

Implications for epidemiologic research on variation by pesticide in studies of farmers and their families

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Epidemiologic studies rely on participants' recall to classify their exposure to specific pesticides. As exposure classification evolves, an important issue is whether the recall of pesticide application details can be used to derive measures of exposure intensity or cumulative exposure. A preliminary analysis of biomonitoring data for farmers before, during, and after a pesticide application suggests variation for different pesticides in the proportion with detectable urinary concentrations, urinary levels, and patterns of uptake and elimination. These findings, and the limited predictive modeling done to date, suggest that chemical-specific differences need to be considered in exposure classification schemes. An analysis of biomonitoring data for farm spouses and children found few with appreciable changes in the urinary concentration after a pesticide application. These findings point to the need to validate assumptions about exposures in studies of people who are not directly involved in pesticide application.

Key terms 2,4-dichlorophenoxyacetic acid; chlorpyrifos; commentary; epidemiologic study; exposure assessment; farmer; glyphosate.

The estimation of historical exposure, though difficult, is necessary for epidemiologic studies of pesticides and cancer (1). While researchers rely primarily on participants' recollections of past pesticide use, questions have been raised about the accuracy of pesticide recall over the extended time periods needed for cancer development, especially for data collected from cancer cases or the next-of-kin in case-control studies (2). Some methodological work has been done to assess the accuracy of pesticide recall, but the existing data are equivocal (3, 4). Nonetheless, Blair & Zahm (5) have argued persuasively that farmers are uniquely qualified to recall their use of specific pesticides.

A complementary issue is the accuracy of metrics that have been developed to estimate exposure intensity or cumulative exposure (6). This is a more difficult issue because research suggests substantial variation in exposure, even for applicators doing similar applications (7). As a current practice, researchers ask study participants to recall the number of days they applied specific pesticides, the application equipment they used, typical

personal protective equipment use, the number of acres they farm, and typical personal hygiene practices. This information is then used to develop semi-quantitative exposure metrics.

In a recent paper, Dosemeci et al (8) proposed two algorithms to combine subjects' recollections of work practices with generic exposure monitoring information from the literature and from the Pesticide Handlers Exposure Database (PHED) (9). It remains to be determined whether self-reported work practices can be validated over extended time periods and whether these and other semi-quantitative approaches to exposure assessment correlate with objective measures of internal dose.

Epidemiologic studies have also begun to focus on those who have a potential for indirect exposure, for example, farm spouses and children not involved in pesticide application (10), residents in homes or buildings where pesticides may have been applied (11), and residents who live within certain distances of documented pesticide applications (12). Little is known about exposure misclassification under these circumstances.

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Two farm family pesticide biomonitoring studies were reported recently. The investigators measured urinary concentrations of specific pesticides for farmers and their families before, during, and after a pesticide application (13, 14). The results from these studies

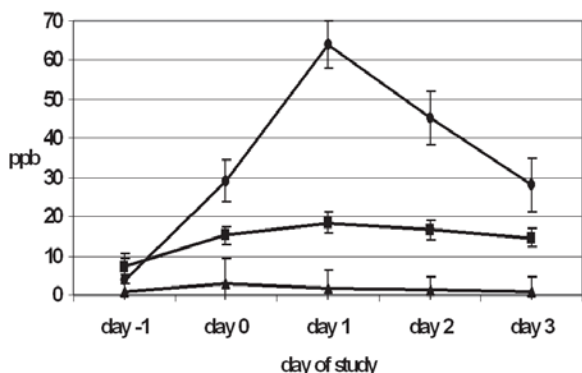


Figure 1. Geometric means and standard deviations for farmers' urinary pesticide concentrations during the Farm Family Exposure Study (13). [—○— = glyphosate, —■— = TCP (3,5,6-trichloro-2-pyridinol), —●— = 2,4-D (2,4-dichlorophenoxyacetic acid)]

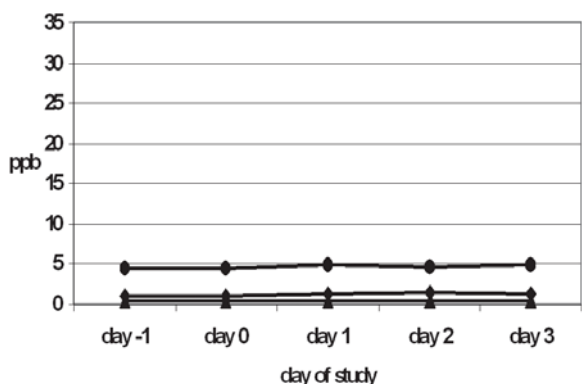


Figure 2. Geometric means for spouses' urinary pesticide concentrations during the Farm Family Exposure Study (13). [—○— = glyphosate, —■— = TCP (3,5,6-trichloro-2-pyridinol), —●— = 2,4-D (2,4-dichlorophenoxyacetic acid)]

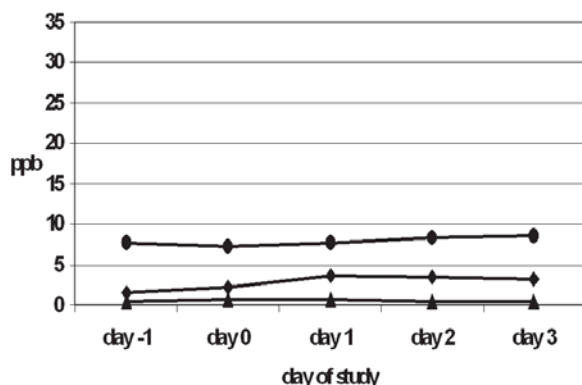


Figure 3. Geometric means for children's urinary pesticide concentrations during the Farm Family Exposure Study (13). (—○— = glyphosate, —■— = TCP (3,5,6-trichloro-2-pyridinol), —●— = 2,4-D (2,4-dichlorophenoxyacetic acid)]

will provide insights into the determinants of internal dose for those directly involved in pesticide application and for their uninvolved family members. The data for farm spouses and children provide some perspective on residential and environmental exposure scenarios (11, 12) of interest to epidemiologists. In this paper, we have analyzed biomonitoring data from one of these studies (13) to illustrate patterns that may be important for exposure assessment in epidemiologic studies.

Variation by pesticide

Mandel and his colleagues (13) collected data for the following three pesticides with different physical and chemical properties: glyphosate, 2,4-dichlorophenoxyacetic acid (2,4-D), and chlorpyrifos. The numbers of farmers, spouses, and children by chemical were 48, 48, and 79, respectively, for glyphosate; 34, 34, and 53, respectively, for 2,4-D; and 34, 34, and 50, respectively, for chlorpyrifos. These three pesticides are excreted predominantly in urine; glyphosate and 2,4-D are excreted unchanged; and chlorpyrifos is excreted primarily as the 3,5,6-trichloro-2-pyridinol (TCP) metabolite. All of the analyses had a 1 part per billion (ppb) limit of detection (LOD).

The results showed appreciable variation by chemical in the proportion of farm family members with detectable urinary concentrations, especially for spouses and children (13). On a quantitative basis, variation by chemical was more substantial for farmers (figures 1–3). This variation is not explained by differences in application method (groundboom was the predominant method), use of chemical-resistant gloves (similar across chemicals), the number of acres treated (48% of glyphosate applications were 100 acres (40.47 ha) or more versus 21% for 2,4-D and 6% for chlorpyrifos), or the application rate (fairly similar for the three chemicals). It is likely, therefore, that the observed differences reflect physical chemical properties of the three pesticides, although other factors remain to be evaluated.

The variation for farmers was also manifest in patterns of uptake and elimination (figure 1). The geometric mean levels of glyphosate peaked at 3 ppb [geometric standard deviation (GSD) 6.4] on the day of application and decreased rapidly, while the 2,4-D and TCP levels peaked the day after the application, at 64 (GSD 6.0) and 19 (GSD 2.8) ppb, respectively, and declined over longer periods of time. This finding suggests the need to consider different pesticide exposure profiles in epidemiologic research.

A characteristic of the exposure distributions for farmers was a marked skew to the right. The range was greatest for 2,4-D and smallest for glyphosate. For TCP, and especially for glyphosate, most of the values were near the LOD.

In contrast to the findings for farmers, there was relatively little quantitative difference by chemical for the farm spouses and children (figures 2 and 3). Although detectable values were rare for glyphosate and much more common for 2,4-D and TCP (13), the urinary concentrations for 2,4-D and TCP were close to the LOD. In addition, the urinary concentrations did not change appreciably after pesticide application for most of the spouses and children. Exceptions tended to be family members who participated in the pesticide application or had potential dermal contact with the pesticide in the mixing area or fields. The fact that pesticide levels did not generally increase for farm residents other than the applicator suggests the need to validate exposure assumptions in studies of persons with so-called indirect pesticide exposure (11, 12).

For TCP, general population values have been reported for adults and children (15, 16) in studies with an LOD of 1 ppb. These findings were fairly similar to those for the farm spouses and children (13) in terms of the percentage with detectable concentrations (82% versus 97% for adults and 93% versus 100% for children) and average values (arithmetic means for spouses 4.5 versus 6.5 ppb; geometric means for children 6.4 versus 7.6 ppb). These findings suggest that there can be overlap in the exposure distributions for urban and farm residents, even in the period immediately after farm pesticide applications. Whether this situation will continue to be the case for TCP as residential uses are phased out, or hold for other pesticides, remains to be determined.

Exposure misclassification

Biomonitoring studies provide an estimate of the proportion of applicators that shows detectable pesticide levels for the specific application scenarios studied. Arbuckle et al (14) reported that 79% of those who used 2,4-D and 84% of those who applied 4-chloro-2-methylphenoxyacetic acid (MCPA) had urinary levels equal

to or exceeding their LOD of 1 ppb. Mandel et al (13) found that 60% of glyphosate applicators had detectable urinary levels, with corresponding proportions of 100% for 2,4-D and TCP.

Since biomonitoring data are sometimes used to evaluate the accuracy of questionnaire responses about pesticide use, it bears some emphasis that the proportion of applicators with exposure confirmed through biomonitoring is a function of the LOD. Given a low enough LOD, 100% of farmer applicators would be expected to show detectable values for any chemical. The LOD, however, is usually not based on the inherent toxicity of a pesticide. Therefore, while the proportion of farmers or family members with detectable exposure is of some interest, it is much more important to develop methods to estimate the proportion that has biologically relevant exposures (17). That type of exposure assessment requires integrating exposure estimates and knowledge of the inherent toxicity of specific pesticides.

Biomonitoring studies can be designed to estimate systemic pesticide dose in milligrams per kilogram of body weight. Systemic dose provides a basis for comparing human exposures with available toxicologic data. In addition, systemic dose provides a better indicator of pesticide dose than urinary concentration, which is a function of the amount of pesticide excreted and urinary volume. Using data for glyphosate (13), we calculated systemic doses based on each farmer's urinary concentrations, urinary volumes, excretion rate, and body weight. Our method is summarized in the appendix. We have plotted these values in a cumulative probability plot in figure 4.

The glyphosate systemic doses ranged up to 10^{-3} mg/kg. This range can be compared to the United States regulatory reference dose of 2 mg/kg a day for glyphosate or to other available toxicologic information about this chemical (18). Comparison of the range of systemic doses with levels of toxicologic significance can provide a basis for both exposure categorization and a weight-of-evidence evaluation of epidemiologic findings (17).

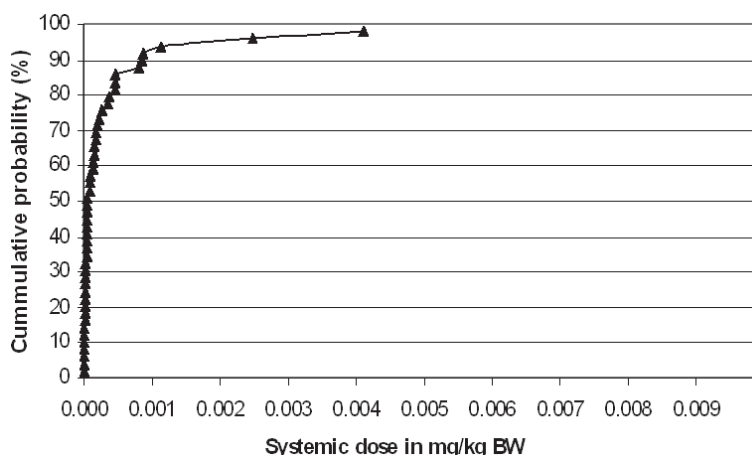


Figure 4. Cumulative probability distribution of farmers' glyphosate systemic doses. (—▲— glyphosate, BW = body weight).

Predictors of exposure

A goal of many biomonitoring studies is to identify important predictors of pesticide dose. In a recent publication, Arbuckle et al (14) fit models that accounted for 44% of the variation in urinary values for the phenoxy herbicide MCPA and 39% of the variation for the phenoxy herbicide 2,4-D. However, there was little overlap in predictors for the two herbicides, and the one common predictor, spray tank volume, had a negative relationship with MCPA urinary concentration and a positive relationship with 2,4-D urinary concentration. Also, for MCPA, the type of pesticide formulation was found to be an important predictor of urinary concentration. This finding was not unexpected since chemical properties of pesticide formulations (especially dermal penetration), along with the number of acres treated, the application rate (pounds/acre), and the use of chemical-resistant gloves, have proved to be important predictors of exposure (17). The fact that two closely related phenoxy herbicides had different predictors suggests the need to validate generic exposure algorithms with chemicals that have a range of physical and chemical properties.

Concluding remarks

It is widely accepted that biomonitoring studies, under appropriate circumstances, provide the best estimate of pesticide dose in relation to specific pesticide application scenarios (19). Our analysis of data from one multichemical biomonitoring study of farm families shows substantial variation in urinary pesticide concentrations by chemical. This variation was more pronounced on a qualitative basis for spouses and children not involved in pesticide application and more pronounced on a quantitative basis for farmers (13).

Biomonitoring studies can be designed to estimate systemic dose. This measure accounts for differences by chemical in uptake and excretion, enables comparison with levels of toxicologic significance, and should reduce the variability in predictive modeling that results from the limitations of urinary concentration as a quantitative indicator of pesticide dose. Available data suggest that chemical-specific differences may be an important consideration for exposure estimation in epidemiologic studies and, particularly, in the development of exposure categorizations that have biological significance.

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Appendix

Calculation of systemic dose for glyphosate

We multiplied the urinary concentration of glyphosate in each day's 24-hour composite urine sample, corrected for field and laboratory recovery, by the daily urine weight to yield the micrograms excreted on the day of application and for 3 days thereafter (days 0–3). For modeling purposes, we took the sum of the micrograms excreted for days 0–3 (S_0) to be the amount of glyphosate available for excretion at the start of day 0. Likewise, the amounts to be excreted on days 1–3 were taken to be S_0 minus the amount excreted prior to that day. We estimated each person's excretion rate (k) on the basis of an open single-compartment pharmacokinetic model as the slope of the regression line of the loga-

rithm of the daily residual amounts versus time (over days 0–3), multiplied by 2.303. The fraction that remained to be excreted after day 3 was then estimated for each person from the equation $F=e^{-kt}$, where k is the person's excretion rate and t is 4 days. S_0 divided by $(1-F)$ estimates glyphosate excretion (S_1) had we collected urine until all of a person's systemically available glyphosate had been excreted. We then divided S_1 by 95%—the percentage of pharmacokinetic recovery from animal studies—to estimate the amount of glyphosate that should have been recovered in urine with complete recovery (S_2). S_2 divided by a person's body weight equals the systemic dose.