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Assessing pesticide and nonpesticide exposures in agricultural settings is a daunting task. This is especially the case when such assessments are undertaken as a component of health studies to evaluate cancer risk. In this review, key exposure assessment issues are outlined and discussed in the context of pesticide-specific health risk assessments and three recent studies of large, geographically defined farmer and farm family populations. The specific topics addressed include the assessment of cumulative exposures to both older and more recently registered pesticides, the role of biomarker studies in exposure assessment, and uses of data on nonroutine high-exposure events.

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In agricultural settings, exposure assessment activities can be undertaken as support of regulatory decision making (eg, to register or not register a pesticide for a particular application) and as a component of observational health studies. Health risk assessments are typically performed under the auspices of government agencies and incorporate conservative default assumptions in the absence of more definitive data. In assessments undertaken by the Office of Pesticide Programs (OPP) of the United States (US) Environmental Protection Agency (EPA), for example, OPP acknowledges that combined point estimates "will overstate, sometimes significantly, the potential exposure that the vast majority of the general population group actually receives" (US Environmental Protection Agency Office of Pesticide Programs. General principles for performing aggregate exposure and risk assessments. Federal Register notice of 28 November 2001. Available from: URL: http://www.epa.gov/pesticides/trac/science/aggregate.pdf). The implied intent is to err on the side of protecting public health; that is, in a risk assessment context, overestimation of exposure is inherently of less concern than underestimation, as it would result in an overstatement rather than understatement of health risks. Nevertheless, if an initial assessment were to suggest that particular pesticide uses pose unacceptable risks, registrants could develop additional exposure data to improve the precision of aggregate exposure estimates and, hence, that of the risk assessment as well.

Observational health studies are typically initiated to provide evidence concerning factors that influence the risk of disease. In the context of such a study, the overestimation of exposure is to be avoided as it could lead to an understatement of health risks at a given exposure concentration. In addition, having at least an accurate ordering of study subjects by increasing dose category is the key to carrying out a meaningful dose-response analysis. In this respect, there is incentive to categorize relative exposures as accurately as possible since misclassification, even if nondifferential, may distort or dampen disease associations when there is a real underlying relationship between exposure and outcome. Having reliable exposure estimates can also be helpful when biological plausibility is being judged. Thus, in epidemiologic studies, there is good reason to assess relative and absolute exposure as accurately as possible, whereas, in risk assessment applications, underestimation is of greater concern than the overestimation of likely exposure.

Potential roles of biomarker studies in risk assessment

Two reports chose to focus on biological monitoring as a means of assessing or validating exposure in a risk assessment context. The study by Lunchick et al (1) tested

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an existing EPA risk assessment for applications of a nematocide to potato fields by comparing predicted EPA dose estimates with those derived from a urinary biomarker study of 23 applicators. The geometric mean dose calculated from the field study was 20 to 40 times lower than the range of predicted EPA estimates. Nevertheless, individual estimates for several applicators were close to or within the range of the dose predicted by the EPA. Equipment maintenance and inappropriate work practices were identified as contributing to the higher readings for these applicators. The findings of this study are informative in several respects. First, they call attention to tasks with a higher potential for exposure. Second, they provide additional data for performing probabilistic exposure assessments and determining appropriate restrictions on pesticide use.

The other report, by Fenske (2), covered a variety of exposure assessment tools, including fluorescent tracer techniques for assessing dermal exposures (3, 4). Practical uses of these techniques were described, and it was shown that tracer measurements of dermal exposure to malathion during mixing and spray applications correlated well with levels of metabolite excretion in urine (5). In this example, biological monitoring served to validate an environmental measurement procedure as a marker of internal dose. Additional examples included the use of biological monitoring to assess children's exposure to agricultural pesticides from multiple sources and through multiple pathways (6–8). In one example, global positioning system (GPS) and geographic information system (GIS) tools were used to track the activities of children in relation to biomarker results (2). An immediate advantage of biomarker studies is that the findings can be used to evaluate the effectiveness of existing control strategies and also as a basis for proposing new ones. It is not yet evident how best to incorporate biological monitoring into exposure assessments used in health studies of diverse farm populations. However, a clearer picture of exposure patterns for agricultural pesticides is emerging with the accrual of additional targeted and background biological monitoring data.

Exposure assessment considerations in observational health studies

A highly disciplined approach is needed when exposure assessments are planned and conducted in complex work settings, as exemplified by the assessments supporting three agricultural health studies (9–11). The key assessment steps are identifying and prioritizing the agents to be studied in the targeted workplaces, characterizing how and when exposures occur, assessing the heterogeneity of exposure across jobs and work settings, selecting appropriate measures or indices of exposure to specific agents, and obtaining data that enable participants to be assigned qualitative or quantitative values for each measure. The selection of suspect agents is particularly important. In chemical production settings, agents of interest can include raw materials, chemical intermediates, final products, and unwanted, possibly more toxic, by-products. The number of candidate agents in a large manufacturing complex can run into the hundreds, and their presence may have changed greatly over the time periods of interest. In such environments, a structured approach to exposure assessment is required, whereby relevant agents or exposure scenarios are targeted with the toxicologic hazard, the likelihood of meaningful exposure, and the potential for correlated exposure to multiple agents as the bases.

An agricultural job-exposure matrix developed for all of British Columbia (BC) appears to have been particularly well conceived along these lines (9). First, the matrix covered a 50-year period. Over that period, BC farmers were reported to have had contact with 290 agents, of which approximately 180 were active pesticide ingredients. These lists were compiled from consultations with local farm experts and through referencing growers' production guides published over the past 90 years by the BC Ministry of Agriculture and Food. Although some 240 active ingredients were available to BC farmers in 1995, the top 10 accounted for 56% of the pesticides sold that year. In the United States, approximately 900 active ingredients and more than 20 000 pesticide products were registered for use in 1996 (12). The BC matrix incorporated data on exposure agent, time period, and type of work (a combination of region, crop, job title, and task). The prevalence, frequency, and intensity of exposure, as well as the hazard level, were assessed for each agent using expert judgment and task-specific exposure data from sources such as the Pesticide Handlers Exposure Database (PHED). This matrix is being utilized in support of several cancer case-control studies of BC residents. What sets the assessment apart is the attention to historical descriptions of farming practices that should enable subsequent investigation of a variety of exposure scenarios that would be lost with a one-dimensional agent-by-agent approach.

The characterization of exposures can be determined from personal or proxy interviews, hard copy records, and expert judgment. Personal interviews conducted concurrent with exposure are undoubtedly superior to retrospective interviews conducted years later and after illness events. The approach followed by Dosemeci and his colleagues (11) in the Agricultural Health Study in the United States combines questionnaire data on exposure scenarios with expert judgment and the PHED, plus other published data, to estimate intensity scores for individual pesticides. This study is prospective in design so that, with each new questionnaire cycle, additional exposure-related information is being collected. A particular advantage of the approach over previous case–control studies is that the exposure information is being gathered prior to the occurrence of the cancer outcomes being studied. Questionnaires were administered beginning in 1994 and included questions about current work practices and those of 10 years prior. As acknowledged by the authors, information related to the estimation of exposure intensity, such as personal protective equipment (PPE) use and application techniques, was collected generically and not for each specific pesticide. This approach could result in an artificial correlation between intensity scores for different pesticides. Estimates of mean intensity level, as derived from the exposure algorithms, appear to be rather constant across farmer age groups (11). This is somewhat surprising in that a recent survey of PPE use among California farmers showed "better" pesticide protection practices among younger than older farmers (13). The reasons for the differences in the results between these two surveys are not clear.

Indices of exposure should be appropriate for the targeted health outcomes and likely modes of action, if known. Cumulative dose (duration times average intensity of exposure) during relevant time windows is a typical choice of exposure metric in cancer studies. While in many occupational settings duration of exposure can be determined directly from employment records, estimating exposure duration in agricultural settings is complicated by the intermittent nature of applications, and intensity levels may vary greatly according to task as well.

Assessing average exposure intensity requires judgment preferably supplemented by modeling and direct measurement data. The main strategies for estimating exposure intensity are (i) expert judgment, (ii) predictive modeling from usage or emission data, (iii) direct measurement in environmental media and via personal sampling, and (iv) dose reconstruction through the use of biomarkers.

The exposure assessment for the Ontario Farm Family Health Study, a reproductive health study of approximately 2000 farm families, included questionnaires on pesticide use and handling practices, as well as on the biological monitoring of a 6% sample of farmer applicators during their first seasonal application of two sentinel herbicides (10). One objective was to identify factors, such as work practices, that might be predictive of higher or lower urinary excretion levels of two targeted phenoxy herbicides. It was thought that, if the predictive factors were sufficiently similar, a single algorithm could be developed for estimating exposures based on questionnaire responses. The factor weightings differed sufficiently, however, for the two herbicides so as to question the robustness of the models and even the reliance on pesticide use indicators as proxy measures for dose. Nonetheless, aside from the limited success of the modeling effort, this study provided well-documented data on the range of herbicide exposures experienced by Ontario farmers during application days.

In general, biological monitoring studies offer the advantage of integrating aggregate pesticide intake across multiple exposure routes and safety measures. Temporal and toxicokinetic considerations may limit their use in retrospective dose reconstruction depending on retention rates of urinary metabolites or macromolecular adducts. Nevertheless, in a study of pesticide manufacturing operations, we were able to estimate clearance rates for the compound of interest by collecting multiple urine samples after the end of a shift and to estimate daily intake while accounting for several factors influencing the differential clearance of the compound (14). These results were helpful in assessments of exposures by job category for use in clinical studies and for making recommendations for further exposure reduction measures.

Pearce and his colleagues have discussed several limitations in the use of biomarkers in cancer epidemiology (15). Apart from temporal difficulties in estimating historical exposure, single chemical biomarkers may not adequately reflect exposure to a complex mixture of substances. For example, alkyl phosphate metabolites may at least partly represent direct exposure to the less toxic alkyl phosphates formed as degradation products in animals, crops, water, and the general environment rather than to the organophosphate pesticides for which they are intended to be a biological marker (16). When recognized in advance, such issues can often be addressed at the design stage of an investigation by combining the use of traditional and newer biomarker approaches to exposure assessment.

Correlated exposures and nonroutine, high-exposure events

Two additional exposure-related considerations are worth specific mention in the context of agricultural health studies. The first relates to the development of cumulative exposure indices to multiple pesticides, particularly in reference to evaluations of cancer occurrences. Because cancer is predominantly a disease of older persons, it is likely that cases will have occurred among people with many years of farming. In addition to the estimated 900 active ingredients registered in 1996, there may have been potential exposure to many active compounds no longer on the market. Long-term farmers would be expected to have utilized both the older and more recent products as they became available. In studies such as the Agricultural Health Study, this use is apt to result in correlated exposure indices among various pesticides for individual farmers, and hence in difficulty to ascribe the effects to specific agents or combinations of agents. The degree of correlation could also be affected by reliance on common "intensity-related" factors, such as application technique, PPE use, and personal hygiene, that were not collected specific to individual products (11). Since pesticide usage information is generally less complete or less reliably known for past years (eg, prior to the 1970s), this lack could even lead to hidden confounding or misspecification of putative agents. One approach to coping with complex exposure scenarios over long time periods is to examine outcomes on multiple dimensions, for example, single agents, combinations of agents occurring together, and special circumstances associated with processes or practices unique to a period of time (17).

The second consideration relates to accounting for nonroutine, high-exposure events. Questions regarding past events of high pesticide exposure have been incorporated into the Agricultural Health Study (18). Capture of such data provides an opportunity to characterize low-frequency, high-intensity exposures that might not otherwise be identified. Issues of recall bias aside, the relative frequency of such events may be reflective of mean exposure intensity. For example, in a chemical manufacturing study that incorporated continuous personal monitoring of toluene diisocyanate (TDI) concentrations and the monitoring of acute exposure incidents, parallel trends were observed between time-weighted-average concentrations of TDI and both the frequency of daily peak TDI concentrations and TDI-related acute exposure incidents across job categories and over a period of several decades (19). In this example, an analysis of nonroutine exposure incident rates would have proved to be a reasonable surrogate for categorizing relative exposure intensities.

Through a unique set of circumstances, we also carried out a retrospective exposure assessment combining concurrent accounts of a 1953 trichlorophenol reactor accident (data on work activities and practices of personnel engaged in clean-up after the accident and medical findings) with reconstructed 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) dose estimates derived from biomonitoring data (20). With these data, a model was developed relating TCDD body burden to work activity and time period. The model showed that by far the highest daily dose rates occurred during clean-up activities in the reactor room over the first 3 weeks after the accident. Thereafter, increased safety measures were taken (eg, enhanced PPE use) and chloracne and other health complaints were greatly reduced. These findings were used in a cancer study and again point to the value of seeking out prior accounts of routine and nonroutine exposure in retrospective assessments of work exposures.

Although assessing past agricultural exposures remains challenging, there are opportunities to utilize both historical records and state-of-the-art exposure assessment techniques to optimize our understanding and characterization of such exposures.

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