

Sessions on the epidemiology of agricultural exposure and cancer

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The epidemiology of agricultural exposures and cancer is complex. In the large literature base on this subject, the numerous exposures are characterized by an assortment of methods, which have, in turn, been related to multiple cancer types with varying degrees of specificity. To date, the results of epidemiologic studies have been inconsistent. A clear picture of the epidemiology of cancer in relation to agricultural exposures has yet to emerge, and this lack hampers the assessment and management of risk and confounds researchers, civil authorities, business interests, and the public. The integration of toxicology, molecular biology, and modern exposure assessment methods has the potential of improving the epidemiologic studies of agricultural exposures and cancer. The papers presented at the International Symposium on Agricultural Exposures and Cancer have highlighted some of these issues and provided a platform with which to identify areas to improve the epidemiology of cancer and agricultural exposures.

The summaries of cancer among farmers, pesticide manufacturers, and commercial pesticide applicators introduced the breadth of this topic. The populations potentially affected by agricultural exposures are diverse and have been studied to varying degrees. Studies that focus on licensed pesticide applicators and agriculture producers, such as the Agriculture Health Study (1), consider the epidemiology of cancer in a population with multiple agriculture-based exposures that may contribute to cancer morbidity and mortality. The frequency, intensity, and duration of these exposures are influenced by seasonal factors characteristic of agricultural production among specific populations. Exposure assessment has, to date, been primarily qualitative, although methods for quantitative exposure estimates are being explored. In contrast, pesticide manufacturing workers may be routinely exposed to a smaller number of pesticides on a routine basis (2). These workers may well be exposed to other chemicals on the job, however, as, with agricultural production operations, the epidemiologic research will focus on one or a few main exposures. The

research on these populations has largely evaluated the mortality experience of cohorts of small-to-moderate size. Contrary to those in studies on agricultural production workers, the exposures in these cohorts are more routine and potentially higher; however, the exposure classifications also tend to be more qualitative or semi-quantitative.

These large studies of pesticide manufacturers and agricultural workers have produced varying results. This situation is not altogether unexpected, given the differences in study design, decreasing exposure with industrial hygiene practice improvements over time, and the very different populations under study. Accordingly, the extent to which the results are generalizable to all populations exposed to similar chemicals may be limited. The larger studies of agricultural exposures and cancer, such as the Agriculture Health Study and the mortality studies of pesticide manufacturers, are conducted in highly developed countries. The cancer experience and pesticide exposure profiles in less developed countries are very different. In less developed countries several factors contribute to higher exposure experience, including pesticide misuse, poor enforcement of regulations, lower literacy rates, and a pressure to grow food.

The symposium discussion of these papers raised questions about exposure assessment, genetic susceptibility, and biological mechanism. The problem of exposure assessment, particularly for the characterization of past exposure and the proper definition of cumulative exposure, is limiting the understanding of the epidemiology of agricultural exposures and cancer. Biological monitoring would better characterize the exposures and help epidemiologists develop more quantitative exposure assessments. Biological monitoring has not been available for most epidemiologic studies, particularly for characterizing exposures in the distant past. A challenge for epidemiologists is to utilize current exposure monitoring data to improve exposure reconstructions. The importance of understanding the biological mechanisms and differential susceptibility involved were emphasized.

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The integration of toxicology with epidemiology would be useful for developing targeted epidemiologic studies. For example, the role and mechanism of endocrine disruption by specific chemicals, and how individual genetics may modify these effects, should be incorporated into studies of hormonally mediated cancers.

The complexity of the epidemiology of agricultural exposures was characterized further with the presentations and discussions pertaining to lymphoproliferative and hormone-dependent cancers.

A variety of agricultural exposures, herbicides, insecticides, other chemicals, and zoonotic viruses have been associated with non-Hodgkin's lymphoma. However, the reported associations are not consistent, and sometimes not intuitive (eg, a higher risk of non-Hodgkin's lymphoma in association with phenoxy herbicides with a lower content of 2,3,7,8-tetrachlorodibenzo-p-dioxin (3)). The link between non-Hodgkin's lymphoma and meat packing workers suggests agricultural exposures other than chemical ones may be important. The variety of exposures encountered by agricultural workers makes it difficult to isolate unique exposure disease scenarios; thus grouping exposures by function (eg, immunosuppressive ability) may help elucidate the risk of certain cancers in these populations. Hormonally dependent cancers, such as breast, ovarian, testicular, and prostate cancers, require special consideration when associations with environmental exposures are evaluated. Current exposure scenarios in more developed countries, such as the United States, may not be the best populations for studying associations between agricultural exposures and these cancers. In countries like Thailand, as discussed by Dr Muir, the exposures are higher and other distinctive characteristics of the populations (eg, high soy diet) provide unique opportunities for evaluating links between agricultural chemicals and hormonally dependent cancers (4). Because the etiology of these diseases is complex, the integration of biological markers of exposure, outcome, and susceptibility will improve the epidemiology.

The discussion of these presentations recognized the importance of better exposure characterization for recent and cumulative exposure. The concept of an etiologic window of exposure, for example, exposure during early puberty, may be important; however, valid estimation of exposure in this window will be a challenge. Furthermore, the hormonally dependent cancers represent a complex mix of diseases that are affected by a variety of known risk factors, such as reproductive history, diet, and body mass. Whether agricultural exposures have a direct, indirect, or hormonally mediated effect on carcinogenesis, and the role of interaction with known risk factors remains unclear.

The final session on epidemiology considered scenarios in which the validity and reliability of exposure

and outcome classification can influence the epidemiology of agricultural exposures. A primary challenge for epidemiologists will be to resolve the question of childhood cancer in relation to agricultural exposures. Studies reporting associations for childhood non-Hodgkin's lymphoma and acute lymphoblastic leukemia with pesticides have suffered from limited exposure characterizations (5). Geographic information systems (GIS), as a method for exposure characterization, offer intriguing possibilities as a means with which to minimize bias from the self-report of exposure from a questionnaire. However, these ecologic methods of exposure assessment will require refinement if they are to be applied to an individual with certainty. On the issue of childhood cancer, larger studies with much better exposure assessment protocols are needed.

Advances in cancer biology present the potential for exploring the effects of agricultural exposures on persons with varying susceptibility. These advances provide unique opportunities for focusing on the epidemiology of diseases of unknown or mixed etiology (6). Understanding the multiple mechanistic pathways of environmental exposures and which people in a population are susceptible to the exposures may improve the epidemiologist's ability to identify the presence or absence of risk correctly.

A fundamental problem identified by speakers and discussants throughout the epidemiology sessions is the difficulty of estimating exposure in epidemiologic studies of agricultural populations. While not unique to agricultural populations and exposures, the highly variable, multifaceted nature of agricultural exposures complicates the task of creating meaningful exposure metrics from often limited exposure information. Informative epidemiologic studies require more than the establishment of farming as an occupation or presence or absence on a farm. Even when more-detailed information is available, the methods of exposure estimation are not well characterized, nor are the qualitative algorithms easily converted to quantifiable estimates of exposure (7). Complexities such as appropriate attention to within-worker variability, which may be as large as between-worker variability, need to be considered in exposure models.

The discussion of this session highlighted the challenges for conducting and interpreting epidemiologic studies of agriculture exposures and cancer. How well the results of epidemiology studies align with the risk assessment paradigm based on the toxicology of specific chemicals in animal models fosters considerable debate. Epidemiology may or may not validate or refute the paradigm put forth by risk assessment. However, it is important to recognize that the disciplines of epidemiology and toxicology have unique strengths and weaknesses for evaluating the health hazards of

chemicals. Both disciplines are also evolving rapidly as advances in chemical analytic methods and powerful computational tools provide for a better integration of spatially referenced disease incidence data and molecular markers of susceptibility, exposure, and effects. Exposure assessment and causal inference remain challenges for epidemiology, but the results are directly related to the life experience of the target species and population. Risk assessment based on animal models and other toxicologic assays provide precise and, usually, valid answers, but it may be argued that it is not exactly the question to be asked. The inclusion of the known toxicology of agricultural exposures and relevant biology pertaining to host susceptibility when hypotheses are formulated should help develop more informative epidemiologic studies. A detailed understanding of the exposure scenarios, in the context of the hypotheses under study, will also be of considerable importance in aiding the reporting of a consistent message about the risks associated with agricultural exposures.

References

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