Use of a crop and job specific exposure matrix for retrospective assessment of long term exposure in studies of chronic neurotoxic effects of agrichemicals

Leslie London, Jonathan E Myers

Abstract

Rationale—Job exposure matrices (JEMs) are widely used in occupational epidemiology, particularly when biological or environmental monitoring data are scanty. However, as with most exposure estimates, JEMs may be vulnerable to misclassification.

Objectives—To estimate the long term exposure of farm workers based on a JEM developed for use in a study of the neurotoxic effects of organophosphates and to evaluate the repeatability and validity of the JEM.

Methods—A JEM was constructed with secondary data from industry and expert opinion of the estimate of agrichemical exposure within every possible job activity in the JEM to weight job days for exposure to organophosphates. Cumulative lifetime and average intensity exposure of organophosphate exposure were calculated for 163 pesticide applicators and 84 controls. Repeat questionnaires were given to 29 participants three months later to test repeatability of measurements. The ability of JEM based exposure to predict a known marker of organophosphate exposure was used to validate the JEM.

Results—Cumulative lifetime exposure as measured in kg organophosphate exposure, was significantly associated with erythrocyte cholinesterase concentrations (partial $r^2=5\%$; $p < 0.01$), controlled for a range of confounders. Repeatability in a subsample of 29 workers of the estimates of cumulative (Pearson's $r=0.67$; 95% confidence interval (95% CI) 0.41 to 0.83), and average lifetime intensity of exposure (Pearson's $r=0.60$ 95% CI 0.31 to 0.79) was adequate.

Conclusion—The JEM seems promising for farming settings, particularly in developing countries where data on chemical application and biological monitoring are unavailable.

(Occup Environ Med 1998;55:194-201)

Keywords: exposure assessment; job exposure matrix; validity; repeatability; agriculture

Accurate estimation of exposure is critical for the validity and power of studies investigating the adverse long term health effects of agrichemicals.¹⁻³ For example, non-differential

exposure misclassification usually leads to an underestimation of the effect of agrichemical exposure,¹⁻⁴ particularly where study power is low (due either to small sample size or to a small true relative risk (<2)). This situation is often the case with agrichemical health risks,¹⁻³ where the strengths of associations have typically been shown to be relatively weak.³⁻⁷⁻⁸ For these reasons, rigorous efforts should be made to improve characterisation of exposure in epidemiological studies beyond a dichotomous "exposed versus non-exposed" variable, and to ensure the accuracy and validity of such assessments.

The use of job exposure matrices (JEMs)⁹⁻¹⁰ has been proposed as a method of characterising workplace exposure where industrial hygiene measurements, biological monitoring data, or industry records are unavailable or inaccurate. Typically, a JEM makes use of a matrix with job history variables on one axis, chemical agents on the other, and an estimate of exposure listed within the cells of the matrix. Traditionally, the relation between job history and exposure has been expressed as a dichotomous (exposed or unexposed) or ordinal variable (high, medium, or low). However, more recent work suggests the value of probabilities of exposure within the matrix to produce greater accuracy of risk estimation.¹¹ Various methods to refine JEMs have been developed, particularly relative to their applicability to populations different from those in which the JEM was initially developed.¹²⁻¹³

For example, more recently, the applicability of JEMs to agricultural work has been described.¹⁴⁻¹⁷ French researchers report a JEM for agrichemical exposure in vine growing that uses information from agronomic records grouped by calendar year of spray activity, farm location, and agrichemical specific data on application method, duration of application, hectareage, and quantity applied to estimate cumulative exposure to a specific agrichemical among farmers in a vine growing area of France.¹⁶ A similar JEM that also takes into account type of crop production has been developed for use in two Italian case-control studies on cancer currently in progress.¹⁵ Both groups of researchers report validating the constructs inherent in the JEMs by comparing results with an assessment by agricultural experts and obtaining good agreement. However, no comparison of these JEMs against farmer records or biological monitoring data was possible, and further research to establish

Occupational and Environmental Health Research Unit, Department of Community Health, University of Cape Town, Private Bag Rondebosch, 7700, South Africa
L London
J E Myers

Correspondence to:
Dr L London, Occupational and Environmental Health Research Unit, Department of Community Health, University of Cape Town, Anzio Rd, Observatory, 7925, South Africa.

Accepted 4 October 1997

Table 1 Occupational history variables

	Variables (n)
For every job performed in a lifetime:	
Age at start of job	1
Duration of job	1
Industry	1
Job description	1
Geographical location	1
For every farm job in a lifetime:	
Duration of job	1
Seasonality of work	1
Exposure to the tot system*	1
Type of farm (produce)	1
Performance of 13 specific job tasks with 9 additional subtasks†	22
Intensity of specific job activities by month	12
Use of, types of, and reasons for use of personal protective equipment	15
Previous poisoning events	3

* The tot system is a practice by which farm workers are given wine as part of their remuneration. Although it is no longer legal in South Africa, it is still occasionally practised.

† Table 2 shows the most important job tasks and subtasks.

Table 2 Weightings used in an agricultural JEM

Weighting for job tasks:		
Tractor spraying with mist blower:		
Also mixes indoors	100	
Also mixes but outdoors	80	
No mixing	70	
Tractor driver of handsprayer configuration	50	
Mixing of pesticides (separate from spraying):		
Mixes indoors	100	
Mixes outdoors	80	
Handspray from back of a tractor:		
Also mixes indoors	100	
Also mixes outdoors	80	
No mixing	70	
Backpack spray:		
Also mixes indoors	100	
Also mixes outdoors	80	
No mixing	70	
Maintenance of equipment (separate from spraying)	20	
Thinning work in orchards	10	
Shaping work in vineyards	5	
Monitors in orchards	5	
Occupational gardening (of farmer's garden)	5	
Animal dipping	50	
Weighting for farming type:*		
Crop sector:	Active organophosphate (kg)	Biological equivalent of active organophosphate
Pome	4.98	156.93
Vine	0.24	1.65
Stone	2.46	41.89
Wheat	0.03	0.36
Citrus	1.03	30
Potato	0.01	0.07
Other sectors	0.001	0.1

* Based on industry data on yearly agrichemical usage/hectare.^{22 28 29}

criterion validity was indicated as necessary by both researchers.

Several factors suggest the usefulness of JEMs for occupational epidemiological studies in South African agriculture: unlike the situation in some developed countries,¹⁸ South Africa, despite being a substantial user of pesticides,¹⁹ lacks a statutory reporting system for hazardous agrichemical use,^{20 21} which could be used to base exposure estimates. Moreover, as a result of appalling neglect of the health and safety needs of farm workers,^{22 23} environmental monitoring for hazardous chemical exposures has neither been enforced nor practiced in South African agriculture. Furthermore, there is evidence that farm based records on the use of pesticides are poorly maintained,²⁴ thus limiting the use of farmer records for the retrospective reconstruction of exposures in field studies. The JEMs also have particular value when the subject's recall for job activity exceeds their ability to recall information relevant to particular chemical exposures, as might be expected in agricultural

settings,^{14 15} particularly where education levels are low, as is common among South African farm workers.²⁵

Given these considerations, a job exposure matrix (JEM) was developed to characterise long term chemical exposure in the agricultural workplace for a study investigating the relation between long term low dose organophosphate exposure and adverse neurological and neurobehavioural effects.²² We describe the application of this JEM to the study involving 164 pesticide applicators and 83 non-exposed control workers from deciduous fruit farms in the rural Western Cape Province of South Africa in 1993. The aim of this paper is to assess the validity and repeatability of the JEM as a tool for characterisation of chemical exposure in agriculture.

Methods

A cross sectional analytical design was used to investigate potential neurological and neurobehavioural effects of long term organophosphate exposure among workers from 113 farms belonging to three large fruit cooperatives in the region over the period January to March 1993. The sampling design, dictated partly by considerations of confounders for neurobehavioural assessment, included all applicators on a farm as well as one non-spraying control group matched for age and educational status, for every two applicators selected. In total, 164 applicators and 83 non-applicators from fruit farms in the Western Cape were interviewed by seven trained interviewers fluent in the subject's vernacular language at peak spraying season. Exclusion criteria related to confounders for neurobehavioural performance such as clinical evidence of vitamin deficiency, encephalopathy of known origin, use of psychotropic medication, and previous neurological injury. The participants represented 70% of the applicator population in the area and the overall methods for the study are described in more detail elsewhere.²²

Every lifetime job was explored for the frequency and duration of possible exposure to agrichemicals, with attention to distinguishing organophosphate from other exposures. For any jobs in farming, factories, forestry, and local government, special questionnaire modules were applied to elicit specific additional exposure information²⁶ because of the known risk of exposure to agrichemicals in these jobs.²⁷ In total, each lifetime job, generated up to 61 variables to characterise exposure (tables 1 and 2).

The JEM developed for this study incorporated a weighting both for specific job activity and for the type of farm (crop) on which the subject worked. Figure 1 shows the steps in the JEM estimation. A worked example is given in the appendix.

The weighting attached to each job activity (table 2) was developed in consultation with experts in industry and industrial hygiene personnel.^{22 28 29} Estimates of relative exposure were expressed as percentages on a scale based on a typically high exposure activity, such as driving a tractor with a mist blower having a relative exposure of 100. The JEM was thus able

Figure 1 Assessing exposure to organophosphates among farm workers with a job exposure matrix (shaded area is the core component of the job exposure matrix).

Table 3 Measures of long term occupational exposures among fruit farm workers

	<i>n</i>	<i>Mean</i>	<i>(SD)</i>	<i>Median</i>	<i>Range</i>
CUMULTR (days)	247	249.86	(495.11)	20.80	0-1651.2
CUMULTOT (days)	247	455.44	(641.57)	175.90	0-4669.8
POMDYS (days)	245	444.89	(625.41)	195.00	0-4669.8
EXWGHT (kg OP)	247	5.65	(8.17)	2.05	0-63.71
EXWGHTB (BE OP)	247	177.17	(257.66)	63.24	0-2007.8
EXWGHTI (log kg/year)	246	0.21	(0.23)	0.12	0-1.09
EXWGHTBI (log BE/year)	246	1.69	(1.06)	1.59	0-4.14

CUMULTR (days) = cumulative lifetime days of driving a tractor while operating a mist blower applying agrichemicals; CUMULTOT = cumulative lifetime days of any relevant job with agrichemical exposure weighted for the estimate of exposure in each job activity; POMDYS = cumulated lifetime days of any relevant job activity with agrichemical exposure only in pome fruit farming weighted for the estimate of exposure in each job activity; EXWGHT = cumulated lifetime days of any job activity in any past job with agrichemical exposure weighted for the estimate of exposure in each job activity and for kg organophosphate (OP) by crop sector; EXWGHTB = cumulative lifetime days of any relevant job activity in any past job with agrichemical exposure weighted for the estimate of exposure in each job activity and for biological equivalent of organophosphate (BE OP) by crop sector; EXWGHTI = average lifetime intensity of days of any relevant job activity in any past job with agrichemical exposure weighted for the estimate of exposure in each job activity and for kg OP use by crop sector; EXWGHTBI = average lifetime intensity of days of any relevant job activity in any past job with agrichemical exposure weighted for the estimate of exposure in each job activity and for BE OP use by crop sector.

n Includes 163 subjects in current jobs as mist blower operators as well as nine workers currently not exposed who had previous employment as a mist blower operator.

to take into account reported direct exposures (application, mixing) as well as indirect exposures (such as field contacts, presumed spray drift, and other routes).

Weightings for farming type were derived from crop sector specific yearly agrichemical use patterns derived from secondary data sources^{28, 29} and were then applied to job activity weighted days. The weightings used were for either kg active ingredient of organophosphate, or for biological equivalent units (BEs) (kg standardised by the inverse of the oral LD₅₀ of the chemical). Because this is more closely related to acute toxicity, this study of long term exposure focused primarily on the JEM measure based on kg. The methods and rationale for this standardisation have been described elsewhere.^{22, 28, 29}

The JEM was used to derive cumulative and average lifetime intensity exposure estimates. Average lifetime intensity of exposure was based on the formula:

$$\log ((\text{cumulative days} / \text{working life}) + 1)^{30}$$

Because of the introduction of a weighting that standardises for kg organophosphate used a year, cumulative exposure as derived from the JEM is in total kg organophosphates and is expressed free of years. This is by contrast with typical estimates of cumulative exposure in occupational studies that produce estimates based on years worked. For similar reasons, the JEM produced estimates of average lifetime intensity of exposure in kg organophosphate/year, unlike typical intensity estimates that are free of time measures. Notwithstanding the units, the principles behind standard estimates of cumulative and average lifetime intensity³¹ would still apply to exposure estimates derived in this study.

Cumulative exposure estimates are generally appropriate for the investigation of dose-response relations in chronic diseases, although there may be instances in which peak exposures may be more relevant,³² or in which non-linear relations are more suitable.³³ However, for most agrichemicals with neurotoxic potential, there are few empirical data on the nature of the dose-response relation and the assumption of a linear dose-response relation implicit in the

use of cumulative exposure may be considered a reasonable strategy.¹⁷ Different measures of long term exposure were calculated for exposure experienced only on deciduous fruit farms (POMDYS in fig 1) and for past exposure experienced only in driving a mistblower tractor (CUMULTR in fig 1).

Several exposure variables were used in exposure-effect analyses as independent exposure variables and were not incorporated in the JEM. These included recent occupational exposure, current and past use of personal protective equipment, current knowledge and attitude score, past poisoning with pesticides, domestic use of agrichemicals or containers, current water sources, and potential lifetime residential exposure.

Red cell cholinesterase has a recognised association with exposure to organophosphates and is known to have a longer lasting effect than plasma cholinesterase. Tolerance to lowered concentrations of red blood cell cholinesterase is thought to occur with chronic exposures,^{34, 35} and for these reasons, an association between erythrocyte cholinesterase and JEM based exposure may be a useful way of establishing validity. Predictive validity of the JEM was therefore assessed by modelling its explanatory power for haemoglobin standardised³⁶ erythrocyte cholinesterase. Separate bivariate linear regressions were performed for each different measure of long term exposure (table 3). Also, a multiple linear regression, with forward stepwise selection, was performed with a criterion of improvement in the proportion of the explained variance at $p < 0.15$. The model selected from a range of variables including long term JEM derived organophosphate exposure, current status as a pesticide applicator, days since last reported contact with an organophosphate, age, serum albumin, alcohol consumption, and use of personal protective equipment. There was no collinearity between age and either cumulative exposure (EXWGHT) or average intensity (EXWGHTI) of exposure ($r < 0.3$).

A 10% random subsample (29 subjects) underwent repeat interviews with one interviewer three months after the survey. Data from repeat questionnaires were compared with initial interview data by means of

Table 4 Repeatability of questionnaire data (n=29 pairs)

Exposure variable	Correlation coefficient*	95% CI
CUMULTOT	0.67	0.41 to 0.83
POMDYS	0.67	0.40 to 0.83
EXWGHT	0.6	0.31 to 0.79
EXWGHTI	0.38	0.02 to 0.66
Cumulative dipping exposure days	0.64	0.35 to 0.81
Cumulative marker exposure days	0.99	0.987 to 0.997

* Pearson correlation coefficient.

Pearson's correlation coefficients for continuous data.³⁷ Laboratory methods for erythrocyte cholinesterase estimation were also checked for repeatability based on 56 blinded split samples, which had a Pearson's correlation coefficient of 0.96 as described in detail elsewhere.³⁸

Results

Subjects reported an average of 3.3 jobs each, most commonly in agriculture (88.2%). Table 3 shows measures of long term occupational exposure. Mist blower activities contributed 45% of total cumulative weighted exposure days in the whole sample. The difference between measures CUMULTR (mist blower weighted exposure) and CUMULTOT (weighted exposure from all routes) shown in table 3 reflects the contribution of other routes of exposure such as handspray with pesticides (20.5%), backpack spraying (7.5%), general orchard work (12.3%), and gardening (1.8%). In terms of actual days spent in specific activities, thinning (part of general orchard work) was reported as an activity by more subjects (224 thinned while 172 operated a mist blower) and average real lifetime days spent thinning was almost as common as mist blower operation (496 thinning; 516 mist blower). However, because of their relative weighting (table 2), mist blower operation accumulated more than four times the total cumulative weighted days by thinning activities in the sample as a whole. Only two workers experienced pesticide exposure in non-farming jobs and the bulk of exposures of mist blowers and non-mist blowers occurred on the deciduous fruit farms as shown by the small difference in mean values for CUMULTOT and POMDYS (table 3). This suggests that past long term exposures among this group were relatively homogeneous.

Of note was that 48 subjects (19%) reported exposure in the past as human markers for aerial spraying, with 24 subjects (9.7%) reporting

Figure 2 Cumulative exposure to organophosphates (kg) weighted on job activity and crop sector by current applicator status.

Figure 3 Average lifetime intensity of exposure to organophosphates (kg/y) weighted on job activity and crop sector by current applicator status.

exposures as a human marker in their current job. Although these exposures may be considered to be episodic, they are likely to involve high levels of exposure and deserve independent attention in exposure-effect analyses.

Figures 2 and 3 present the distribution of the main long term occupational exposure variables of interest: cumulative kg organophosphate (EXWGHT), and average lifetime intensity of exposure—kg organophosphate exposure/year (EXWGHTI). The data are stratified by current applicator status, and indicate that there is considerable lifetime exposure among workers who are not currently applying pesticides. This included nine subjects who were currently included as non-sprayers but who had previously been pesticide applicators as well as subjects with other exposed jobs. Only six subjects (2.4%) recorded no exposures during their lifetime.

Table 4 shows repeatability of the JEM based on repeat questionnaire. Moderately good correlation coefficients are shown for cumulative exposure variables but less so for average intensity of exposure. Activities with episodic high level exposures such as dipping and human marker duty showed good repeatability.

Linear regression of erythrocyte cholinesterase with years of farming employment yielded a non-significant and positive regression coefficient ($\beta=0.049$; $SE=0.026$; $p=0.063$). Similar regressions with the various JEM derived long term exposure measures (table 3) showed negative regression coefficients, but all the models explained little variance (model r^2 s all <0.04). For cumulative exposure (EXWGHT), β was -0.076 ($SE=0.035$; $p=0.03$) and for average intensity of exposure (EXWGHTI), β was -3.628 ($SE=1.244$; $p=0.004$).

Table 5 shows the results of multiple linear regression of erythrocyte cholinesterase and cumulative exposure (EXWGHT). The modelling explained $<10\%$ of overall variance and only two variables were significant predictors of cholinesterase. Long term cumulative organophosphate exposure predicted about 5% of the model variance and was a greater predictor than age. Similar results were found with average lifetime intensity of exposure (EXWGHTI) in the model (data not presented here).

Discussion

Application of the agrichemical JEM in this study seems to have generated exposure assessments of adequate repeatability, of sufficient range to facilitate the detection of exposure-

Table 5 Significant predictors of standardised* erythrocyte cholinesterase among deciduous fruit farm workers†

Variable	Range	Regression coefficient	Standard error	Partial r^2	p Value
Cumulative lifetime kg OP (EXWGHT)	0-63.71	-0.107	0.038	0.045	0.006
Age	20-72	0.080	0.034	0.014	0.018
Model $r^2 = 0.05$					

* Standardised erythrocyte cholinesterase = erythrocyte cholinesterase/haemoglobin concentration.³⁶

† Linear modelling with forward selection; criteria for inclusion based on improvement in the proportion of explained variance at $p < 0.15$.

p Value gives significance of the regression coefficient.

effect relations and with explanatory power suggestive of a degree of validity. However, several potential threats to validity need to be considered in making use of JEMs.

The results of the JEM used in this study are critically dependent on the weightings (table 2). Ratings for job activities were based on extensive interviews in the industry²⁹ and were revised on several occasions with the Delphi technique. Similar iterative techniques were used by Nanni *et al*¹⁴ to improve exposure characterisation for agricultural studies. Although such iteration may represent a form of validation, more formal evaluation of JEMs is essential.¹³ Validation by one or more field industrial hygiene studies of workers involved in the job activities identified in the scale to confirm or adjust the original estimates should be performed for this JEM in future.

Similarly, the accuracy of the crop weighting is dependent on the precision and homogeneity of secondary data sources used to calculate these factors.^{28, 29} Errors in the size of relative hectareage on different crop sectors may produce large differences in intensity of agrichemical use, and the use of an average applied to the sector assumes a homogeneous pattern of use, which is clearly not always the case.¹⁷ For example, South African agriculture makes use of a multiplicity of agrichemicals^{22, 28}: about 1800 agrichemicals are available for use including >25 different organophosphates for fruit farming alone, and about 10 to 15 new agents are registered on average per year.^{22, 29} By comparison, Zimbabwe has about 500 registered agrichemical formulations,³⁹ Senegal about 200, and Malaysia 320.⁴⁰

One way to circumvent the lack of homogeneity is to further stratify the estimation of sector based patterns of use by geographical area¹⁵ or other measurable variables known to influence these patterns. However, for organophosphate insecticides in the fruit industry, secondary data suggest that differences in geographical patterns of use seem to be minimal, and for deciduous fruit farming, confined to non-organophosphate agrichemicals.^{28, 29} Inclusion of further strata to the JEM may introduce unworkable levels of complexity to the matrix and may only be worth attempting where heterogeneity of use patterns is both known and substantial. In any event, data confirm that the bulk of lifetime exposures among subjects in this study took place in deciduous fruit farming, and thus the application of JEMs reliant on sectorwide data on the organophosphate agrichemical market should apply equally across the study group.

Another source of heterogeneity in patterns of use may arise as a result of different job activities with chemical specificity.¹⁷ For example, back-

pack sprayers on fruit farms may only apply herbicides. To assess this, job activities associated with specific exposures were clearly identified during field data collection. In the example of backpack spraying, subjects were asked whether the spraying was for herbicide or insecticide, and if they were unable to distinguish, whether the spray was directed at the tree or at the ground.

Further possible refinements to the JEM, not attempted with this study, should be mentioned. The inclusion of the use of personal protective equipment as a component of the JEM has been successfully demonstrated elsewhere.¹⁷ However, use of personal protective equipment in South Africa is low^{21, 24} as is the case in many developing⁴¹⁻⁴³ and developed countries^{17, 44} and may not have a substantial influence on worker exposure, particularly when reconstructing past exposures. None the less, data on use of personal protective equipment should be measured, and in the main study²² this was examined independently of the JEM for possible associations with adverse health outcomes.

Routes of environmental exposure should also be taken into account. For example, non-occupational exposures have been implicated in studies of neurotoxic disease in Canada^{45, 46} and Israel,⁴⁷ and farm workers may be contaminated by indirect means such as spray drift,⁴⁷ crop residues,⁴⁸ or by consumption of contaminated water. In South Africa, data suggest that farm workers' residences are often within or adjacent to orchards, vineyards, or fields,²⁴ and in the absence of any empirical data to the contrary, domestic environmental exposure resulting from contamination of drinking or washing water, or from direct drift of spray into households may be substantial.²⁷ Moreover, improper storage and disposal of chemicals,^{21, 24, 49} reuse of agrichemical containers for domestic purposes such as for drinking water or washing,²¹ and the use of farm agrichemicals for the control of domestic pests⁵⁰ may be additional sources of exposure. Although not included in the JEM, the main study²² examined all these variables independently in exposure-effect analyses.

A third concern is the need to incorporate historical changes in patterns of use of agrichemicals in JEM estimates¹⁵⁻¹⁷ so as to avoid substantial misclassification and bias. However, evidence from a study of bulb farmers in The Netherlands suggests that within a particular functional group of agrichemicals, there may be consistency of use of one of several members of the same class of agrichemical.¹⁷ Under these circumstances, a JEM for organophosphate exposure may be

less sensitive to these changes in patterns of use. In fruit farming in the Western Cape, the use of one organophosphate (parathion) has been largely replaced by another (azinphos methyl) over a period of 10 to 20 years.²⁸ None the less, further research would be indicated to include period specific patterns of use in a JEM for agriculture in South Africa. Moreover, if a specific chemical is implicated in adverse health effects, such consistency within a group will be of little use to exposure-effect analyses.

Despite this range of possible biases, the study has suggested a limited degree of predictive validity to the JEM. In the bivariate linear regressions of standardised erythrocyte cholinesterase on measures of long term exposure, the crudest metric (years of farming employment) yielded a non-significant and positive regression coefficient, suggesting anomalously that longer duration of service was associated with higher concentrations of cholinesterase. However, when more complex JEM derived weighted exposures were used, these regression coefficients were negative, as would be expected with greater exposure. Moreover, the model r^2 s for the most weighted JEM variables (EWWGHT and EXWGHTI) were significant ($p < 0.04$) and this remained the case in the multiple regression (table 5), showing that the value of the JEM is less sensitive to confounding by age. Presumably, repeated exposures to low doses of organophosphates may lead to persistent lowering of red cell concentrations of cholinesterase. Although the strength of this association is small (partial $r^2 = 0.05$), this result suggests that the JEM used to construct historical exposure in this study was able to discriminate between broad organophosphate exposures, and the findings warrant further exploration.

The reliability of a JEM is critically dependent on the accuracy of information provided by respondents. When reliability of data on job activity is shown to be good,¹⁷ the estimates generated from the JEM may be used with confidence. There is evidence that self reported work histories have adequate validity for distant recall⁵¹ and for farmers reporting pesticide exposure.¹ Data from this study suggest

that for cumulative exposure, repeatability of estimates from the JEM are adequate. However, even when misclassification of component data for the JEM exists, the effect on estimates of risk in dose-response studies may not necessarily be substantial¹³ if it can be shown empirically that the JEM is insensitive to changes in the relevant variables making up the JEM.¹⁷

Interpretation of the results of the JEM must take account of the differences between exposure, subject dose, and tissue dose.³² On the one hand, use of a rate of agrichemical application/hectare is a reasonable proxy for estimating subject exposure, given that agrichemical applications are calculated on quantities/hectare. This will most closely approximate an epidemiological measure of dose for subjects. However, it should be remembered that because of the many factors influencing uptake, metabolism, and distribution of the chemical dose in specific tissues is rarely a linear function of exposure dose, and estimates of exposure-effect relations may either be underestimated or overestimated depending on the pharmacokinetics of the chemical agent concerned.⁵³

Conclusion

The JEM does not necessarily reflect absolute exposure, but may usefully provide a ranking within a population under study, or an exposure score to compare across groups. Despite the limitations of JEMs, these methods of exposure ascertainment offer a substantial advance over conventional dichotomous exposed/non-exposed categories. Careful attention to the assumptions underlying the particular JEM will improve exposure characterisation and the power of exposure-effect analyses. Data from this study show that the JEM derived for use in agriculture seems to have acceptable reliability, and suggest a degree of validity based on its ability to predict red blood cell cholinesterase, a known biological marker of organophosphate exposure. The JEM therefore seems promising for epidemiological use in farming studies, particularly in developing countries where data on chemical application and biological monitoring are often unavailable.

Appendix

Use of a job exposure matrix (JEM) to estimate cumulative lifetime and average lifetime exposure to organophosphates

Steps in deriving long term exposure with a JEM for agriculture:

Job activities are weighted according to exposure estimate for each activity and for the crop sector involved (table 2).

Within each job:

- (A) Compute the actual days spent in different activities potentially exposed to organophosphates for each activity separately.
- (B) Multiply the duration of each activity (A) by the estimate of exposure for each activity (table 2).
- (C) Sum activity weighted duration (B) of all activities with potential exposure to organophosphates in that job. This generates total activity weighted exposure days for the job.
- (D) Multiply the summed activity weighted duration for the job (C) by constants specific to the type of production on that farm (table 2) to derive weighted a) kg or, b) biological equivalent of organophosphate exposure.

Then for all jobs:

- (E) Derive cumulative exposure by summing all the exposures derived above (D) for every lifetime job for: (a) kg or (b) biological equivalent of organophosphate.
- (F) Derive average lifetime exposure by dividing (E) by working life-years for each subject according to a log transformation:

$$\text{Average lifetime intensity of exposure} = \log ((\text{cumulative weighted days exposed to organophosphates}/\text{working life}) + 1).^{30}$$

A job exposure matrix for agricultural work, a simple example:

- M is 29 years old and began working at the age of 20. His working lifespan is therefore nine years.
- Currently, M has worked as a tractor sprayer on a fruit farm for seven years spraying, on average, eight months a year, five days a week (1212 spraying days). M's job also entailed mixing the organophosphate indoors. In the same job, M also worked in the fruit orchards doing thinning for six seasons, on average two days a week for two weeks/year (24 thinning days) and occasional gardening for the farmer (28 gardening days).
- In his previous job, M worked on a vineyard as a seasonal worker for two years for a month every time doing general vine maintenance (48 days). M was also twice asked to help with insecticide spraying by backpack for a single day at a time. M was not required to mix the insecticides with this activity.

	Step A	Step B	Step C	Step D	Step E cumulative exposure	Step F average lifetime inten- sity exposure
Job 1 activity:						
Vineyard maintenance	48	2.4				
Backpack spray	2	1.4				
Total job 1			3.8	(a) 0.002 (b) 0.017		
Job 2 activity:						
Mistblower	1212	1212				
Thinning	24	2.4				
Gardening	28	1.4				
Total job 2			1215.8	(a) 16.588 (b) 522.744		
Total all jobs					(a) 16.590 (b) 522.744	(a) 1.045 (b) 6.259

(a) = kg organophosphate; (b) = biological equivalents.²⁷⁻²⁹

This study was supported by research grants from the International Development Research Centre (IDRC-Canada), the South African Medical Research Council, and by the Guy Elliot Research Fellowship in the Department of Medicine at the University of Cape Town. We thank Ms Anele Midgeley for her assistance in preparing the manuscripts.

- Blair A, Zahm S. Methodological issues in exposure assessment for case-control studies of cancer and herbicides. *Am J Ind Med* 1990;18:285-93.
- Maroni M, Fait A. Health effects in man from long term exposure to pesticides. A review of the 1975-91 literature. *Toxicology* 1993;78:1-174.
- Blair A, Zahm S, Pearce NE, et al. Clues to cancer aetiology from studies of farmers. *Scand J Work Environ Health* 1992;18:209-15.
- Copeland KT, Checkoway H, McMichael J, Holbrook RH. Bias due to misclassification in the estimation of relative risk. *Am J Epidemiol* 1977;105:488-95.
- Rothman KJ. *Modern epidemiology*. Boston: Little Brown, 1986.
- Blair A, Stewart PA. Do quantitative exposure assessments improve risk estimates in occupational studies of cancer? *Am J Ind Med* 1992;21:53-63.
- Council for Scientific Affairs. Cancer risk of pesticides in agricultural workers. *JAMA* 1988;260:959-66.
- Lilienfeld DE, Gallo MA. 2,4-D, 2,4,5-T and 2,3,7,8-TCDD: an overview. *Epidemiol Rev* 1989;11:28-58.
- Hoar SK, Morrison AS, Cole P, et al. An occupational and exposure linkage system for the study of occupational carcinogenesis. *J Occup Med* 1980;22:722-5.
- Pannet B, Coggon D, Acheson ED. A job-exposure matrix for use in population based studies in England and Wales. *Br J Ind Med* 1985;42:777-83.
- Bouyer J, Hemon D. Comparison of three methods of estimating odds ratios from a job-exposure matrix in occupational case-control studies. *Am J Epidemiol* 1993;137:472-81.
- Kromhout H, Heederik D, Dalderup LM, et al. Performance of two general job-exposure matrices in a study of lung cancer morbidity in the Zutphen cohort. *Am J Epidemiol* 1992;136:698-711.
- Kauppinen TP, Mutanen PO, Seitsamo JT. Magnitude of misclassification bias when using a job-exposure matrix. *Scand J Work Environ Health* 1992;18:105-12.
- Nanni O, Ricci M, Lugaresi C, et al. Iterative use of a priori exposure matrices to improve the characterisation of chemical exposures in agriculture work studies. *Scand J Work Environ Health* 1993;19:191-9.
- Migli L, Settini L, Masala G, et al. Pesticide exposure assessment: a crop exposure matrix. *Int J Epidemiol* 1993;22(suppl 2):S42-5.
- Daures JP, Momas I, Bernon J, et al. A vine-growing exposure matrix in the Hérault area of France. *Int J Epidemiol* 1993;22(suppl 2):S36-41.
- Brouwer DH, Brouwer EJ, Van Hemmen JJ. Estimation of long-term exposure to pesticides. *Am J Ind Med* 1994;25:573-88.
- Heikkilä P, Kauppinen T. Occupational exposure to carcinogens in Finland. *Am J Ind Med* 1992;21:467-80.
- London L. Agrichemical hazards in the South African farming sector. *S Afr Med J* 1992;81:560-4.
- Barlin-Brinck M. *Pesticides in South Africa—an assessment of their use and environmental impact*. Durban: The Wildlife Society of South Africa, 1991.
- Emanuel K. *Poisoned pay: farmworkers and the South African pesticide industry*. Johannesburg: Group for Environmental Monitoring and The Pesticide Trust, 1992.
- London L, Myers JE, Nell VN, et al. An investigation into neurological and neurobehavioural effects of long-term agrichemical use among deciduous fruit farm workers in the Western Cape, South Africa. *Environ Res* 1997;73:132-45.
- Myers JE. Occupational health of farmworkers. *S Afr Med J* 1990;78:562-3.
- London L. Agrichemical safety practices on farms in the Western Cape. *SA Med J* 1994;84:273-8.

- Donaldson A, Roux A. Education, employment and income of black South Africans in 1985. *Development Southern Africa* 1994;11:131-43.
- Stewart PA, Stewart WF, Heineman EF, et al. A novel approach to data collection in a case-control study of cancer and occupational exposure. *Int J Epidemiol* 1996;25:744-52.
- London L, Myers JE. Critical issues in agrichemical safety in South Africa. *Am J Ind Med* 1995;27:1-14.
- London L, Myers JE. Agrichemical usage patterns and workplace exposure in the major farming sectors in the Southern Region of South Africa. *South African Journal of Science* 1995;91:515-22.
- London L, Myers JE. *Agrichemical hazards and the work process in agriculture in the Western Cape*. Rondebosch, Cape Town: Department of Community Health, University of Cape Town, 1993. (Occupational Health Research Unit Report number 1.)
- Berberian IG, Enan EE. Neurotoxic studies in humans occupationally exposed to pesticides. *J Soc Occup Med* 1987;37:126-7.
- Checkoway H, Pearce NE, Crawford-Brown DJ. *Research methods in occupational epidemiology*. New York: Oxford University Press, 1989:18-45.
- Checkoway H, Rice CH. Time-weighted averages, peaks and other indices of exposure in occupational Epidemiology. *Am J Ind Med* 1992;21:25-33.
- Seixas NS, Robins TG, Becker M. A novel approach to the characterisation of cumulative exposure for the study of chronic occupational disease. *Am J Epidemiol* 1993;137:463-71.
- Coye MJ, Lowe JA, Maddy KT. Biological monitoring of agricultural workers exposed to pesticides: I. Cholinesterase activity determinations. *J Occup Med* 1986;28:619-27.
- Lotti M. Central neurotoxicity and behavioural effects of anticholinesterases. In: Ballantyne B, Marrs TM, Aldridge WN, eds. *Clinical and experimental toxicology of organophosphates and carbamates*. Stoneham, MA: Butterworth, 1992:465-87.
- McConnell RS, Cedillo L, Keifer M, et al. Monitoring organophosphate insecticide-exposed workers for cholinesterase depression: new technology for office or field use. *J Occup Med* 1992;34:34-7.
- Rosner B. *Fundamentals of biostatistics*, 3rd ed. Boston, Massachusetts: PWS Kent, 1990.
- London L, Thomson ML, Sacks S, et al. Repeatability and validity of a field kit for estimation of cholinesterase in whole blood. *Occup Environ Med* 1995;52:57-64.
- Loewensen R. *Epidemiological studies of the effects of agrichemicals. Paper presented to Zimbabwe Occupational Safety Council, Safety and Health at Work Conference*. Harare: Zimbabwe Congress of Trade Unions, 1989.
- Pesticides Trust. *The FAO code: missing ingredients. Prior informed consent in the international code of conduct on the distribution and use of pesticides. Final report October 1989*. London: PAN International and Pesticides Trust, 1989.
- Mwanthi M. Agrochemicals: potential hazards to health. *Africa Health* 1994;16:18-9.
- Gupta SK, Jani JP, Saiyed HN, et al. Health hazards in pesticide formulators exposed to a combination of pesticides. *Indian J Med Res* 1984;79:666-72.
- Matos EL, Loria DJ, Albano N, et al. Pesticides and intensive cultivation: effects on working conditions and workers' health. *Pan American Health Organisation Bulletin* 1987;21:405-21.
- Moses M. *Field survey of pesticide-related working conditions in the US and Canada. Monograph*. San Francisco: PAN International, 1988.
- Barbeau R, Roy Cloutier L, Plasse L, et al. Environmental and genetic factors in the aetiology of Parkinson's disease. In: Yahr MD, Bergmann KJ, eds. *Parkinson's disease. Advances in Neurology*. New York: Raven Press, 1986;45:299-306.
- Kaplan JG, Kessler J, Rosenberg N, et al. Sensory neuropathy associated with Dursban (chlorpyrifos) exposure. *Neurology* 1993;43:2193-6.
- Richter ED, Rosenvald Z, Kaspi L, et al. Sequential cholinesterase tests and symptoms for monitoring organophosphate absorption in field workers and persons exposed to pesticide spray drift. *Toxicol Lett* 1996;33:25-35.
- Davies JE, Stevens ER, Staiff DC, et al. Potential exposure of apple thinners to phosalone. *Bull Environ Contam Toxicol* 1982;29:592-8.
- Brown AC, Fourie HO. Pesticidal poisoning in the Republic of South Africa. *Community Health in South Africa* 1987;3:8-10.
- London L, Ehrlich R, Rafudien S, et al. Pesticide poisoning notification in the Western Cape 1987-91. *S Afr Med J* 1994;84:269-72.
- Migli L, Masala G. Methods of exposure assessment for community-based studies: aspects inherent to validation of questionnaires. *Appl Occup Environ Hyg* 1991;6:502-7.
- Ford DP, Schwartz BS, Rothman N. Assessment of exposure and dose in neurotoxicology: clinical and epidemiologic applications. In: Bleecker ML, Hansen JA, eds. *Occupational neurology and clinical neurotoxicology*. Baltimore: Williams and Wilkin, 1994:23-42.
- Smith TJ. Occupational exposure and dose over time: limitations of cumulative exposure. *Am J Ind Med* 1992;21:35-51.