16. Exposure assessment of pesticides in cancer epidemiology

Mustafa Dosemeci

16.1 Introduction

Pesticides are defined as 'substances or mixture of substances intended for destroying, preventing, repelling or mitigating any pest, including chemicals intended for use as plant regulators, defoliants or dessicant' (CFR 1986). The purpose is to control insects, animal vectors, and plants in human disease and to increase agricultural productivity. The generic term 'pesticides' includes insecticides, herbicides, fungicides, rodenticides, fumigants, growth regulators, and repellents.

In many epidemiological studies dealing with pesticides and cancer, assessment of exposure to agricultural pesticides has been limited to the use of surrogates of exposure such as type of farm operation, years of application, number of acres or animals treated, crop type, or frequency of pesticides use (Zahm *et al.* 1997). A limited number of studies have obtained information on years of use, days of application per year, and use of protective equipment while handling specific pesticides (Blair and Zahm 1995). Previous epidemiological studies have considered pesticides as a group without further characterization of chemical-specific exposures. Some epidemiological studies have evaluated risk of cancers by chemical-specific exposures, and frequency or duration (Baris *et al.* 1998; Blair *et al.* 1998), but intensity of exposure to individual pesticides has been largely ignored. This chapter briefly reviews procedures used to evaluate pesticide exposures in epidemiological studies of cancer, particularly in the agricultural setting and provides suggestions for more accurate assessment methods.

16.2 Methods for assessing exposure to pesticides in epidemiological studies of cancer

Accurate assessment of exposure to occupational and environmental risk factors is needed to assure that epidemiological studies meet their objectives in investigating the exposure–disease relationship. The basic principle of exposure assessment for epidemiological studies is to identify the determinants of exposure variability within the study population and to classify study subjects accurately with respect to their level of exposure to the risk factor of interest.

Exposure to pesticides may occur while transporting, mixing, loading, or applying chemicals, through cleaning or repairing equipment, or from re-entering treated fields. Factors affecting the level of exposure include type of activity (e.g. application, mixing, loading, or harvesting), method of application (e.g. air blast, backpack, aerial spray, hand spray, or ground boom application), pesticide formulation (e.g. dilute spray, aerosol, or dust), application rate (e.g. lbs. active-ingredient/acre), use of personal protective equipment [PPE] (e.g. gloves, respirators, face shield, boots, or overalls); and personal work habits and hygiene (e.g. changing into clean clothes/washing hands or taking bath/shower after the use of pesticide; frequency of health care visits). The challenge is to incorporate these exposure modifiers into an estimation of intensity of pesticide exposure (Dosemeci *et al.* 2002). The procedures for assessing exposures to pesticides depend on the availability of exposure information. The availability of pesticide exposure information in epidemiological studies can range from a simple job title (Blair *et al.* 1993) to subject-specific interview (Dosemeci *et al.* 2002) or biological monitoring data (Aronson *et al.* 2000). The following procedures have been used for assessing exposure to pesticides in epidemiological studies of cancer.

16.2.1 Assessing exposure using farmers and agricultural settings as surrogate

In early occupational epidemiological studies on cancer, job or industry titles have been used as surrogates of exposure to occupational risk factors, assuming that every study subject with the same job or industry title have the same level of exposure to all the risk factors in that occupation or industry. Epidemiological analyses usually have been carried out by evaluating the risk of cancer either among farming occupations (e.g. Dosemeci *et al.* 1994*a*; Settimi *et al.* 2001), pesticide applicators (Torchio *et al.* 1994; Fleming *et al.* 1999), or in various agricultural settings (Nanni *et al.* 1998; Rautiainen *et al.* 2002). Recently, several meta-analyses have been conducted to investigate cancer risk with farming, using agricultural settings as surrogates for pesticide exposures. These meta-analyses in agricultural settings evaluated risks of leukemia (Keller-Byrne *et al.* 1995), multiple myeloma (Khuder and Mutgi 1997), prostate cancer (Keller-Byrne 1997*a*), non-Hodgkin's lymphoma (Keller-Byrne *et al.* 1997*b*), and brain cancer (Khuder *et al.* 1998). Investigating cancer risk by occupation or industry may not be an appropriate approach to evaluate dose–response relationship between specific pesticide and cancer risk, but is a very useful tool for screening or for hypothesis generating studies.

16.2.2 Assessing pesticide exposure by job exposure matrices

Job-exposure matrices (JEMs) are designed to assign *a priori* exposure levels for study subjects based on their job and industry titles obtained from their work histories in case–control and surveillance studies (see Chapter 8).

In earlier applications of JEMs, exposure levels have been usually assigned directly on job title/industry combinations and they were limited to the specific study and not applicable for other studies (Acheson 1983). However, in later JEM applications (Dosemeci *et al.* 1994*b*), assignments of exposure levels have been carried out separately for job titles and industries and then integrated to specific occupation/industry combinations using an algorithm (Dosemeci *et al.* 1989) to be applicable to any dataset having work histories with the same coding scheme. These JEMs are generic, can be applied to any occupational study, and have assignments of exposure levels (i.e. level of intensity), exposure probabilities (i.e. likelihood of occurrence of exposure), confidence on the assignments (i.e. accuracy of the estimates), and source indicators (i.e. whether the origin of exposure is based on the occupation or the industry). Although they provide us with semi-quantitative evaluations, assessing exposure by JEMs is a very practical approach in the evaluation of dose–response relationships. For example, the development of a JEM for pesticides have been described in detail (Wood *et al.* 2002) and several JEMs for pesticides have been applied in various case–control studies, including pancreatic cancer (Ji *et al.* 2001), reproductive disorders (Tielemans *et al.* 1999), and neurotoxicity (London and Myers 1998).

JEMs are very useful tools for investigations of an occupational or environmental agent and cancer risk. They provide us with an opportunity to group several occupations and industries by common pesticide exposures. However, they have some limitations compared to the workplace- or subject-specific exposure evaluation. Even though JEMs consider the exposure variability for a given job title in various agricultural settings, they do not provide us with available information between different farms or pesticide-used workplaces. For example, they still assume that the level of pesticide exposure for farmers is the same regardless of the variability between different farms. JEMs also has a potential for misclassification by ignoring the variability of exposure between farmers working in the same farm or pesticide applicators working in the same workplaces. If a higher level of quantification was needed, as in some risk-assessment studies, then subject-specific exposure assessment approaches would be necessary to ensure the accuracy of the estimates.

16.2.3 Subject- and pesticide-specific exposure assessment using determinants of pesticide exposure

Because of the large exposure variability between individuals within the same pesticide-exposed jobs, such as farmers or pesticide applicators, subject-specific exposure information can play a significant role in reducing the potential exposure misclassification by considering the between-individual variability. One of the efficient ways of collecting subject-specific exposure information is the administration of the interview to study subjects. Questions related to the determinants of subject-specific exposures provide us with a great opportunity to calculate the overall exposure level for each study subject.

In the large prospective cohort of Agricultural Health Study (AHS) (Alavanja *et al.* 1996), a quantitative method was developed to estimate pesticide exposures of over 58,000 pesticide applicators in North Carolina and Iowa (Dosemeci *et al.* 2002). Self-reported exposure information on pesticide use from questionnaires as well as pesticide monitoring data from the literature, the Pesticide Handlers Exposure Database (PHED), and results of EPA pilot AHS pesticide monitoring surveys were utilized to estimate the levels of exposure to pesticides.

Questionnaire information

At enrollment into the study, approximately 58,000 pesticide applicators completed a questionnaire with time- and intensity-related pesticide exposure questions. The time-related information consisted of the duration (i.e. number of exposed years) and frequency (i.e. average annual number of days used) of handling (i.e. mixing, application for 22 pesticides: 10 herbicides, nine insecticides, one fumigant, and two fungicides). Intensity-related information included frequency of mixing pesticides, method of application, repairing application equipment, and use of PPE.

All applicators who completed the enrollment questionnaire were also given a self-administered take-home questionnaire to obtain additional information. Information includes pesticide handling, use of an enclosed mixing system, type of tractor (open cab or enclosed cab with or without a charcoal air filtration system), procedures used to clean pesticide application equipment, personal hygiene (e.g. timing of changing into clean clothes/washing hands, or taking bath/shower after application), the practice of changing clothes after a spill, and frequency of replacing old gloves, as well as information on lifestyle factors. In this questionnaire time- and intensity-related information was obtained for an additional 28 chemicals (i.e. eight herbicides, thirteen insecticides, three fumigants, and four fungicides).

Pesticide monitoring data

The pesticide monitoring data were extracted from more than 200 available published articles that had numerous measurements of pesticide exposures in relation to mixing, application, or work practices in agricultural settings. These articles provided extensive monitoring data on applicators' dermal, inhalation, and internal exposures.

Methods for determining dermal exposure include washing or wiping of the skin (Van Hemmen 1992), the use of pseudo-skin (e.g. pads or patches, special clothing, coveralls, caps, and gloves) (Nigg and Stamper 1985), and fluorescent tracer technique (Fenske 1988, see Chapter 9). In the assignment of exposure weights, the researchers relied on the results obtained by pseudo-skin and fluorescent tracer techniques, since the data from comparison studies suggested that washing or wiping may yield lower levels of exposure than sampling by means of pads and gloves (Fenske *et al.* 1989). Respirators were used to trap the inhaled particles and vapour to measure inhalation exposure in the early monitoring (Nigg and Stamper 1985). Later on, personal air sampling has been used to monitor the level of breathing zone pesticide exposure of applicators (Brouwer *et al.* 1992). Internal doses of pesticides are usually monitored by the measurements of the parent compound or its metabolites in urine, blood, faeces, adipose tissue, exhaled air, or sweat. The details of biological monitoring of internal doses of pesticides have been reported recently in two review articles (Maroni *et al.* 2000; Aprea *et al.* 2002).

The second source of information on monitoring data is the PHED (1992). The US Environmental Protection Agency (EPA), in conjunction with Health and Welfare Canada and the American Crop Protection Association, developed the PHED, a non-chemical specific summary database for investigating pesticide exposure to hands and to other dermal surfaces of the body, and inhalation while engaged in mixing, loading, and application activities.

The PHED consists of data collected from about 100 studies submitted primarily by companies that wish to register a specific pesticide. Even though this database contains many more records than any published study, there is some concern about its relevance to actual exposure situations because of the controlled, almost experimental, conditions under which the application occurs.

The other source of information used to assign exposure scores for the algorithms was the results of a pilot exposure monitoring survey conducted by the US EPA at six AHS farms in Iowa and North Carolina. For example, this monitoring survey showed that hand-spray applications resulted in approximately three times more exposure to the applicator than the ground-boom applications, which is consistent with the literature (Rutz and Krieger 1992; Brouwer *et al.* 1994).

Development of algorithms intensity levels

The questionnaire responses were used to develop chemical-specific exposure scenarios. Quantitative intensity levels for a given exposure scenario were calculated using two algorithms based on the reported information from the enrollment and take-home questionnaires. The first algorithm had fewer exposure variables than the detailed second algorithm, which is based on the information both from the more detailed self-administered take-home questionnaire and the enrollment questionnaire.

The enrollment algorithm and weights for the variables from the enrollment questionnaire are as follows:

Intensity = (Mix + Appl + Repair) × PPE

where: **Mix** = mixing status: score

- Never = 0
- <50% of time = 3
- 50% + of time = 9

Appl = application method:

- Aerial-aircraft = 1
- Distribute tablets = 1
- In furrow/banded = 2
- Boom on tractor = 3
- Backpack = 8
- Hand spray = 9
- Seed treatment = 1
- Air blast = 9
- Mist blower/fogger = 9
- Ear tags = 1
- Inject anima = 2
- Dip animal = 5
- Spray animal = 6
- Pour on animal = 7
- Powder duster = 9
- Gas canister = 2
- Row fumigation = 4
- Pour fumigant = 9

Repair = repair status

- Does not repair = 0
- Repair = 2

PPE = personal protective equipment use:

- Never used PPE = 1.0
- Face shields/goggles = 0.8
- Fabric/leather gloves = 0.8
- Boots = 0.8
- Cartridge respirator = 0.7
- Disposable clothing = 0.7
- Rubber gloves = 0.6

In the take-home questionnaire, more pesticide-specific exposure information was used than that from the enrollment questionnaire. For example, intensity variables, such as mixing conditions, application type, and PPE used were collected by group of chemicals (i.e. herbicides, crop insecticides, livestock insecticides, fungicides, and fumigants). In addition, detailed questions were asked about work practices such as washing pesticide equipment after application, frequency of replacing old gloves, personal hygiene behaviour on changing into clean clothes and washing hands or taking bath/shower after application, and changing clothes after a spill.

For the information obtained from the take-home questionnaire, the following algorithm was used to calculate the intensity level for each exposure scenario:

$$\textbf{Intensity} = [(\textbf{Mix} \times \textbf{Enclosed}) + (\textbf{Appl} \times \textbf{Cab}) + \textbf{Repair} + \textbf{Wash}] \times \textbf{PPE} \times \textbf{Repl} \times \textbf{Hyg} \times \textbf{Spill}$$

where:

Enclosed = using enclosed mixing system

- Yes = 0.5
- No = 1.0

Cab = tractor with enclosed cab and/or charcoal filter

- Both cab and filter = 0.1
- Cab, but not filter = 0.5
- No cab, and no filter = 1.0

Wash = status of washing pesticide equipment after application

- Don't wash = 0.0
- Hose down sprayer = 0.5
- Hose down tractor = 0.5
- Clean nozzle = 3.0
- Rinse tank = 1.0

Repl = replacing old gloves

- Change after each use = 1.0
- Change once a month = 1.1
- Change when worn out = 1.2

Hyg = personal hygiene: changing clean clothes and washing hands or taking bath/shower

- Change clothing right away = 0.2
- Change clothing at the end of the day = 0.4
- Change clothing at the end of the next day = 1.0
- Always use disposable clothing = 0.2
- Hands/arms washed right away = 0.2
- Bath/shower right away = 0.2
- Bath/shower at lunch = 0.4
- Bath/shower at the end of the day = 0.6
- Hand/arms only at the end of the day = 0.6

Spill = changing clothes after a spill

- Right away = 1.0
- Always use disposable clothing = 1.0
- At lunch = 1.1
- At the end of the day = 1.2
- At the end of the next day = 1.4
- Later in the week = 1.8

In both algorithms, an additive model was used for mixing, application, repair, and washing activities, because they are independent contributing factors for the overall body exposure, while a multiplicative model was used for the PPE and other potential protective factors, such as variables for 'Enclosed', 'Cab', 'Repl', 'Hyg', and 'Spill', because they are dependent to the basic exposure determinants.

To generate weights for the variables in the algorithms, the results of various monitoring data between individual exposure variables (e.g. mixing vs. applying) as well as within a selected variable (e.g. for 'Appl' variable: ground boom vs. backpack; for 'Cab' variable: open cab vs. closed cab) were compared using the results presented in these articles. The ratio between exposure levels of mixing and application depends on the method of application. For example, mixer/loaders have approximately 9-fold higher exposures than aerial applicators (Chester *et al.* 1987), hence the score '9', and have 3-fold higher exposure than ground-boom applicators (Rutz and Krieger 1992; Brouwer *et al.* 1994), which were assigned a score of '3'. The level of exposure for mixing/loaders was almost the same as the exposure level for hand-spray applicator (Rutz and Krieger 1992), which were assigned a score of '8'. The comparison between two application types, hand spray and ground boom, showed approximately 3-fold intensity differences (i.e. on the average, hand-spray application has three times more exposure than ground-boom application) using various monitoring results summarized in two review articles (Rutz and Krieger 1992; Van Hemmen 1992). In another study, both air-blast and hand-spray applications generated approximately three times higher intensity in levels of exposure than ground-boom applications (Nigg *et al.* 1990). The intensity levels of exposure were reviewed in their association with the use of various type of protective equipment. Rubber gloves provided approximately 50 per cent protection among fruit growers (De Cock *et al.* 1995). Similarly, closed cabs on tractors provided approximately 50 per cent protection, and closed cabs with air filter provided almost 90 per cent protection compared to tractors without cabs (Carman *et al.* 1982). To estimate intensity scores for PPEs, articles providing data on exposures by parts of the body were also used, by calculating proportion of the particular body part, which can be protected using PPE, in the overall body exposure (Davies *et al.* 1983; Marchado *et al.* 1992). There was almost no published data on measurements of human exposure from application of pesticides to animals. An NCI study in Iowa provided some data for estimating scores for the application techniques of hand spraying, pour on animal, and backpack, but not for other application methods (Stewart *et al.* 1999).

Relative comparisons between different application methods and various types of protective equipment in the PHED provided additional exposure information to refine the scoring system. For example, in the PHED, gloves provided about 40–50 per cent protection of the overall body exposure, regardless of application method, which is similar to the magnitude of protection reported in the peer-reviewed scientific literature (De Cock *et al.* 1995).

The AHS (Alavanja *et al.* 1996) was designed to capture chemical-specific intensity and duration-related pesticide exposure information. The enrollment and take-home questionnaires provided detailed information on mixing status, application techniques, types of PPE used, work practices, and personal hygiene, which are the known major determinants of exposure to pesticide in agricultural settings. These exposure data allowed us to develop quantitative exposure scores, including daily intensity or lifetime cumulative exposure to a specific pesticide, for use in analyses of disease risk and pesticide exposure.

To develop a weighting factor for each of the exposure variables, the study relied mostly on the results of the different exposure measurements from monitoring studies that used different individual pesticides for the same variables. Pesticide monitoring surveys suggest that the intensity of exposure variables, such as mixing status, application technique, or PPE type, is largely independent of the pesticide used (Stamper *et al.* 1988; Krieger *et al.* 1990). For example, studies indicated that the ratio of exposure levels between two application techniques or between mixing and a particular application technique was similar for different pesticides. These findings provided some additional confidence that the use of the non-chemical specific PHED to estimate relative-intensity weight factors might be a reasonable approximation of actual chemical-specific weight factors.

The exposure assessment approach proposed here represents a step forward in the estimation of pesticide exposure in an epidemiological cohort. The approach utilizes a mixture of professional judgement and the existing literature data to quantify potential pesticide exposure in a more detailed manner than has been attempted before. The intensity scores derived in these algorithms require further validation. The literature suggests that there is a substantial inter-applicator variability of exposure even for the same type application procedure (Van Hemmen 1992). Even with the many complexities in estimating exposures, a recent study has suggested that pesticide experts, industrial hygienists, and crop growing experts can identify the most important determinants of external exposures (De Cock *et al.* 1996).

16.2.4 Suggestions for future exposure assessment procedures

The main goal of the exposure assessment for epidemiological studies is to identify the variability of an exposure in the study population and then classify study subjects accurately with respect to their variability of exposure. In traditional exposure assessment approaches, we usually limit ourselves to dealing with the variability of external risk factors either in their concentrations in the ambient air or their intake into the body without considering the variability of host factors that determine the amount of internal dose from the external exposure. Because our main goal is to reduce the exposure misclassification in the evaluation of dose–response relationships between occupational/environmental exposures and cancer risks, there is also a need to consider the variability of genetic susceptibility factors that eventually determine the internal dose, biologically effective dose, or in the case of evaluating cancer risk, cancer-causing dose of the external risk factors.

The evaluation of gene–environment interactions has power limitations when the prevalence of environmental risk factors and/or genetic susceptibility markers are low in the study population and multiple genetic markers interact with the exposure of interest. Recently, a method for estimating the biologically effective dose has been developed by integrating levels of external exposure with the protective ability of genetic susceptibility markers. In this process, the level of external occupational or environmental exposure may either be reduced or increased depending on the capacity of Phase I (activation), Phase II (detoxification), and DNA-repair enzymes. In this approach, genetic susceptibility markers (e.g. CYP1A1, CYP2E1, NAT1, NAT2, GSTM1, GSTT1, or DNA repair capacity) are used as if they were internal PPE. For example, low capacity of activation enzymes (e.g. CYP1A1) and high capacity of detoxification (e.g. NAT2) and DNA repair enzymes would have higher protective functions than high capacity of activation enzymes and low capacity of detoxification and DNA repair enzymes that may result in reducing cancer-causing doses of xenobiotics. This approach allows us to evaluate relationships between an unlimited number of genetic susceptibility markers and the exposure under investigation, without losing power. The challenge is to find appropriate biological markers that interact with pesticides in the carcinogenesis process. To find the appropriate markers, the starting point is to evaluate the gene–pesticide interactions on cancer risk estimates, and identify biomarkers related to pesticides and cancer site. Then protective factors of each pesticide-related biomarkers can be used as an internal protective factor to estimate the biologically effective dose.

Another way of reducing potential exposure misclassification caused by the retrospective nature of exposure assessment is to design prospective exposure assessment procedures based on biological monitoring data. The accuracy of the biological monitoring data depends on the time windows that represent the internal dose. If the chemical is a persistent one and the measured value represents the time window of the exposure period, such as the case for DDT or PCBs, then the biological monitoring would be a good index for the exposure assessment procedures. However, if the half-life of the chemical is short, such as for a couple of days as in 2,4-D or MCPA, then the current monitoring level would not be representative for the biological effective level of exposure needs to be used in epidemiological studies. If this were the case, then the only solution would be a prospective study design with frequent monitoring programs to cover the biologically effective dose. Depending on the half-life of the pesticide of interest, a prospective exposure assessment with estimated biologically effective dose would be the best approach for future epidemiological studies of pesticide and cancer.

16.3 Selection of the optimal index of pesticide exposure in occupational cancer epidemiology

A wide variety of exposure indices, ranging from very simple ones (e.g. ever/never exposed or duration of exposure) to complex ones (e.g. time-weighted cumulative exposure or biologically effective dose), have been developed and used in occupational epidemiological analyses. They can be classified into three major categories based on their associations with disease outcomes. The first group is the time-dependent exposure indices, such as duration of exposure, frequency of exposure, latency of exposure, and recentness of exposure. The second category is the intensity-dependent exposure indices, such as average intensity, highest intensity, longest intensity, and peak exposure. The last category is the combination of the first and the second, the time- and intensity-dependent indices, such as cumulative exposure, time-weighted cumulative exposure, intensity by duration, intensity by latency, intensity by recentness, cumulative exposure by latency, cumulative exposure by recentness, internal dose, or biologically effective dose. The selection of the optimum exposure index is based on the mechanism of the exposure–disease relationship. An exposure index may be optimum for certain relationships, acceptable for others, or may be totally inappropriate for some other relationships. Before deciding which index would be optimal, it is important to know about the characteristics of the metabolism of the agent of interest, such as the level of metabolic saturation, half-life in the body, and activity of metabolic enzymes.

The other important clue may come from epidemiological observations. For example, a cross-tabulation disease risk by a time-dependent exposure, such as duration of exposure, and by an intensity-dependent exposure index, such as average intensity, could give useful information for the selection of an optimum exposure index. If both the duration of exposure at various intensity levels and the intensity of exposure at various duration levels do not show associations with the disease risk, then it is unlikely that cumulative exposure would be an optimum index for that association. Because the role of exposure in disease process is the key factor for the selection of the optimum exposure index, and because the biologically effective dose requires understanding of the mechanism, it is recommended that the use of either of these indices be considered as a potential optimal index of exposure in the evaluation of an exposure– disease relationship.

References

Acheson, E. D. (1983). What are Job Exposure Matrices? in Acheson, E. D. (ed.) Job-exposure matrices: Proceedings of a conference held in April 1982 at the University of Southampton. Southampton, U.K.

Alavanja, M. C., Sandler, D. P., McMaster, S. B., Zahm, S. H., McDonnell, C. J., Lynch, C. F., Pennybacker, M., Rothman, N., Dosemeci, M., Bond, A. E., and Blair, A. (1996). The agriculture health study. *Environ Health Perspect*, **104**, 362–9.

Aprea, C., Colosio, C., Mammone, T., Minoia, C., and Maroni, M. (2002). Biological monitoring of pesticide exposure: a review of analytical methods. *Journal of Chromatography Analytical Technological and Biomedical Life Science*, **769**, 191–219.

Aronson, K. J., Miller, A. B., Woolcott, C. G., Sterns, E. E., McCready, D. R., Lickley, L. A., Fish, E. B., Hiraki, G. Y., Holloway, C., Ross, T., Hanna, W. M., SenGupta, S. K., and Weber, J. P.

(2000). Breast adipose tissue concentrations of polychlorinated biphenyls and other organochlorines and breast cancer risk. *Cancer Epidemiology, Biomarkers and Prevention*, **9**, 55–63.

Baris, D., Zahm, S., Cantor, K. P., and Blair, A. (1998). Agricultural use of DDT and risk of non-Hodgkin's lymphoma: pooled analysis of three case-control studies in the United States. *Occup Environ Med*, **55**, 522–27.

Blair, A., Dosemeci, M., and Heineman, E. F. (1993). Cancer and other causes of death among male and female farmers from twenty-three states. *American Journal of Industrial Medicine*, **23**, 729–42.

Blair, A. and Zahm, S. H. (1995). Agricultural exposures and cancer. *Environmental Health Perspectives*, **103**, 205–8.

Blair, A., Cantor, K., and Zahm, S. H. (1998). Non-Hodgkin's lymphoma and agricultural use of the insecticide Lindane. *American Journal of Industrial Medicine*, **33**, 82–7.

Brouwer, D. H., Brouwer, E. J., and Van Hemmen, J. J. (1992). Assessment of dermal and inhalation exposure to Zineb/Maneb in the cultivation of flower bulbs. *Annals of Occupational Hygiene*, **36**, 373–84.

Brouwer, D. H., Brouwer, E. J., and van Hemmen, J. J. (1994). Estimation of long-term exposure to pesticides, *American Journal of Industrial Medicine*, **25**, 573–88.

Carman, G. E., Iwata, Y., Pappas, J. L., O'Neal, J. R., and Gunther, F. A. (1982). Pesticide applicator exposure to insecticides during treatment of citrus trees with oscillating boom and airblast units. *Archives of Environmental Contamination and Toxicology*, **11**, 651–9.

CFR (1986). Protection of Environment. *Office of Federal Register, National Archives and Records Administration*. 40-162.3. US Government Printing Office, Washington, DC.

Chester, G., Hatfield, L. D., Hart, T. B., Leppert, B. C., Swaine, H., and Tummon, O. J. (1987). Worker exposure to, and absorption of, cypermethrin during aerial application of an 'ultra low volume' formulation to cotton. *Archives of Environmental Contamination and Toxicology*, **16**, 69–78.

Davies, J. E., Dedhia, H. V., Morgade, C., Barquet, A., Maibach, H. I. (1983). Lindane poisonings. *Arch Dermatol*, **119**, 142–4.

De Cock, J., Heederik, D., Hoek, F., Boleij, J., and Kromhout, H. (1995). Urinary excretion of THPI in fruit growers with dermal exposure to captan. *American Journal of Industrial Medicine*, **28**, 245–56.

Dosemeci, M., Stewart, P. A., and Blair, A. (1989). Evaluating occupation and industry separately to assess exposure in case-control studies. *Applied Industrial Hygiene*, **4**, 256–9.

Dosemeci, M., Hoover, R. N., Figgs, L., Devesa, S., Grauman, D., Blair, A., and Fraumeni, J. F. Jr. (1994*a*). Farming and prostate cancer among African Americans in the southeastern United States. *Journal of National Cancer Institute*, **86**, 1718–19.

Dosemeci, M., Cocco, P., Gomez, M., Stewart, P. A., and Heineman, E. F. (1994*b*). Effects of three features of a job-exposure matrix on risk estimates. *Epidemiology*, **5**, 124–7.

Dosemeci, M. and Stewart, P. A. (1996). Recommendation to occupational hygienists to minimize the effects of exposure misclassification on risk estimates. *Occupational Hygiene*, **3**, 169–76.

Dosemeci, M., Alavanja, M. C. R., Rowland, A., Mage, D., Zahm, S. H., Rothman, N., Lubin, J., Sandler, D. P., and Blair, A. (2002). A quantitative approach for estimating exposure to pesticides in the agricultural health study. *Annals of Occupational Hygiene*, **46**, 245–60.

Fenske, R. A. (1988). Correlation of fluorescent tracer measurements of dermal exposure and urinary metabolite excretion during occupational exposure to malathion. *American Industrial Hygiene Association Journal*, **49**, 438–44.

Fenske, R. A., Birnbaum, S. G., Methner, M., and Soto, R. (1989). Methods for assessing field worker hand exposure to pesticides during peach harvesting. *Bulletin of Environmental Contamination and Toxicology*, **43**, 805–13.

Fleming, L. E., Bean, J. A., Rudolph, M., and Hamilton, K. (1999). Mortality in a cohort of licensed pesticide applicators in Florida. *Occupational and Environmental Medicine*, **56**, 14–21.

Ji, B. T., Silverman, D. T., Stewart, P. A., Blair, A., Swanson, G. M., Baris, D., Greenberg, R. S., Hayes, R. B., Brown, L. M., Lillemoe, K. D., Schoenberg, J. B., Pottern, L. M., Schwartz, A. G., and Hoover, R. N. (2001). Occupational exposure to pesticides and pancreatic cancer. *American Journal of Industrial Medicine*, **39**, 92–9.

Keller-Byrne, J. E., Khuder, S. A., and Schaub, E. A. (1995). Meta-analysis of leukemia and farming. *Environmental Research*, **71**, 1–10.

Keller-Byrne, J. E., Khuder, S. A., and Schaub, E. A. (1997*a*). Meta-analyses of prostate cancer and farming. *American Journal of Industrial Medicine*, **31**, 580–6.

Keller-Byrne, J. E., Khuder, S. A., Schaub, E. A., and McAfee, O. (1997*b*). A meta-analysis of non-Hodgkin's lymphoma among farmers in the central United States. *American Journal of Industrial Medicine*, **31**, 442–4.

Khuder, S. A. and Mutgi, A. B. (1997). Meta-analyses of multiple myeloma and farming. *American Journal of Industrial Medicine*, **32**, 510–16.

Khuder, S. A., Mutgi, A. B., and Schaub, E. A. (1998). Meta-analyses of brain cancer and farming. *American Journal of Industrial Medicine*, **34**, 252–60.

Krieger, R., Blewett, C., Edmiston, S., Fong, H., Gibbons, D., Meinders, D., O'Connell, L., Ross, J., Schneider, F., and Spencer, J. (1990). Gauging pesticide exposure of handlers (miner/loaders/applicators) and harvesters in California agriculture. *La Medicina del Lavoro*, **81**, 474–9.

London, L. and Myers, J. E. (1998). Use of a crop and job specific exposure matrix for retrospective assessment of long-term exposure in studies of chronic neurotoxic effects of agrichemicals. *Occupational and Environmental Medicine*, **55**, 194–201.

Maroni, M., Colosio, C., Ferioli, A., and Fait, A. (2000). Biological monitoring of pesticide exposure: a review. Introduction. *Toxicology*, **143**, 1–118.

Marchado, J. G., Matuo, T., and Matuo, Y. K. (1992). Dermal exposure of pesticide applicators in staked tomato crops: efficiency of a safety measure in the application equipment. *Bulletin of Environmental Contamination and Toxicology*, **49**, 529–34.

Nanni, O., Falcini, F., Buiatti, E., Bucchi, L., Naldoni, M., Serra, P., Scarpi, E., Saragoni, L., and Amadori, D. (1998). Multiple myeloma and work in agriculture: results of a case–control study in Forli, Italy. *Cancer Causes and Control*, **9**, 277–83.

Nigg, H. N. and Stamper, J. H. (1985). Field studies: methods overview in dermal exposure related to pesticides use. *ACS Symposium Series*, **273**, 95–108.

Nigg, H. N., Stamper, J. H., and Mahon, W. D. (1990). Handgun applicator exposure to ethion in Florida citrus. *Bulletin of Environmental Contamination and Toxicology*, **45**, 463–8.

PHED, Pesticide Handlers Exposure Database (1992). US EPA, Health and Welfare Canada and the American Crop Protection Association. *Versar Publications*, Version 1.0. Springfield.

Rautiainen, R. H. and Reynolds, S. J. (2002). Mortality and morbidity in agriculture in the United States. *Journal of Agricultural Safety and Health*, **8**, 259–76.

Rutz, R. and Krieger, R. I. (1992). Exposure to pesticide mixer/loaders and applicators in California. *Review of Environmental Contamination and Toxicology*, **129**, 121–39.

Settimi, L., Comba, P., Bosia, S., Ciapini, C., Desideri, E., Fedi, A., Perazzo, P. L., Axelson, O. (2001). Cancer risk among male farmers: a multi-site case–control study. *International Journal of Occupational Medicine and Environmental Health*, **14**, 339–47.

Stamper, J. H., Nigg, H. N., Mahon, W. D., Nielsen, A. P., and Royer, M. D. (1989). Pesticide exposure to greenhouse handgunners. *Archives of Environmental Contamination and Toxicology*, **18**, 515–29.

Stewart, P. A., Fears, T., Kross, B., Ogilvie, L., and Blair, A. (1999). Exposure of farmers to phosmet, a swine insecticide. *Scandinavian Journal of Work and Environmental Health*, **25**, 33–8.

Tielemans, E., Burdorf, A., te Velde, E. R., Weber, R. F., van Kooij, R. J., Veulemans, H., and Heederik D. J. (1999). Occupationally related exposures and reduced semen quality: a case–control study. *Fertility and Sterility*, **71**, 690–6.

Torchio, P., Lepore, A. R., Corrao, G., Comba, P., Settimi, L., Belli, S., Magnani, C., and di Orio, F. (1994). Mortality study on a cohort of Italian licensed pesticide users. *Science of Total Environment*, **149**, 183–91.

Van Hemmen, J. J. (1992). Agricultural Pesticide exposure databases for risk assessment. *Review of Environmental Contamination and Toxicology*, **126**, 1–85.

Wacholder, S., Dosemeci, M., and Lubin, J. H. (1991). Blind assignment of exposure does not always prevent differential misclassification. *American Journal of Epidemiology*, **134**, 433–7.

Wood, D., Astrakianakis, G., Lang, B., Le, N., and Bert, J. (2002). Development of an agricultural job-exposure matrix for British Columbia, Canada. *Journal of Occupational Environmental Medicine*, **44**, 865–73.

Zahm, S. H., Blair, A., and Ward, M. H. (1997). Pesticides and cancer. *Occupational Medicine: State of the Art Review*, **12**, 269–89.