Chapter 13

Dose Prediction Modeling for Epidemiologic Assessment of Pesticide Exposure Risks in Occupational Cohorts

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Epidemiologic studies designed to evaluate the effects of commonly used turf pesticides may have limited power to detect health risks and may be subject to bias from exposure measurement error. To increase the accuracy and precision of dose estimation for both risk assessment and epidemiologic research, valid models must be developed. Further, repeated measures of exposures over time are necessary to estimate both inter- and intra-individual variation. To address some of these issues, a national study of TruGreen Chemlawn employees was initiated in 2003. In the pilot study, conducted in Richmond, Virginia, up to 19 days of 24-hour urine samples were collected from 22 individuals. In 2004, urine samples were collected from a total of 113 volunteers in the spring, summer and fall, from 5 locations across the United States. The design of this study, the selection of national locations and pesticides, urine sampling methodology, and statistical modeling efforts are described.

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Most epidemiologic studies are limited by the lack of valid pesticide exposure data, or more correctly, absorbed dose data. One way to quantify dose is to use biological monitoring techniques that measure urinary concentrations of pesticides. However, for prospective studies with large cohorts following individuals over many years, this is highly impractical and, for retrospective studies, it is not possible. Although the accurate measurement of exposure or dose in prospective cohort studies is theoretically possible, it is practically very difficult. The cost, time commitment, and feasibility of enrolling subjects to provide long-term biological samples are insurmountable. Thus, prospective cohort studies, conducted to evaluate chronic effects of occupational exposures, often rely on many of the same exposure estimation techniques employed in retrospective studies. These techniques may not provide information of sufficient quality to improve our state of knowledge. New methods of dose estimation must be developed specifically for cohorts that are occupationally exposed. Workers employed as professional applicators provide a unique opportunity to develop these methods.

Epidemiologic Studies of Pesticide Applicators

Researchers at the National Cancer Institute in Maryland are following a cohort of approximately 40,000 Chemlawn workers (now called TruGreen Chemlawn) employed as professional turf applicators in the United States. This prospective mortality study, which has a retrospective component, will make use of semi-quantitative estimates of pesticide use such as the number of days worked per year and will be based on the branch where the employee worked, the amount of pesticide purchased for the branch, the period of employment, his/her job title, and the pesticide application program offered at the branch. Individual pesticide use or exposure cannot be estimated due to the lack of records for each individual employee [1,2]. The NCI has recently reported on the retrospective component of the cohort study and, although the cohort was young with a short duration of employment and a short period of follow-up, a significant increase in non-Hodgkin's Lymphoma (NHL) was observed among professional turf applicators employed for three or more years (Standardized Mortality Ratio (SMR) = 7.11, CI = 1.8, 28.4) [3]. As expected, due to the healthy worker effect, which can be described as the phenomenon where cohorts of employed individuals exhibit lower death rates than the general population due to the fact that severely ill individuals are often excluded from employment, the cohort had significantly decreased mortality as compared to the US population from the combined all causes of death. Overall, there were 45 cancer deaths (59.6 expected, SMR = 0.76). Mortality from bladder cancer was significantly increased, but only one subject reported direct occupational contact with pesticides. Overall, there were four deaths due to NHL (SMR = 1.14) and three were male lawn applicators (SMR = 1.63). The authors conclude that the NHL

excess is consistent with several earlier studies, but may be due to chance. If adequate measures of exposure or preferably dose can be developed for this cohort, the continued follow-up of these employees presents an excellent opportunity to evaluate health risks associated with some of the commonly used turf pesticides.

Pesticides Commonly Used in the Turf Industry

The phenoxy herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) and other related herbicides have been used extensively in the professional turf industry and are the subject of considerable investigation. Many epidemiologic studies have been conducted and are currently underway to evaluate the chronic effects of these pesticides in occupational groups, and although the current weight of epidemiological evidence may be suggestive of an association between the use of 2,4-D and some cancers, a cause-effect relationship has not been established. A number of reviews concerning exposure and the possible health effects of 2,4-D, dicamba (benzoic acid herbicide, 3,6-dichloro-2-methoxybenzoic acid), and related phenoxy herbicides such as mecoprop (2-(2-methyl-4-chlorophenoxy) propionic acid, MCPP; phenoxypropionic herbicides) and their dioxin contaminants are available in the literature. Until quite recently (2000), chlorpyrifos was used extensively for insect control in the turf industry. By many companies, it has now been replaced by the pyrethroid insecticide bifenthrin (2-methyl-1,1-biphenyl-3-yl)-methyl-3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl cyclopropanecarboxylate) and the chloro-nicotinyl insecticide imidacloprid (1-[(6-chloro-3-pyridinyl)methyl]-N-nitro-2-imidazolidinimine)).

No information is available on the exposure or dose of professional turf applicators to the chlorpyrifos replacement insecticides imidacloprid and bifenthrin. Considering the extensive use throughout North America, it is surprising that only one study of applicator exposure to imidacloprid (while spraying mangoes) has been published in the peer-reviewed literature [4]. Similarly, we found only one study published on bifenthrin exposure [5] and one with pest control operators (PCOs) to the pyrethroid cyfluthrin [6,7]. No studies on fungicide biomonitoring in professional turf applicators were found in the literature search.

Pesticide Exposure and Dose Prediction Modeling

The methods used to predict pesticide exposure or dose following occupational or environmental exposures depend largely on the intended use of the information. Models that have been developed to evaluate pesticide exposures for registration or re-registration purposes are generally based on worst-case scenarios and are designed to apply across all individuals.

Assumptions may include 100% absorption of a pesticide through skin and constant body weight and breathing rates for all individuals. These deterministic models do not typically allow for individual variation; are generally based on the estimation of exposure, not dose; are usually conducted under experimental, not observational settings; and are most often designed to present worst-case estimates of exposure.

Under experimental settings, deterministic pesticide dose prediction models have been developed for the purpose of assessing uptake of pesticides from contaminated turf and these models have been evaluated [8,9]. Estimates of potential bystander exposure to several herbicides have been made to establish re-entry intervals for product registration in Canada [10]. Although necessary for risk assessment and product registration, these types of models may only be useful for the semi-quantitative estimation of environmental exposure to pesticides in domestic settings. They do not allow for the individual prediction of dose, and do not account for multiple sources of exposure.

A number of predictive models have also been developed to estimate agricultural exposure to pesticides for registration purposes [11]. For example, the Pesticide Handlers Exposure Database provides exposure information for mixers, loaders, applicators, and flaggers, under a number of environmental, hygienic (protective clothing), and working conditions (type of spray equipment) [12]. This information can aid in the construction of prospective and historical exposures for individuals in epidemiologic studies, if appropriate information on glove use, protective clothing worn, and application procedures is collected over time. Biological validation studies using this database are important so that factors affecting total body dose can be evaluated [11]. This would allow for an evaluation of the assumptions used in exposure assessment and could provide estimates of the individual variation in dose relative to potential exposure. In the absence of this type of information, similar exposure groups can be defined but the relationship between potential exposure and dose is unknown, as is the variation in dose within these groups.

When the goal of pesticide dose prediction is for the improvement or evaluation of exposure assessment methods for epidemiologic research, the approach is somewhat different to that used for registration or risk assessment purposes. Instead of attempting to predict dose with the use of exposure information, individual dose is measured (or estimated) with the use of biological samples and information is collected to evaluate the factors that influence dose. One excellent example of this type of work is the validation studies underway for the Agricultural Health Study (AHS). The National Cancer Institute (NCI), the National Institute of Environmental Health Sciences (NIEHS), and the U.S. Environmental Protection Agency have initiated the AHS, which is being conducted in Iowa and North Carolina. As part of this large cohort study (75,000 adults), detailed monitoring of pesticide dose will be conducted on 200 families, and investigators will attempt to relate the internal

dose to pesticide application procedures and protective practises, and account for both direct and indirect exposures. The questionnaire information will also be supplemented with data from the Pesticide Handlers Exposure Database [13]. Other researchers at the University of Minnesota have conducted a comprehensive Farm Family Exposure Study to evaluate factors associated with exposure to 2,4-D, glyphosate, and chlorpyrifos and absorbed dose [14]. Reporting of results is underway.

In Canada, researchers at the University of Guelph and from Health Canada are conducting a farmer dose evaluation study of approximately 300 farm families. In this study, the internal dose of 2,4-D will be evaluated for the farm operator, the spouse, and one child in the family. Factors contributing to internal dose such as contamination of drinking water, drift of chemicals, and the use of personal protection devices will be evaluated [15].

A number of studies have been conducted to evaluate the exposure of professional turf applicators to pesticides, including the herbicides 2,4-D, MCPA (4-chloro-2-methylphenoxyacetic acid), Mecoprop (2-(4-chloro-2-methyl phenoxy) propionic acid) (MCPP), and Dicamba (3,6-dichloro-O-anisic acid), a benzoic acid compound [16-18]. In a large sample of 98 professional turf applicators from 20 companies in Southern Ontario, daily dose estimates of 2,4-D ranged from 0.004 to 19 mg/day with a geometric mean of 0.42 mg/day [16]. Doses of mecoprop were consistently higher and ranged from 0.006 to 23 mg/day with a geometric mean of 0.584 mg/day. Individuals who sprayed pesticides only had the highest average doses in the study and, contrary to current thinking, those who were involved in spraying and mixing had, on average, lower doses. Those who only mixed pesticides during the week of the exposure study had the lowest doses in the study. Based on job titles, applicators had the highest absorbed dose, followed by owners of the companies and managers. Again, current thinking would have predicted that owners receive the lowest doses. Since these workers were repeatedly exposed to varying amounts of pesticides, a method of dose estimation was developed to predict total weekly dose that would allow for different use patterns by each individual [19]. Further, since accuracy of dose estimates is dependent on the collection of 24-hour urine samples, both creatinine excretion and self-reported missed samples were used to evaluate collection completeness [20]. During a one week period, the volume of pesticide applied was weakly related to the total dose of 2,4-D absorbed (R^2=0.21) [16]. Two additional factors explained a large proportion of the variation in dose: the type of spray nozzle and the use of gloves. Job satisfaction and current smoking influenced the dose but were not highly predictive. In the final multiple regression models predicting total absorbed dose of 2,4-D and mecoprop, 63 to 68 percent of the variation was explained. Commonly used job titles and duties performed explained only 11 and 16 percent of the variation in dose, respectively [21]. The amount of pesticide sprayed over the work week was more predictive of dose than the use of job titles or tasks performed [21].

The future application of these Canadian models for epidemiologic research will depend on their external validity, availability of information and records from employers, the feasibility of contacting study subjects, and cost. Clearly, an external validation of this model for use in epidemiologic studies of professional turf applicators in the United States is desirable, given the lack of consensus concerning the carcinogenic and/or reproductive effects of many commonly used pesticides in the current epidemiologic literature, and the lack of studies on the chronic hazards associated with exposure to some of the newer replacement compounds.

Measurement Issues in Epidemiologic Studies

An overview of current methods of pesticide exposure assessment and measurement error issues is provided in a companion chapter (Harris, 2005) in this Series. In occupational epidemiologic studies of pesticide exposures it has generally been assumed that industrial usage records serve as a surrogate estimate of pesticide exposure and total body dose is assumed to increase as the amount used increases. However, in the absence of adequate records of pesticide use, job titles and length of employment data have been used as proxies of exposure, but these do not result in quantitative estimates of dose [2].

Previous work demonstrates that in professional turf applicators an estimate of dose based on pesticide use records will result in a substantial exposure misclassification [16,17,21]. Therefore, estimating use based on pesticide purchase (as proposed in the NCI cohort study), may result in even greater misclassification of exposure. If absorbed dose estimates are based on pesticide use data (a proxy for exposure) for epidemiologic studies, the sample size necessary to detect a significant health effect would be close to six times higher than if the perfectly measured dose was used [16]. If the recent research on the relationship between pesticide use and resulting dose is generalizable to professional turf applicators as a whole, this presents serious implications for the effectiveness of current studies to detect any statistically significant association between pesticide exposure and adverse health effects.

Objectives

The primary objective of this study was to obtain repeated measurement of pesticide exposures within individuals over time, to evaluate the factors associated with absorbed dose, and to validate previously developed dose prediction models in a national sample of TruGreen Chemlawn workers. The design, execution, and proposed statistical models are described.

Methods and Materials

The graphical representation of the study design is presented in Figure 1. The pilot study, conducted in 2002, was designed to obtain repeated 12- or 24-hour urine samples from 10 individuals over a 5-day period in the summer and over a two week period in the fall. These periods were timed to coincide with the heaviest spraying of insecticides (bifenthrin, imidacloprid) and herbicides (MCPA, mecoprop, and dicamba) at the Richmond, Virginia branch. The comprehensive evaluation of the urinary excretion of these pesticides was designed to obtain information on the toxicodynamics and toxicokinetics of these pesticides in humans following repeated exposures.

Following a verbal presentation to the Richmond branch, recruitment of volunteers was much greater than expected and requests for the tree and shrub applicators to participate were received. Thus, the study was expanded to include these employees in addition to the turf applicators. A total of 22 workers signed informed consent to participate and complete samples (19 days of 24 hours urine samples) were obtained from 12 individuals. Subjects were paid $10 a sample, for a total of $190 if they completed the entire study.

Development of Worker Exposure Questionnaire

A previously developed questionnaire was revised to include information relevant to insecticide use and exposure for pilot testing in 2003. It was designed to measure all known variables that could potentially increase or decrease pesticide exposure in relation to the amount handled, with a focus on dermal absorption. Potential factors include: age/sex; smoker/non smoker; length of training; licensed/non-licensed; number of years employed/licensed; pesticide formulation (granular vs. liquid); type of spray equipment used (i.e. injection, high or low pressure nozzles); mixing/filling duties; protective equipment worn (gloves, overalls, rubber boots, etc.); occurrence of spills during mixing, application, etc.; frequency of uniform laundering; and personal hygiene (washing prior to lunch, etc.). Based on some of the previous work by Slovic and others [22-24], questions on risk and risk/benefit perceptions were developed and questions to elicit self-reported exposures were formulated. The revised questionnaire was tested in the group of 22 workers from the Richmond, VA branch in the summer and this resulted in minor changes in question numbering and skip patterns. The questionnaire was revised and given each Friday (i.e. 2 more times for each volunteer) during the fall herbicide monitoring study.

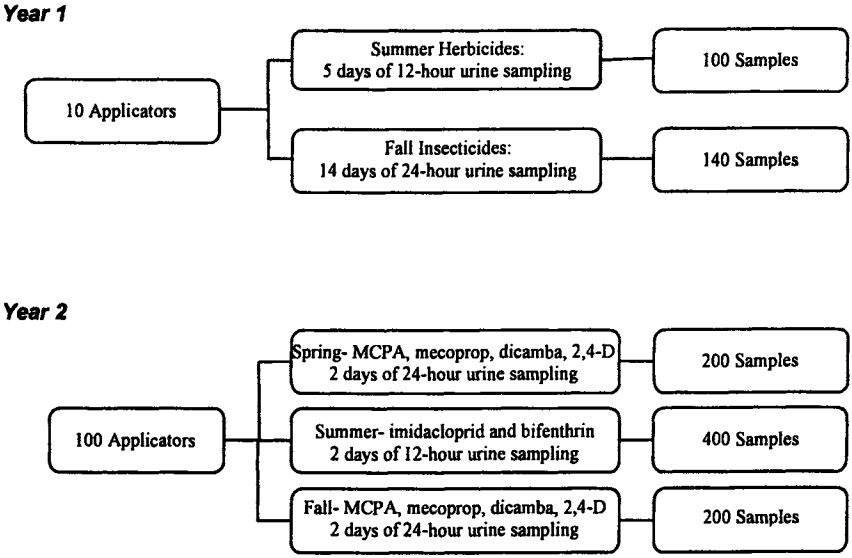

Figure 1. TruGreen Chemlawn Dose Monitoring Study Design

National Study

Branch Selection

Due to the seasonal and often short-term nature of employment in the lawn care business, initial contact with subjects in 2004 was through five TruGreen Chemlawn branches. For the National Study, we planned to sample five branches and/or franchises to reflect national differences in pesticide programs and timing of applications. The 5 geographic locations chosen for National Study were: 1) Northeast; 2) Southeast; 3) Northwest; 4) Southwest; and 5) Central.

To participate in the National Study, all locations were required to use both insecticides and herbicides and needed to be of sufficient size to obtain a total sample size of 100 employees (i.e. approximately 20 employees per branch). Logistically, we needed to select sites so that our sampling season was as long as possible (April to November, 2004) and that the fieldwork could be conducted with a small number of staff. Further, direct or 1-stop flights from Richmond/ Dulles/ Williamsburg area were preferred. Pesticide use data (all pesticide products and monthly use for all locations in the US and Canada) was provided by the TruGreen Chemlawn corporate office. After careful

consideration of each branch's pesticide use patterns, particularly the use of both insecticides and herbicides throughout the year, location, and length and intensity of each insecticide and herbicide spray season, a list of 17 branches representing six of the company's eight regions was presented by study personnel to TruGreen Chemlawn corporate management (see Figure 2). After consideration of the number of employees at each branch and the potential level of cooperation of each branch, 5 TruGreen Chemlawn branches were selected by TruGreen Chemlawn corporate managers for inclusion in the study: Sterling, Virginia (D.C. West); Plano, Texas; Puyallup, Washington; Plainfield, Illinois; and Salt Lake City, Utah.

Subjects and recruitment

Following final approval of study locations, individual branch and operations managers (generally two to four at each location) were contacted and group meetings with applicators were arranged for the spring sampling period (see Figure 1). Potential participants were given both oral and written information on study background, aims, and procedures, and the 113 employees from the five locations willing to participate provided signed consent. General inclusion criteria included being at least 18 years of age and having potential contact with pesticides as part of the employee's job description. At two study locations, however, the inclusion criteria were modified at the request of the branch operations managers. In Puyallup, Washington, employees in training were not entered into the study, and Plainfield, Illinois, only herbicide applicators were enrolled. Subjects included both licensed and non-licensed pesticide applicators and were remunerated with $20 per sampling week ($60 total for completion of all 3 seasons) for their contribution to the study. In addition, each subject was allowed to keep the soft-sided cooler bag and ice packs used during sample collection to keep urine samples cold.

A summary of the volunteer enrolment and retention is presented in Table I. Volunteers were actively recruited in the spring and summer (new hires). We were able to visit all national sites three times, except for Plainfield, IL, where logistics prevented a third visit. Retention of study subjects was excellent and dropout was primarily due to layoff or termination of employment.

Sample Collection and Analysis

For the nationwide study, urine samples were collected during three different spraying seasons: the spring (April and May) and fall (October and November) herbicide sprays and summer insecticide spray (June and July). Each study participant was provided with one 3 L urine collection container (Simport

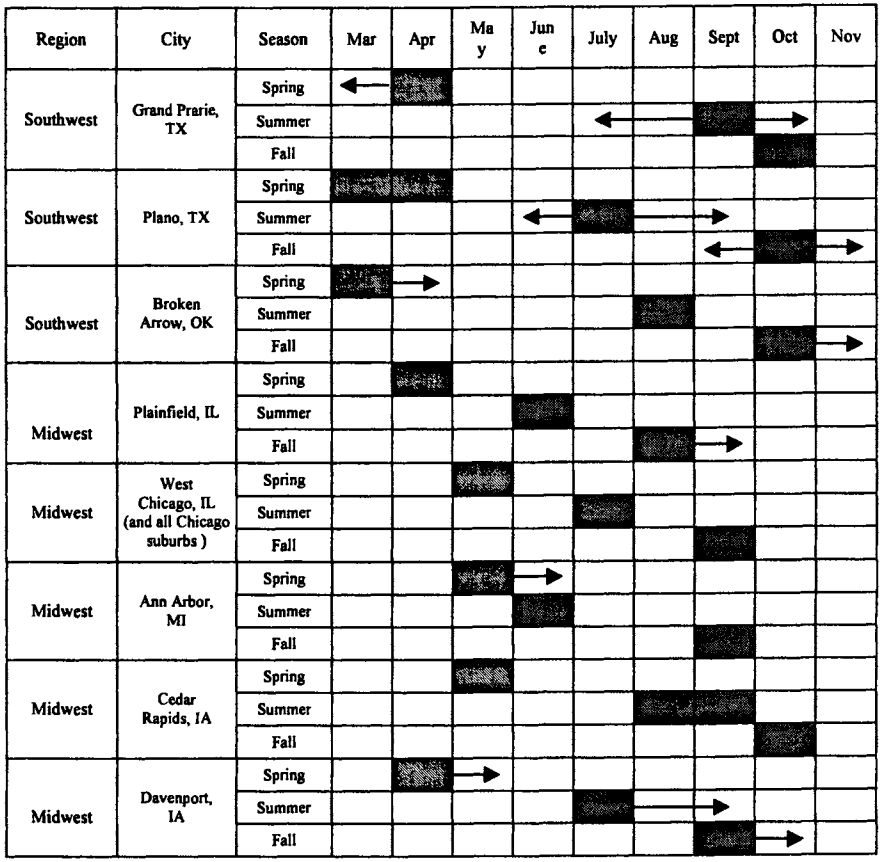

Figure 2. Optimal months (2003) for biological sample collection in select US cites in the Southwest and Midwest. Arrows indicate semi-optimal months.

Plastics Limited, Fisher catalogue number 14-J75-116) for each collection interval, a soft-sided cooler bag, and 2 frozen ice packs. Total urine output was collected for two consecutive 24-hour periods (herbicide) or four consecutive 12- hour periods (insecticide) following a minimum of 3 consecutive workdays. Subjects were asked to store all samples in their cooler bag with ice packs or in the refrigerator when possible during each collection period, and study personnel retrieved and processed samples at the end of each 24-hour interval. Upon collection, samples were visually observed for any inconsistencies in appearance or volume, total sample volume was recorded, and specific gravity was measured using the Leica AR200 digital hand-held refractrometer (Leica catalogue number 13950000). Each sample was divided into three 40 mL

aliquots (in 50 mL Corning graduated plastic tubes, Corning catalogue number 430828) and two 100 mL aliquots (in 125 mL Nalgene rectangular HDPE bottles, Nalgene catalogue number 2007-0004), packaged in accordance with Federal dangerous goods shipment guidelines, and overnight shipped in insulated diagnostic shippers (Saf-T-Pak item STP-320) with frozen ice packs and ice blankets to Virginia Commonwealth University. Upon arrival, samples were immediately frozen and were stored at -20° C until analysis.

To evaluate completeness of urine collection, one 40 mL aliquot from all 24-hour urine samples was analyzed for creatinine content by Scientific Testing Laboratories (Richmond, Virginia). If necessary, urine volumes will be corrected for self-reported missed sample collection [20]. Urine samples are currently undergoing analysis for MCPA, mecoprop, bifenthrin metabolites, imidacloprid metabolites, dicamba, and 2,4-D using solid-phase extraction followed by positive/negative ion electrospray ionization HPLC/MS/MS; a method developed as part of the project in the Chemical Response and Terrorism Preparedness Laboratory at the Virginia Department of Consolidated Laboratory Services (Richmond, Virginia). This method is capable of quantifying levels of all analytes to 1 part per billion (1.0 μg/L) [25]. Although the study was originally designed to evaluate herbicides and insecticides separately (i.e. a focus on herbicides in the spring and fall and insecticides in the summer, see Figure 1) the development of a method to simultaneously measure all analytes will provide much more useful data on individual variability.

Information Obtained from Employers

Daily pesticide use records (volume used and area sprayed) for each subject in the pilot and national studies have been obtained from the operations

Table I: Summary of Nationwide Study Subject Enrolment

City	*Subjects Enrolled*	*Spring Completed/ Enrolled*	*Summer Completed/ Enrolled*	*Fall Completed/ Enrolled*
Sterling, VA	33	28/31	19/31	22/33
Plano, TX	14	14/14	14/14	14/14
Puyallup, WA	19	13/13	17/17	11/19
Salt Lake City, UT	27	22/22	19/27	15/27
Plainfield, IL	20	20/20	15/20	N/A
Total	113	97/100	84/109	62/93

managers at each location. These records will be used to compare with self-reported employee exposures and as a gold standard for estimating dose with the urinary concentration data.

Discussion

Given the lack of consensus concerning the carcinogenic effects of 2,4-D and other pesticides, the lack of absorbed dose information for some of the pyrethroids, and the more recently introduced insecticide (imidacloprid) in the current epidemiologic and toxicologic literature, professional turf applicators are an important cohort of workers for future epidemiologic studies. Their exposures will likely exhibit the substantial variation necessary to establish dose-response relationships. Moreover, their exposures to other biological factors, chemicals, and other pesticides, which could confound relationships, will generally be less than that of other occupational groups, such as farmers.

The results of this study will help to refine pesticide dose prediction for both epidemiology and risk assessment. The design of the study, to include repeated measurements in individuals over time, will allow for the evaluation of variability in exposures over time, for individuals and different pesticides. This work is unique. Moreover, pesticide exposure prediction models can be developed and tailored specifically as the available information permits. For example, if it is impossible to contact individual employees in a retrospective study, an exposure prediction model that includes information available from employers such as number of training days, size of business, number and gender of employees, along with individual or group pesticide use records would be more predictive of individual/group exposures than a model containing measurement of pesticide use alone. If however, it is possible to contact individual employees, the accuracy of prediction of individual exposure is likely to be increased through the ability to add a few more important predictor variables.

Future dose prediction model efforts ultimately depend on the proposed use of the model but currently include the development of a statistical model that:

1) Predicts total weekly dose and may include any of the explanatory variables that have been evaluated in this study. This model will be most useful for long-term monitoring in the industry and determining effective abatement strategies.
2) Will be restricted to allow only the inclusion of predictor variables on which information can be collected from contact with the employers and access to their records. This model will be most useful in longer-term or short-term retrospective studies in which it is not possible to contact individual subjects or the validity or reliability of the information collected from the subjects is questionable.

3) Will be restricted to allow only the inclusion of explanatory variables on which information can be collected from contact with the employers, access to their records, and contact with the individual subjects, while considering the logistics of collecting the information

A comparison of models 2 and 3 with model 1 will allow for the evaluation of the potential misclassification of exposure (differential and non differential) when it is not possible to collect all the information that will be obtained in the current study as reported in this chapter. In addition, models 2 and 3 may be directly applied to estimate dose in a prospective or retrospective epidemiologic study with the added benefit of some understanding of exposure misclassification. This allows for an upward adjustment of sample size in the design phase of any future proposed studies or a calculation of the potential bias of risk estimates in current studies. Although we will base our models (1, 2 or 3) on estimation of weekly dose of individual applicators, we believe that the model(s) can be adjusted to estimate seasonal and lifetime dose, which will be more useful for the evaluation of chronic health effects associated with pesticides exposures.

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