the specific chemical used in the application. The concentrations of both glyphosate and 2,4-D were measured directly in the urine since these chemicals are not metabolized to any extent by mammals. The primary metabolite of chlorpyrifos, 3,5,6-trichloro-2-pyridinol (TCP), was measured to estimate exposure to chlorpyrifos. The limit of detection was 1 ppb (parts per billion) for all three chemicals. Samples below the limit of detection were assigned a value of half the limit of detection (0.5 ppb). Urinary levels were corrected for analytic recoveries as determined by an analysis of fortified samples prepared in the field and in the laboratory.

Data analysis

Geometric means were calculated as the *n*th root of the product of *n* numbers using SAS software (26). These means were calculated for urinary concentrations and for the change in concentration postapplication versus urine concentrations the day before the application. Scatter plots of the 24-hour urine pesticide concentrations were also generated for each day to graphically display the distribution of the results for each participant group (all participants: applicators, spouses, and children). In this report, we present a summary of the magnitude of the exposures and some determinants of exposures for the spouses and children.

Results

Altogether 11 164 applicators from a list containing 36 168 names were screened, and about 9% were eligible. The most frequent reasons for ineligibility were not living on the farm and not having eligible children living on the farm. There were 95 families in the study, 45 in Minnesota and 50 in South Carolina. All in all, these families made 116 pesticide applications, mostly by ground boom, since more than one chemical was applied on some farms (table 1). Glyphosate was applied to 48 farms, 2,4-D to 34 farms, and chlorpyrifos to 34 farms. There were 182 children, 86 boys and 96 girls, with an average age of 10.1 years on the 2,4-D farms, 11.1 years on the chlorpyrifos farms, and 11.5 years on the glyphosate farms (table 2).

Compliance with the 24 hour collections appeared to be good; however, more children than applicators were missing voids in the 24-hour composites. A greater number of children (N=14, 1.7%) than applicators (N=2, 0.4%) and spouses (N=3, 0.6%) had a missing composite sample. While there was no way of validating the completeness of the 24-hour samples, only 3% of the composite samples from the applicators and spouses were from fewer than three voids or were less than 300 grams. Children had up to 18% of the composite samples represented by fewer than three voids or less than 300 grams. Creatinine concentrations were available for most of the samples. At the point of the writing of the report, no samples had been excluded due to low creatinine.

Glyphosate

Twenty-nine percent of the applicators reported that they had applied glyphosate in the week before their participation in the Farm Family Exposure Study. An analysis of the samples for the day before application showed that 15% of the glyphosate applicators had urine concentrations above the detection limit (table 3). The geometric mean concentration was highest (3 ppb) on the application day (figure 1) and declined thereafter. Direct contact with the skin and spills or accidents were associated with higher urinary values. Two percent of the spouses had detectable urine concentrations on the day prior to the application, and 4% had detectable levels on the day of application. The maximum concentration for a spouse on these days was 3 and 2 ppb, respectively. Seven and twelve percent of the children had detectable levels of glyphosate on the pre-application and application days, respectively. For the children, the geometric means for these days were less than the limit of detection, and the maximum values were 17 and 29 ppb, respectively (table 3). The main determinant of exposure was helping with the application or presence during mixing and application; however, not all of the children present were observed to have direct contact with the application process, field, or chemical. There was no correlation between the urinary concentrations and the distance of the house from the application area, and there was no correlation with the washing of the applicators' clothes. As shown in figure 1, the daily measured glyphosate levels of the spouses and children were fairly consistent over the 5-day testing period.

Table 1. Number of families and pesticide applications by state. (2,4-D = 2,4-dichlorophenoxyacetic acid)

State	Number of families	Number of applications			
		2,4-D	Chlorpyrifos	Glyphosate	Total
Minnesota	45	17	6	25	48
South-Carolina	50	17	28	23	68
Total	95	34	34	48	116

Table 2. Children's demographic information by chemical for all applications. (2,4-D = 2,4-dichlorophenoxyacetic acid)

Chemical	N	Gender		Age (years)	
		Male	Female	Mean	Range
2,4-D	53	31	22	10.1	4–17
Chlorpyrifos	50	19	31	11.1	4–18
Glyphosate	79	36	41	11.5	4–18

Table 3. Urinary biomonitoring results for the pre-application days and the day of peak concentration for each chemical. (2,4-D = 2,4-dichlorophenoxyacetic acid, <LOD = below limit of detection.)

Day	Glyphosate			2,4-D			Chlorpyrifos		
	Geometric mean*	Range [a]	Detectable percentage	Geometric mean*	Range [a]	Detectable percentage	Geometric mean*	Range [a]	Detectable percentage
Pre-application									
Applicator	<LOD	<LOD–15	15	4	<LOD–231	71	7	2–44	100
Spouse	<LOD	<LOD–3	2	1	<LOD–20	41	5	2–24	100
Children	<LOD	<LOD–17	7 [b]	1	<LOD–53	62	8	2–32	100
Application									
Applicator	3	<LOD–233	60	64	2–1856	100	19	4–293	100
Spouse	<LOD	<LOD–2	4	1	<LOD–20	56	5	1–35	100
Children	<LOD	<LOD–29	12	4	<LOD–640	81	8	1–120	100

[a] Parts per billion; limit of detection =1 ppb, <1 imputed as 0.5.
[b] Three children missed collection on the pre-application day, and one collection was missing for the application day.

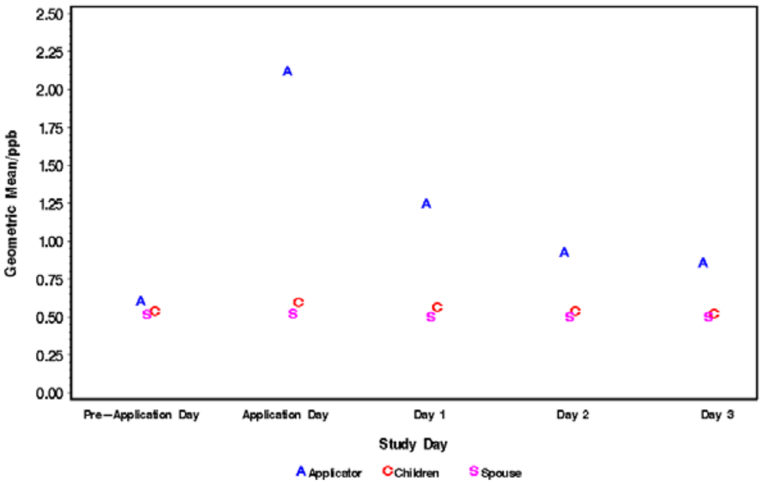

Figure 1. Geometric mean of glyphosate (ppb) by study day and family member. (ppb = parts per billion)

2,4-Dichlorophenoxyacetic acid

Seventy-one percent of the applicators had detectable 2,4-D in their urine before the application, with a geometric mean of 4 ppb and a range from below detection to 231 ppb (table 3). The geometric mean peaked on day 1 (64 ppb), and all the applicators had detectable concentrations in their urine (table 3). According to the field observations, skin contact was associated with increased exposure, as was repairing equipment.

Forty-one percent of the spouses had detectable 2,4-D concentrations in their urine before the application, the values ranging from below detection to 20 ppb (table 3). The maximum postapplication concentration was measured on day 1, with a geometric mean of 1 ppb and a range from nondetectable to 20 ppb (table 4).

The geometric mean urinary 2,4-D concentration of the children on the farms where 2,4-D was applied was 1 ppb (range from below the detection limit to 53 ppb) (table 3). Overall, 62% had detectable concentrations at baseline, while 81% had detectable concentrations the first day after the application. The geometric means changed only slightly during the study period (figure 2).

For the spouses and children, being present during the application and being observed to have direct contact with the chemical or process was associated with a greater change in the urinary concentration from baseline (table 4). The median urinary concentrations for children who had direct exposure was 12 ppb, and the

Table 4. Maximum change from baseline for 2,4-dichlorophenoxyacetic acid (2,4-D) and 3,5,6-trichloro-2-pyridinol (TCP) for the spouses and children with direct, some, or no observed contact or exposure to the chemical during the application process.

Type of contact or exposure opportunity	2,4-D [a]			TCP [a]		
	N	Median	Range	N	Median	Range
Direct						
Spouses	1	15.5	..	1	9.5	–
Children	8	12.3	−1–587	8	11.4	−3–110
Some						
Spouses	7	1.5	0–6	4	0.5	−15–2
Children	24	1.9	−1–61	16	4.1	−16–22
None						
Spouses	26	0.2	−3–15	29	1.8	−6–89
Children	21	3.6	−3–24	26	1.4	−20–20

[a] Parts per billion; limit of detection =1 ppb, <1 imputed as 0.5.

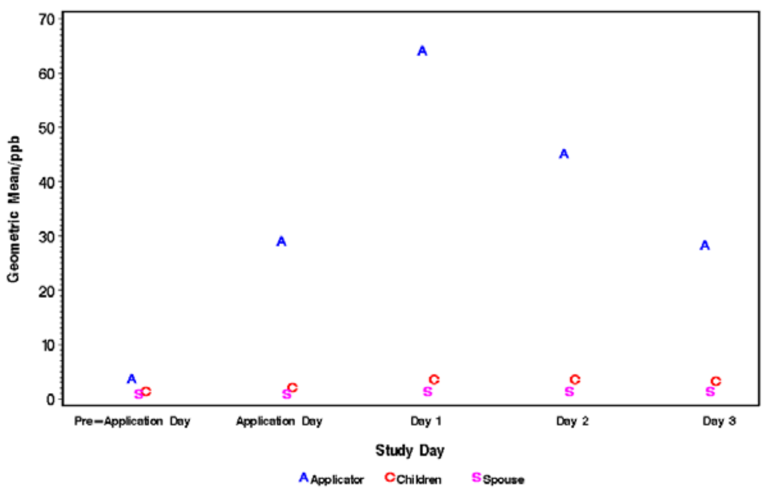

Figure 2. Geometric mean of 2,4-dichlorophenoxyacetic acid (2,4-D) by study day and family member. (ppb = parts per billion)

median urinary concentration for the one spouse with direct exposure was 16 ppb. For the children the values ranged between –1 and 587 ppb. For most of the spouses and children, the change from baseline was negligible.

The number of acres treated and the number of loads were not associated with the 2,4-D urinary concentrations of the spouses. For the children, the change from the baseline median urinary concentration was highest (7 ppb) for applications to 100 or more acres (1 acre = 0.41 hectares) and for the greatest number of loads (data not shown). The distance from the house to the field of application was not associated with the median urinary concentration for either the spouses or the children. The urinary concentrations of the spouses who washed the applicator's clothes were similar to those of the spouses who did not wash the clothes.

Chorpyrifos

All the applicators had detectable TCP in their urine at baseline, with concentrations that ranged from 2 to 44 ppb (table 3). The maximum geometric mean TCP concentration occurred on day 1 (figure 3). Self- reports of skin contact, repairing or washing the application equipment, and having a tractor without an enclosed cab were associated with exposure. All the spouses had detectable levels of TCP at baseline, the highest geometric means occurring on day 1, but the variation from the other days was negligible (table 3 & figure 3). The children had higher baseline urinary concentrations than the spouses and a slightly higher range of values. One child with a maximum concentration of 120 ppb was present for the entire application.

For both the spouses and the children, being present for the application and having any direct contact with the application process was associated with higher urinary TCP concentrations (table 4); however, the number of loads, the number of acres treated, and the distance from the application to the house did not correlate well with the median urinary concentrations of TCP. For the spouses, washing the clothing used during pesticide application was not associated with exposure.

Discussion

A total of 95 applicators, 95 spouses, and 182 children from two states, Minnesota and South Carolina, participated in the Farm Family Exposure Study. Twenty-four-hour urine samples were collected on five consecutive days beginning with the day prior to the application of one of the three pesticides under study – glyphosate, 2,4-D, and chlorpyrifos. The results of the study showed that exposure to farm family members can be quantified using biological markers of exposure, and the exposure was variable by chemical largely, though not exclusively, determined by the degree of direct contact with the application process.

The applicators had the highest urinary pesticide concentrations, the children had much lower values, and the spouses had the lowest values. For each family member, the exposure profiles differed for the three chemicals. For the applicators, the urinary glyphosate concentrations peaked on day 0, while the peaks for 2,4-D and chlorpyrifos occurred on day 1. The geometric means differed substantially by chemical. The values were highest for 2,4-D and lowest for glyphosate. The spouses and children had urinary levels that changed little on the average during the study. The percentage with detectable values differed by chemical, and there were small differences in the geometric means. These data indicate the importance of the chemical-specific considerations when exposure assessments are planned in epidemiologic studies.

The lowest urinary concentrations were found for the spouses, primarily because they spent the least amount

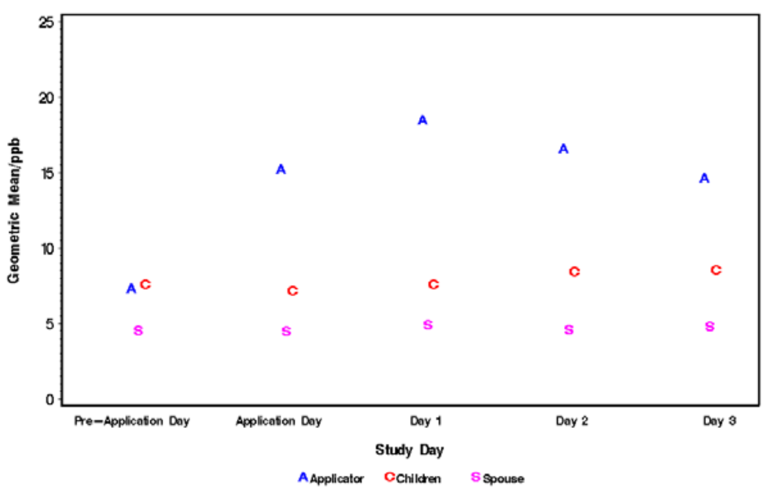

Figure 3. Geometric mean of 3,5,6-trichloro-2-pyridinol (TCP) by study day and family member. (ppb = parts per billion)

of time in the application area. Children were frequently present in the field and would help with the application, providing the opportunity to have direct contact with the chemical. However, few children had appreciable changes in their urinary concentrations during the study period, and not all of those with appreciable changes were directly involved with the application process or present in the field during the application. Their urinary concentrations remain unexplained.

There are some limitations of this study that should be considered when the results are assessed. Only one application was studied, and the extent to which the one application reflects usual practices is difficult to determine. However, the participants were asked to use their normal application procedures, and every effort was made to minimize the possible effect of observing the pesticide application.

In studies such as ours, there is always the possibility of selection bias. To partially address this problem, the applicators were randomly selected from state lists, and every effort was made to enroll those who were eligible. It is possible that the families who agreed to participate in a study with such extensive urine collection were not fully representative of all the eligible families. The extent of this bias is difficult to ascertain, and it is plausible that the exposure estimates either underestimate or overestimate the degree of exposure in the rest of the eligible population.

In this initial analysis of the data some of the covariates thought to be related to exposure prior to the initiation of the study, specifically the number of loads applied, number of acres treated, and the distance to the house from the application field, were not clearly related to exposure. However, additional analyses are needed to fully exploit the extensive database that was collected during the study.

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