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ORIGINAL ARTICLE

Tye E. Arbuckle · Rick Burnett · Donald Cole
Kay Teschke · Mustafa Dosemeci
Christina Bancej · Jun Zhang

Predictors of herbicide exposure in farm applicators

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Abstract ***Objectives***: Most epidemiological studies of pesticides have used self-reports rather than quantitative measurements to assess exposures. The purpose of this study was to identify factors likely to affect exposure under actual field conditions and to measure the sensitivity and specificity of self-reported indications of exposure against urinary measures of herbicide exposure. ***Methods***: A sub-set of the participants in a retrospective cohort study of Ontario farm families volunteered for a pesticide exposure assessment study. Immediately prior, and subsequent to, handling the phenoxy-herbicides 2,4-dichlorophenoxyacetic acid (2,4-D) or 4-chloro-2-methylphenoxyacetic acid (MCPA) for the first time during the season, 126 pesticide applicators provided pre-exposure spot urine samples and a subsequent consecutive 24-h urine sample. At the same time, they completed a questionnaire on pesticide use and handling practices for the first day of pesticide application. ***Results***: Assuming that the presence of 2,4-D in the urine was a measure of true exposure and that questionnaire indications of 2,4-D use were the exposure classification subject to error, then the questionnaire's prediction of exposure had a sensitivity of 56.7% and specificity of 86.4%. The comparable values for MCPA were sensitivity and specificity of 91.6% and 67.4%, respectively. In multivariate models, the variables pesticide formulation, protective clothing/gear, application equipment, handling practice, and personal hygiene practice were significant as predictors of urinary herbicide levels in the first 24 h after application (or spraying) had been initiated (adjusted $R^2 = 44\%$ for MCPA and 39% for 2,4-D). ***Conclusions***: Although similar domains of factors were associated with exposure in both models, the specific factors identified and the signs of the coefficients were sufficiently different between the final models for each herbicide that additional investigations appear to be warranted to determine the sources of the differences and assess the validity of the models and their ability to be generalised.

Keywords Environmental exposure · Herbicides · Bio-monitoring · Predictive modelling · Exposure misclassification

T.E. Arbuckle (✉)
Health Surveillance and Epidemiology Division,
Population and Public Health Branch, Health Canada,
A.L. 0701D, Ottawa, Ontario, K1A 0L2, Canada
E-mail: Tye_Arbuckle@hc-sc.gc.ca
Tel.: +1-613-9411287
Fax: +1-613-9419927

R. Burnett
Office of Policy and Programme Services,
Healthy Environments and Consumer Safety Branch,
Health Canada, Ottawa, Ontario, Canada

D. Cole
Department of Public Health Sciences,
University of Toronto, Toronto, Ontario, Canada

K. Teschke
Department of Health Care and Epidemiology,
University of British Columbia, Vancouver,
British Columbia, Canada

M. Dosemeci
Occupational Epidemiology Branch,
US National Cancer Institute, Rockville, Maryland, USA

C. Bancej
Cancer Division, Health Canada, Ottawa, Ontario, Canada

J. Zhang
Bureau of Infectious Diseases, Health Canada,
Ottawa, Ontario, Canada

Introduction

A major weakness of many epidemiological studies of pesticide health effects has been imprecision in exposure assessment. Traditionally, questionnaires have been used to elicit self-reports of exposure, using any of the following crude measures: any pesticide; use classes (e.g., herbicide, insecticide, fungicide); chemical family (e.g., phenoxyacetic acid, organophosphate); pesticide active ingredient; number of acres applied; or number of years of use for any of the above. Unlike pesticide exposure trials for product registration, rarely have attempts been made in epidemiological studies to quantify internal dose and to identify factors that can modify exposure under actual field conditions. Given the high costs, it is not feasible in large epidemiological studies to collect and analyse biological samples for pesticide residues for every individual. It is therefore important that valid and reliable questions on pesticide exposure be developed that can be used to estimate each individual's exposure.

The Pesticide Exposure Assessment Pilot Study was designed to quantify herbicide exposure in farm applicators and their families, under actual field conditions and to identify the major determinants of that exposure for the pesticide applicator. An additional objective was to consider whether empirical modelling of these exposure determinants might allow improvements in the precision of questionnaire-based exposure estimation.

Farm applicators of herbicides differ from custom (commercial) and turf applicators in the time period of exposure and spray equipment used. For farmers, herbicide spraying is just one of the critical activities that they must do within a short time window to produce a good crop. They must also prepare the land for planting and seed their crops as well as maintain all the relevant pieces of equipment (e.g., tractors, sprayers, cultivators, planters, and fertiliser spreaders).

Methods

The population of the Ontario Farm Family Health Study, a retrospective cohort study of approximately 2,000 farm families in Ontario, provided the initial sampling frame for this bio-monitoring study. Details on the full population and methods have been described elsewhere (Curtis et al. 1999; Savitz et al. 1997; Arbuckle et al. 1999a). Briefly, the cohort study used the Canadian Census of Agriculture and follow-up telephone interviews to identify farm families of reproductive age (wife was under 45 years of age) across the province of Ontario, Canada. The questionnaire-based cohort study was designed to estimate the risk of adverse reproductive outcomes following exposure to pesticides. A sub-set of the participants in the cohort study indicated that they used the phenoxyacetic acid herbicides 2,4-dichlorophenoxyacetic acid (2,4-D) or 4-chloro-2-methylphenoxyacetic acid (MCPA) at the time of interview (1991–1992). In early 1996, this sub-set was contacted by telephone to determine if they were planning to use these herbicides again in the coming growing season. 2,4-D and MCPA were selected as sentinel pesticides that might typify an applicator's exposure to herbicides applied to agricultural crops. These herbicides are structurally similar to each other and are excreted largely unchanged in the urine (Kohli et al. 1974; Harris et al. 1992; Feldman and Maibach 1974; Sauerhoff et al. 1977; Baugher 1994). The estimated half-lives of 2,4-D and MCPA vary from 12 to 72 h (Sauerhoff et al. 1977; Kolmodin-Hedman et al. 1983).

A description of the participant recruitment and methods has been reported elsewhere (Arbuckle et al. 1999b). To be eligible for the study, the farmer had to be planning to use either 2,4-D or MCPA in the coming growing season; was the person who usually handled the pesticides on the farm; lived on the farm property; and was currently living with his spouse. All persons gave written, informed consent prior to their inclusion in the study. The study was reviewed and approved by the appropriate ethics committee. Pesticide applicators were asked to collect a pre-exposure spot urine sample just prior to starting use of either of the two herbicides in the 1996 season and then collect two consecutive 24-h urine samples. The farmers were encouraged to follow their normal routine in the handling and application of the pesticides. Urine samples were kept cool in a soft-sided cooler bag with ice packs until picked up by the field team and transported to the laboratory for pesticide analysis. A multi-residue screening laboratory methodology (refinement of that used in previous human exposure studies (Frank et al. 1985; Harris and Solomon 1992; Harris et al. 1992; Libich et al. 1984) was used to analyse the urine samples using a gas chromatograph-mass spectrometer (GC-MS) ion trap detector. Samples below the detection limit of 1 μg/l were assigned a value of one-half the limit of detection. Urine samples were not adjusted for creatinine due to uncertainty as to the value of such adjustment (Harris et al. 2000) and because the parameter of interest was the average concentration of the pesticide residue in the urine excreted within 24 h of exposure and not in the total dose excreted in a 24-h sample.

A number of different questionnaires were used to collect information on the pesticides used and potential predictive factors that could modify an individual's exposure (Table 1), including: a

Table 1. Information collected by questionnaire potentially predictive of pesticide exposure

Agricultural chemicals diary
Date
Time started and time finished
Product names and registration numbers
Total product used
Number of acres sprayed
Tank size
Sprayer application rate
Number of spray tanks mixed on this day
Method of application
Other individuals handling pesticides
Type of equipment repairs and maintenance
Time spent repairing or maintaining equipment this day
'Day of application' questionnaire
Date
Time started and finished
Location of fields sprayed
Product names and registration numbers
Diluents or additives used
Type of application equipment used
Make, model, nozzle size, and tank capacity of application equipment
Other equipment used
Clothing and gear worn during mixing, loading, application and clean-up
Product names and registration numbers for each pesticide used during the previous 6 days
Post-season telephone interview
Age of sprayer
Personal hygiene practices after handling pesticides
Date when certificate for Grower Pesticide Safety Course expires
Calibration of spray equipment
How nozzles are usually unplugged
Household laundry practices
Incident of high personal exposure to pesticides
Location of home in reference to where pesticides are mixed, loaded and applied, and where equipment is rinsed
Storage of pesticides in the home
Husband's questionnaire (from Ontario Farm Family Health Study)
Education
Off-farm employment
Personal hygiene practices
Farm debt
Perceptions that farm life is harmful to health
Level of stress
Smoking
Date of birth
Body mass index

'day of application' questionnaire that was completed by the applicator within 24 h of applying 2,4-D or MCPA during the monitoring period; an agricultural-chemicals diary of all pesticides used on crops during the growing season; a post-season questionnaire, completed the following winter; and the husband's questionnaire, completed during the cohort study of 1991–1992. No attempt was made to validate reports against records of purchase. Product names were linked to a database of pest control products licensed in Canada, to identify the active ingredients and formulations. In cases where only the active ingredient was supplied, the formulation was unknown.

To measure the extent to which an applicator's self-report of herbicide use on the day of application was a valid indicator of herbicide exposure, we calculated sensitivity and specificity indices using urinary herbicide concentration measured in the first 24-h after initiating spraying (the day-1 urine) as the gold standard. A measurement above the detection limit was considered to be an indicator of 'true' exposure.

As we were not interested in measuring total absorbed dose and wanted to reduce participant burden, a 24-h urine collection was considered to be adequate for modelling. Because their distribution was skewed to the right, day-1 urine levels were natural log transformed and adjusted for any concentration of the pesticide of interest present in the pre-application spot sample (the log difference of the spot sample and the day-1 sample plus 3). The study population was separated into two groups – those applicators reporting use of MCPA on the 1st day of monitoring and those applicators reporting use of 2,4-D; separate predictive models were developed for each herbicide. As there were approximately 130 potential variables derived from the questionnaires that might affect the level of herbicide measured in the urine of applicators, a strategy was devised to reduce and select the variables for multivariate linear regression analyses. As a first step, variables with little variation or a high proportion of missing values were removed. The remaining variables ($n=63$) were assigned to one of six possible domains: demographics/lifestyle of applicator; formulation/quantification of herbicide handled/applied; protective clothing/gear; application equipment features; pesticide handling practices/activities; and personal hygiene practices. Correlations and univariate linear regression analyses were conducted on the variables in each domain, and highly correlated variables were identified and grouped. Remaining variables were then entered into domain-specific multiple linear regression models. Only those factors that were identified as important predictors or had a P value <0.20 (arbitrarily chosen as a conservative value) in the domain-specific multivariate model are reported here. For the cross-domain regression models, variables with a P value <0.1 from each domain-specific model were entered. Backwards elimination was conducted using Akaike's information criterion (AIC) to select the most appropriate models.

Results

A total of 126 farm families participated in the study. All the pesticide applicators were male. Among the applicators, 47.6% had detectable levels of 2,4-D in their day-1 urine samples, while 65.9% had detectable levels of MCPA. Among those applicators reporting use of the sentinel pesticide, the respective values were 79% for 2,4-D and 84.3% for MCPA. Although median levels of the two herbicides were significantly higher in applicators who reported their use, the levels measured in the day-1 samples ranged widely from non-detectable to as high as 410 or 790 μg/l for 2,4-D and MCPA, respectively (Table 2). The urine volumes ranged from 350 to 4,480 ml, with a mean of 1,390 ml and 10% below 700 ml, indicating that the majority of the urine samples fell within the normal range of volume excreted per day. Approximately 90% of those applicators with detectable levels of MCPA in their urine indicated on their questionnaires that they had used MCPA on the study date (Table 3). The corresponding sensitivity of the questionnaire response for 2,4-D was considerably lower (57%). There was no statistically significant difference in the specificity between the two herbicides.

The results of the univariate linear regression analyses examining the predictors of urine levels for each of the two herbicides are set out by domain in Tables 4 and 5. In general, factors from each domain were associated with levels of pesticide residue measured in the urine of applicators.

Across domains, factors associated with *elevated* urinary levels of 2,4-D were: time spent using this her-

Table 3. Sensitivity and specificity of questionnaire-reported applicator exposure to 2,4-D and MCPA based on detectable levels in day-1 24-h urine (*CI* confidence interval)

Herbicide	Sensitivity (95% CI)	Specificity (95% CI)
2,4-D	56.7% (43.2–69.4)	86.4% (75.7–93.6)
MCPA	91.6% (83.4–96.5)	67.4% (51.5–80.9)

Table 2. Descriptive statistics for applicator day-1 urine levels of 2,4-D and MCPA by self-reported indication of use in herbicide applicators

Statistic	Self-reported use of 2,4-D on the application day		Self-reported use of MCPA on the application day	
	Yes ($n=43$)	No ($n=83$)	Yes ($n=89$)	No ($n=37$)
	Average urinary day-1 24-h 2,4-D level (μg/l)		Average urinary day-1 24-h MCPA level (μg/l)	
Arithmetic mean (standard deviation)	27.63 (72.48)	2.58 (7.99)	44.90 (110.36)	1.27 (2.28)
Geometric mean (geometric standard deviation)	5.36 (5.84)	0.90 (2.93)	8.76 (6.91)	0.72 (2.26)
25th Percentile	1.0	0.5	2.0	0.5
Median	6.0[a]	0.5	11.0[a]	0.5
75th Percentile	13.0	1.0	36.0	0.5
Range	0.5–410.0	0.5–66	0.5–790.0	0.5–12.0

[a]Kruskal-Wallis Test $P=0.0001$

bicide; having off-farm employment; having a large spray tank capacity; using a sprayer with an anti-backflow device; and washing spraying equipment (Table 6). The only *protective* factor identified in the multivariate 2,4-D model was the wearing of rubber gloves during mixing or loading of the herbicide.

The major predictors of *reduced* urinary MCPA levels in applicators in the multivariate analysis were: the wearing of rubber boots during cleanup of equipment; having a large spray tank capacity (contrary to the predictive model for 2,4-D); using a tractor with a charcoal filter during application; using a sharp object to unplug spray nozzles; and applying formulations of MCPA other than the amine salt (Table 7). One of the strongest predictors of *elevated* MCPA urine levels was current smoking.

Discussion

Questionnaire data on use of pesticides can provide valuable information on opportunities for pesticide exposure, but less reliable information on internal dose. Using the detection of the herbicide in the applicators day-1 24-h urine sample as the gold standard measure of exposure, we found that the sensitivity of self-reported 2,4-D use was considerably lower than that for MCPA use (56.7% and 91.6%, respectively). In contrast, the specificity for 2,4-D reporting was higher (86.4%) than for MCPA reporting (67.4%), although the confidence intervals did overlap. As eligibility criteria required that they were supposed to be using either 2,4-D or MCPA, it is very unlikely that the applicator failed to report use of these herbicides when, in fact, they had used them. Hence, even eliminating faulty memory as an explanation for the result, there are still major sources of exposure misclassification errors, if based solely on utilisation of an indicator of herbicide use. As most epidemiological studies rely on an individual's recall of pesticide exposures over a much longer time, misclassification errors are likely to be considerably larger than that observed here.

Multivariate predictor modelling explained approximately 40% of the variation in the average day-1 herbicide urine levels with some differences between 2,4-D and MCPA in the predictors identified. In general, protective clothing or equipment reduced the degree of exposure; however, the specific items identified within these domains differed between the two herbicides. Individual variations in herbicide pharmacokinetics among the applicators may explain the moderate predictive value of the models. Other possibilities include factors that were not measured and therefore were not available to be included in the model, or inaccuracies in the data used in the model (for example, misreporting of personal protective equipment use). Other contributing sources of exposure may be contact with previously contaminated surfaces such as the inside or outside of previously used gloves (Garrod et al. 2001), interior of spray rigs, and frequently touched surfaces (Hines et al. 2001). Further, our study's small sample size and the relatively larger number of relevant predictor variables may have created some instability in final parameters. The observed differences between these two herbicide models could be true or chance differences. Modelling of the determinants of pesticide exposure under actual field conditions is still in its infancy, and further work needs to be done to test whether these models are valid and generalisable.

The level of herbicide residue excreted in the urine will be altered by individual differences in absorption, metabolism, distribution and excretion. If a person has come into contact with a pesticide, a number of factors can affect absorption, including: breathing rates; amount of physical exertion; area and location of skin exposed; duration of exposure; skin damage; and the number of hair follicles in the exposed area. Under laboratory conditions, excretion of 2,4-D following a single dermal exposure varies by site of application (Moody et al. 1992). Farm pesticide applicators are likely to be exposed on several sites, including the backs of their hands, and their palms and forearms, and may also have facial and trunk-of-the-body exposure. It has been estimated that approximately 10% of the total dose is excreted in the urine over a 24-h period following a single dermal exposure (Harris 1999). Environmental factors such as temperature and humidity, the form and concentration of the pesticide product (e.g., amine, ester) and presence of other chemicals on the skin or in the pesticide product may also impact on the degree of absorption of the herbicide (Moody et al. 1992; Maibach et al. 1971; Harris and Solomon 1992).

The measuring of the level excreted in the urine, in contrast to the use of skin patches, hand washes or air monitors, represents more accurately the amount absorbed. These latter methods represent only one route of exposure, may not capture all herbicide contact with the entire body surface area and have demonstrated non-uniform deposition on various body regions (Hines et al. 2001; Archibald et al. 1995). The use of a better method that has been developed to estimate dermal exposure, the fluorescent video imaging technique for assessing exposure (VITAE) (Fenske and Birnbaum 1997; Fenske et al. 1986a, 1986b; Archibald et al. 1994), was considered in this study; however, logistical and legal considerations prevented its use with 2,4-D and MCPA. However, this method still does not measure absorption via other routes, such as inhalation or across the surface of the eye.

As the endpoint used in our predictive models is the concentration of the parent herbicide ingredient in the day-1 24-h urine sample, this value represents an average excretion concentration over the 24-h period since first exposure to the pesticide product. In this analysis, the herbicide residues in the day-2 24-h urine sample were not considered, as they could represent exposures on day 2 as well as day 1. Although we recognise that a larger percentage of the absorbed dose might have been eliminated in the day-2 urine sample, we were concerned

Table 4. Results of univariate linear regression for potential predictors of average day-1 24-h urinary 2,4-D levels in pesticide applicators reporting 2,4-D use on first application day. To account for any background exposure, we calculated the log difference of pre-application spot urine 2,4-D level and 24-h day-1 2,4-D + 3. *CI* confidence interval, *Ref* referent category

Domain	Characteristic (*n*)	β (95%CI) for log day-1 urine level	Unit change in day-1 level (µg/l) (95% CI) [exp(β)-exp(0)]	*P*
Clothing/Protective gear worn/handled	Wore dust mask or cartridge respirator for cleanup:			
	No (40)	Ref		
	Yes (3)	–0.99 (–2.53, 0.55)	–0.63 (–0.92, 0.73)	0.20
	Wore full face shield or goggles for mixing/loading:			
	No (26)	Ref		
	Yes (17)	–0.90 (–1.67, –0.13)	–0.59 (–0.81, –0.12)	0.02
	Wore full face shield or goggles for application:			
	No (31)	Ref		
	Yes (12)	–0.84 (–1.70, 0.01)	–0.57 (–0.82, 0.01)	0.05
	Wore full face shield or goggles for cleanup:			
	No (34)	Ref		
	Yes (9)	–0.74 (–1.70, 0.21)	–0.52 (–0.82, 0.24)	0.12
	Wore rubber gloves for mixing/loading:			
	No (10)	Ref		
	Yes (33)	–0.50 (–1.43, 0.44)	–0.39 (–0.76, 0.55)	0.29
	Wore rubber boots for mixing/loading:			
	No (35)	Ref		
	Yes (8)	–0.34 (–1.36, 0.69)	–0.28 (–0.74, 0.99)	0.51
	Wore rubber boots for application:			
	No (36)	Ref		
	Yes (7)	–0.18 (–1.27, 0.90)	–0.17 (–0.72, 1.45)	0.73
	Wore rubber boots for cleanup:			
	No (36)	Ref		
	Yes (7)	–0.18 (–1.27, 0.90)	–0.17 (–0.72, 1.45)	0.73
Quantification of herbicide handled/applied	Hours spent using any pesticides today (continuous)	0.12 (–0.01, 0.25)	0.12 (–0.01, 0.28)	0.07
	Hours spent using 2,4-D today (continuous)	0.13 (–0.01, 0.27)	0.14 (–0.01, 0.31)	0.06
Application equipment features	Tank capacity:			
	< 1,200 l (14)	Ref		
	1,200–1,800 l (7)	0.18 (–0.99, 1.35)	0.20 (–0.63, 2.87)	0.754
	> 1,800 l (22)	0.84 (–0.02, 1.70)	1.32 (–0.02, 4.50)	0.056
	Used tractor with cab today:			
	Yes (24)	Ref		
	No (19)	0.31 (–0.49, 1.11)	0.04 (–0.39, 2.02)	0.44
	Additional equipment used:			
	No sprayer with clean water tank (15)	0.03 (–0.81, 0.87)	0.03 (–0.55, 1.39)	0.94
	No induction hopper transfer system (32)	–0.02 (–0.93, 0.90)	–0.01 (–0.61, 1.46)	0.97
	Anti-backflow device (21)	0.94 (0.20, 1.67)	1.57 (0.22, 4.40)	0.01
Demographics/lifestyle	Employed offsite (6)	0.86 (–0.26, 1.99)	1.37 (–0.23, 6.28)	0.13
	Believe farm life is not harmful to health (14)	0.54 (–0.29, 1.38)	0.72 (–0.25, 2.98)	0.20
	Feel farm life stressful (36)	–0.71 (–1.77, 0.34)	–0.51 (–0.83, 0.41)	0.18
	Currently smoking at least one cigarette/cigar per day (3)	0.62 (–0.94, 2.17)	0.85 (–0.61, 7.80)	0.43
	Source of drinking water:			
	Drilled well (25)	Ref		
	Dug well (14)	–0.31 (–1.18, 0.56)	–0.27 (–0.69, 0.76)	0.48
	Other (4)	0.46 (–0.94, 1.87)	0.59 (–0.61, 5.51)	0.51
Personal hygiene practices	After handling pesticides, usually wash in:			
	Bathroom at home (16)	–0.09 (–0.92, 0.74)	–0.09 (–0.60, 1.09)	0.83
	Mud room at home (13)	–0.44 (–1.30, 0.42)	–0.36 (–0.73, 0.52)	0.31
	Outside home (28)	0.49 (–0.37, 1.35)	0.63 (–0.31, 2.85)	0.25
Pesticide handling practices	Use chemicals to control weeds in yard/lawn (23)	–0.17 (–0.99, 0.65)	–0.16 (–0.63, 0.92)	0.68
	Ways to unplug the nozzles:			
	Blow out by mouth (4)	0.54 (–0.83, 1.91)	0.72 (–0.56, 5.73)	0.43
	Wash out with water (30)	–0.24 (–1.11, 0.63)	–0.21 (–0.67, 0.87)	0.58
	Clean out with sharp object (10)	0.77 (–0.15, 1.68)	1.15 (–0.14, 4.39)	0.10
	Clean out with toothbrush (12)	–0.57 (–1.44, 0.30)	–0.44 (–0.76, 0.35)	0.19
	Clean out with other (4)	–0.84 (–2.19, 0.51)	–0.57 (–0.89, 0.66)	0.21
	Washed equipment on day before:			
	No (38)			
	Yes (5)	–0.67 (–1.90, 0.56)	–0.49 (–0.85, 0.75)	0.28
	Lubricated on day before:			
	No (39)	Ref		
	Yes (4)	–0.90 (–2.25, 0.45)	–0.59 (–0.89, 0.56)	0.18

Table 4. Contd.

Domain	Characteristic (*n*)	β (95%CI) for log day-1 urine level	Unit change in day-1 level (µg/l) (95% CI) [exp(β)-exp(0)]	*P*
	Spent any time maintaining equipment on day before:			
	No (32)	Ref		
	Yes (11)	–0.36 (–1.27, 0.55)	–0.30 (–0.72, 0.73)	0.43
	Washed equipment today:			
	No (34)	Ref		
	Yes (9)	0.75 (–0.20, 1.71)	1.12 (–0.18, 4.52)	0.12
	Hours spent maintaining equipment today (continuous)	0.75 (–0.20, 1.71)	0.57 (–0.21, 2.12)	0.19
Formulations	Active ingredient codes:			
	DXB (amine salts) (25)	Ref		
	XX2 (unknown) (10)	0.05 (–0.94, 1.04)	0.05 (–0.61, 1.84)	0.92
	DXF (low volatile esters) (8)	–0.08 (–1.16, 1.00)	–0.07 (–0.68, 1.72)	0.89

about the complicating influence of additional exposures during day 2 and the effects these might have on the kinetic parameters.

When this study was designed, we assumed that the phenoxy-herbicides 2,4-D and MCPA would be very similar in their pharmacokinetics and would have identical predictive factors for the applicator's exposure. Our results would suggest that misclassification errors will result if researchers make this assumption.

Although approximately 23% of the eligible population refused to participate in this bio-monitoring study, we expect that our results are representative of family farm applicators with similar equipment and work practices. A major limitation of our analysis is that our models did not attempt to control for the use of multiple or combined pesticides, which may have affected the pharmacokinetics of our target herbicides in the applicators.

Differences in sensitivity and predictive factors between 2,4-D and MCPA may reflect an increased dermal absorption potential of MCPA compared with 2,4-D (Harris 1999). The particular formulation of the phenoxy-herbicide may have profound effects on the absorption characteristics of the pesticide product (Arnold and Beasley 1989), with amine and salt formulations but not esters of 2,4-D rapidly hydrolysed and absorbed by most species. However, once absorbed, the phenoxy-acids distribute similarly. In our multivariate analysis of MCPA levels in day-1 urine, we found that the amine salt formulations differed from the potassium or sodium salts and esters, with the amine salts being associated with higher levels in the day-1 urine.

Occupational field studies of pesticide applicators to identify predictors of dose have been rare. A recent study of 94 professional turf applicators used data from two previously published studies to estimate total absorbed dose of 2,4-D during a work week and then developed a model to predict dose (Harris 1999). During a 1-week study period (Saturday to Thursday), each subject provided two consecutive 24-h urine samples, starting on Wednesday morning (day 5). Based on information provided in questionnaires on total daily amounts of pesticide used and the assumption that the ratio of total dose to amount of 2,4-D used remains constant for an individual applicator over time, Harris estimated total daily dose over the one work week, using the two 24-h urine samples taken towards the end of the week. Using information on the toxicokinetics and toxicodynamics of 2,4-D, Harris estimated the total absorbed dose of pesticide for the one-week period. Amount of 2,4-D applied, wearing of gloves during spraying, nozzle type, level of job satisfaction and current smoking status, were identified as predictors of total dose of 2,4-D in multivariate regression analysis. Approximately 65% of the variation in the total dose was explained by this model. Only 20% of the variation in dose of 2,4-D was explained by amount of pesticide used. Other factors such as protective clothing and equipment used during mixing and loading, wearing of short-sleeved shirt during spraying, and company characteristics had no impact on measured dose.

Several differences between the work practices of professional turf applicators and the farmers in our study should be noted. Unlike turf applicators, farmers do not spend most of the season applying herbicides. Turf applicators use hand-held spray equipment, whereas farmers generally apply herbicides using spray tanks with booms mounted on or attached to motorised vehicles. The custom turf applicator is likely to have the longest period of exposure, possibly spraying from spring to fall as he applies pesticides to control weeds and pests in lawns, parks and golf courses. The farm applicator's choice of herbicide, and intensity and time period over which exposure occurs, will depend on a number of factors, including crop varieties, weather conditions, total acreage, spray equipment problems, type of weed infestations, and off-farm employment. During the planting season there is a critically short time in which to optimise the preparation of the land (tilling, fertilising, and spraying of pre-emergent herbicides), planting, and spraying of post-emergent herbicides (at

Table 5. Results of univariate linear regression for potential predictors of average day-1 24-h urinary MCPA levels in pesticide applicators reporting MCPA use on first application day. To account for any background exposure, we calculated the log difference of pre-application spot urine MCPA level and 24-h day-1 MCPA + 3. *CI* confidence interval, *Ref* referent category

Domain	Characteristic (*n*)	β (95% CI) for log day-1 urine level	Unit change in day-1 level (μg/l) (95% CI) [exp(β)-exp(0)]	*P*
Clothing/protective gear worn/handled	Wore dust mask or cartridge respirator for cleanup:			
	No (85)	Ref		
	Yes (4)	–1.34 (–2.77, 0.08)	–0.74 (–0.94, 0.08)	0.06
	Wore full face shield or goggles for mixing/loading:			
	No (59)	Ref		
	Yes (30	–0.06 (–0.70, 0.57)	–0.06 (–0.50, 0.77)	0.84
	Wore full face shield or goggles for application:			
	No (69)	Ref		
	Yes (20)	0.44 (–0.27, 1.16)	0.56 (–0.24, 2.19)	0.22
	Wore full face shield or goggles for cleanup:			
	No (73)	Ref		
	Yes (16)	–0.18 (–0.96, 0.61)	–0.16 (–0.62, 0.83)	0.65
	Wore rubber gloves for mixing/loading:			
	No (20)	Ref		
	Yes (69)	0.07 (–0.66, 0.79)	0.07 (–0.48, 1.20)	0.86
	Wore rubber boots for mixing/loading:			
	No (56)	Ref		
	Yes (33)	–0.66 (–1.68, –0.05)	–0.48 (–0.81, –0.05)	0.03
	Wore rubber boots for application:			
	No (60)	Ref		
	Yes (29)	–0.76 (–1.39, –0.14)	–0.53 (–0.75, –0.13)	0.02
	Wore rubber boots for cleanup:			
	No (61)	Ref		
	Yes (28)	–0.85 (–1.47, –0.22)	–0.57 (–0.77, –0.20)	0.01
Quantification of herbicide applied/handled	Hours spent using any pesticides today (continuous)	0.05 (–0.04, 0.15)	0.06 (–0.04, 0.16)	0.25
	Hours spent using MCPA today (continuous)	0.07 (–0.02, 0.17)	0.08 (–0.02, 0.18)	0.11
Application equipment features	Tank capacity used today:			
	< 962 l (25)	Ref		
	962–1,900 l (39)	–0.87 (–1.58, –0.17)	–0.58 (–0.79, –0.16)	0.02
	> 1,900 l (25)	–0.90 (–1.67, –0.12)	–0.59 (–0.81, –0.11)	0.02
	Used tractor cab and charcoal filter:			
	Used neither (56)	Ref		
	Used tractor cab without charcoal filter (24)	0.24 (–0.44, 0.93)	0.28 (–0.36, 1.54)	0.48
	Used tractor cab with charcoal filter (9)	–0.65 (–1.66, 0.36)	–0.48 (–0.81, 0.43)	0.20
	Additional equipment used:			
	Sprayer with clean water tank: No (47)	0.12 (–0.48, 0.72)	0.13 (–0.38, 1.06)	0.69
	Induction hopper transfer system: No (76)	–0.17 (–1.03, 0.68)	–0.16 (–0.64, 0.97)	0.68
	Anti-backflow device: Yes (34)	–0.21 (–0.83, 0.41)	–0.19 (–0.56, 0.51)	0.50
Demographics/lifestyle	Employed offsite (8)	0.14 (–0.92, 1.19)	0.15 (–0.60, 2.20)	0.80
	Believe farm life is not harmful to health (31)	0.24 (–0.40, 0.88)	0.28 (–0.33, 1.42)	0.45
	Feel farm life stressful (69)	0.26 (–0.48, 1.01)	0.30 (–0.38, 1.74)	0.48
	Currently smoking at least one cigarette/cigar per day (9)	0.88 (–0.10, 1.86)	1.41 (–0.10, 5.42)	0.08
	Source of drinking water:			
	Drilled well (67)	Ref		
	Dug well (16)	0.09 (–0.69, 0.86)	0.09 (–0.50, 1.37)	0.83
	Other (6)	–1.15 (–2.34, 0.04)	–0.68 (–0.90, 0.04)	0.06
Personal hygiene practices	After handling pesticides, usually wash in:			
	Bathroom at home (25)	–0.46 (–1.12, 0.20)	–0.37 (–0.67, 0.23)	0.17
	Kitchen sink (5)	–0.01 (–1.32, 1.30)	–0.01 (–0.73, 2.65)	0.98
	Mud room at home (35)	0.59 (–0.02, 1.19)	0.80 (–0.02, 2.29)	0.06
	Outside home (48)	–0.40 (–0.99, 0.20)	–0.33 (–0.63, 0.22)	0.19
Pesticide handling practices/activities	Use chemicals to control weeds in yard/lawn (37)	0.36 (–0.25, 0.96)	0.43 (–0.22, 1.62)	0.25
	Ways to unplug the nozzles:			
	Blow out by mouth (13)	0.52 (–0.33, 1.36)	0.68 (–0.28, 2.90)	0.23
	Wash out with water (51)	–0.10 (–0.71, 0.50)	–0.10 (–0.51, 0.65)	0.73
	Blow out with compressed air (10)	–0.09 (–1.04, 0.87)	–0.08 (–0.65, 1.38)	0.86
	Clean out with sharp object (16)	–0.53 (–1.30, 0.25)	–0.41 (–0.73, 0.28)	0.18
	Clean out with toothbrush (26)	–0.44 (–1.10, 0.21)	–0.36 (–0.67, 0.23)	0.18
	Clean out with other (5)	–0.03 (–1.34, 1.28)	–0.03 (–0.74, 2.59)	0.96
	Washed equipment on day before (4)	1.09 (–0.34, 2.53)	1.98 (–0.29, 11.50)	0.13
	Spent anytime maintaining equipment on day before (13)	0.63 (–0.21, 1.47)	0.87 (–0.19, 3.35)	0.01
	Washed equipment today (19)	0.59 (–0.14, 1.31)	0.80 (–0.13, 2.7)	0.11

Table 5. Contd.

Domain	Characteristic (*n*)	β (95% CI) for log day-1 urine level	Unit change in day-1 level (μg/l) (95% CI) [exp(β)-exp(0)]	*P*
	Hours spent maintaining equipment today	–0.18 (–0.78, 0.42)	–0.17 (–0.54, 0.52)	0.55
Formulations	Active ingredient codes:			
	MAB (amine salts) (36)	Ref		
	XXM (unknown) (20)	–0.36 (–1.09, 0.36)	0.44 (–0.66, 0.44)	0.32
	MAS (potassium or sodium salt) (20)	–1.32 (–2.16, –0.48)	–0.73 (–0.88, –0.38)	0.00
	MAE (ester) (13)	–1.34 (–2.07, –0.62)	–0.74 (–0.87, –0.46)	0.00

Table 6. Multivariate regression analysis of predictors of average day-1 24-h urinary 2,4-D levels in applicators reporting 2,4-D use on first application day ($n = 43$). Adjusted R-square = 39.1%. *Ref* referent category

Description of variable	β for log Y (95% CI)	*P*	Unit change in day-1 2,4-D urine level (μg/l)
Wore rubber gloves for mixing/loading	–0.98 (–1.79, –0.18)	0.02	–0.63 (–0.83, –0.17)
Hours spent using 2,4-D	0.15 (0.02, 0.27)	0.02	0.16 (0.02, 0.31)
Tank capacity			
< 1,200 l (Ref)			
1,200–1,800 l	0.18 (–0.82, 1.18)	0.72	0.20 (–0.56, 2.25)
> 1,800 l	0.87 (0.16, 1.58)	0.02	1.38 (0.17, 3.85)
Anti-backflow device used	0.94 (0.27, 1.62)	0.01	1.57 (0.31, 4.04)
Employed offsite	0.96 (0.02, 1.89)	0.04	1.61 (0.02, 5.65)
Washed equipment today	0.56 (–0.26, 1.38)	0.17	0.76 (–0.23, 2.99)

Table 7. Multivariate regression analysis of predictors of average day-1 24-h urinary MCPA levels in applicators reporting MCPA use on first application day ($n = 89$). Adjusted R-square = 44.1%. *Ref* referent category

Description of variable	β for log Y (95% CI)	*P*	Unit change in day-1 MCPA level (μg/l)
Wore full face shield or goggles for application	0.64 (0.06, 1.22)	0.01	0.90 (0.07, 2.37)
Wore rubber boots for cleanup	–0.84 (–1.36, –0.32)	0.00	–0.57 (–0.74, –0.28)
Tank capacity used			
< 962 l (Ref)			
962–1,923 l	–0.82 (–1.39, –0.25)	0.01	–0.56 (–0.75, –0.22)
> 1,923 l	–0.65 (–1.36, 0.05)	0.07	–0.48 (–0.74, 0.06)
Used tractor cab and charcoal filter			
Did not use either (Ref)			
Used tractor cab without charcoal filter	0.56 (0.02, 1.14)	0.06	0.76 (0.18, 2.14)
Used tractor cab with charcoal filter	–0.38 (–1.30, 0.54)	0.41	–0.32 (–0.73, 0.71)
Currently smoking ≥ cigarette/cigar per day	1.30 (0.50, 2.09)	0.00	2.66 (0.65, 7.08)
Usually wash-up in mud room	0.44 (–0.04, 0.93)	0.07	0.56 (–0.04, 1.52)
Use chemicals to control weeds in yard/lawn	0.44 (–0.04, 0.93)	0.07	0.56 (–0.04, 1.54)
Usually unplug nozzles using sharp object	–0.71 (–1.33, –0.09)	0.02	–0.51 (–0.73, –0.09)
Formulation codes			
MAB Ref (amine salts)			
XXM (unknown)	–0.72 (–1.38, –0.06)	0.03	–0.51 (–0.75, –0.06)
MAS (potassium or sodium salt)	–1.57 (–2.00, –0.95)	0.00	–0.79 (–0.86, –0.61)
MAE (ester)	–1.38 (–2.09, –0.67)	0.00	–0.75 (–0.88, –0.49)

the appropriate stage of development of the crop and weed species) with the weather conditions. In a particularly wet and cool spring, the farmer may not be able to use the herbicides of choice and may be working under particularly tight time constraints (Arbuckle et al. 1999b). Most of a field crop applicator's yearly exposure to herbicides occurs during a few weeks in May and June.

A recently published study of 15 custom herbicide applicators, using hand wash and thigh patches to estimate exposure, reported that the wearing of gloves was a consistent determinant for significantly reduced hand and thigh exposure to target herbicides (atrazine, 2,4-D 2-ethylhexyl ester, and metolachlor) (Hines et al. 2001). None of the other covariates tested (e.g., amount of herbicide applied, duration, or acreage sprayed) were associated consistently across all herbicides with significant increases or decreases in mean exposure. The investigators also observed high within-worker variability, suggesting that factors varying from day-to-day influenced remaining variability more than individual work practices.

The custom crop applicator will generally spend longer periods of time over the year spraying herbicides for a number of farm operations and may be exposed to a greater variety of herbicides as well as other pesticides. His spray equipment may be larger and more sophisticated than the farm applicator. Generally, each type of herbicide applicator will also be responsible for mixing and loading the herbicides, as well as calibrating, maintaining, repairing and cleaning the application equipment.

Our study, as well as that of Harris (1999), highlights the inadequacies of using only indicators of pesticide use as proxy measures for dose in epidemiological studies. Past studies of farmers have used exposure metrics such as indicators of use, number of acres sprayed, duration of use, and frequency of use (Arbuckle et al. 1999a; Zahm et al. 1990; Hoar et al. 1986). These exposure metrics do not necessarily reflect true dose and can result in substantial misclassification of exposure, especially within categories. Our results confirm that farm pesticide applicators are not uniformly exposed to herbicides during a day of application and that the extent of their exposure may vary with a number of factors that may not be consistent across similar herbicides, let alone all pesticides.

It has been suggested that epidemiologists estimate the magnitude and direction of misclassification of exposure and use these estimates to correct the effect measures (Greenland 1998). Some commonly used techniques include the application of sensitivity and specificity estimates to determine the 'true' effect measure for a dichotomous exposure. However, although this process may improve the validity of the study, it does not account for variations in dose in those individuals who are correctly classified as exposed. For this, inclusion of sub-studies of exposure, such as ours, would be important as part of larger epidemiological studies linking exposures and outcomes.

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