Supplement

Scand J Work Environ Health 2005;31(1):33-39

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This article in PubMed: www.ncbi.nlm.nih.gov/pubmed/16190147

Discussion paper

Scand J Work Environ Health 2005;31 suppl 1:33–38

Effects of errors in the measurement of agricultural exposures

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Kromhout H, Heederik D. Effects of errors in the measurement of agricultural exposures. *Scand J Work Environ Health* 2005;31 suppl 1:33–38.

The measurement error in agricultural exposures can be expected to be substantial given the nature of agricultural production. Agricultural work is often seasonal, and exposures to chemical and biological agents vary in a temporal sense due to the task variety and intermittent nature of most agricultural exposures. Exposure patterns are also often complex in terms of the specific agents involved and entail mixed exposure situations. However, farmers often have stable careers and tend to stay in the same working and living environment. Their conservative attitudes also make them reliable sources of past production patterns, machinery, and chemical use. To reduce the measurement error that potentially obscures relations between agricultural exposures and health outcomes, more effort should be put into revealing actual determinants of agricultural exposures. Knowledge of these determinants can be used in questionnaires for retrospective exposure assessment, either in studies of the general population or within agricultural populations, and can be used to predict exposure more reliably.

Key terms biological active dust; particulate matter; pesticide; variability.

Variability in agricultural exposures

Agricultural exposures to chemical and biological agents can be expected to be governed by seasonal patterns. This and the fact that, in most situations, exposure takes place under outdoor conditions could give rise to large temporal variability in exposure concentrations. The widespread application of pesticides in agricultural production makes farmers and other agricultural workers stand out from the rest of the community in terms of their exposure to these chemicals in general. However, between individuals within the agricultural population and in a temporal sense, the exposure to specific pesticides will vary highly depending on the type of agriculture (livestock versus arable production), type of crop (vegetables, fruits, flowers), type of application method (knapsack, boom sprayer, etc), controls installed (cabin versus no cabin), and use of personal protective devices. Given all these possible variations in determinants of agricultural exposures (and pesticides in particular), it is difficult to accurately assess the intensity, duration, and frequency of exposures.

An impression of the magnitude of this variability in exposure concentrations (and potential measurement error) in agriculture can be obtained from the occupational hygiene literature. From a large database with more than 10 000 repeated personal measurements of inhalable exposures from a wide variety of industries (1), it was estimated that, among people working outdoors in an intermittent process (like farmers working outdoors), daily concentrations, on the average, lie within a 150-fold range, while their individual mean exposures, on the average, are within a 10-fold range. People working indoors in an intermittent process (like farmers working in greenhouses or stables) were estimated to have their daily concentrations lie, on the average, within a 90-fold range, while their individual mean exposure averages within a 10-fold range. Recently, a similar exercise was done for dermal exposures, which are highly relevant in the agricultural environment, especially for exposure to pesticides. With this dermal exposure database with more than 6000 repeated measurements (2) as a basis, it was estimated that, for agricultural re-entry workers exposed to pesticides, daily concentrations averaged within a 10- to 40-fold range. For these workers, no between-worker differences in mean exposure were noted. The most likely explanation for this phenomenon is the comparable tasks of

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these workers and an omnipresent source of exposure (dislodgeable foliar residues). For sheep dippers, the daily concentrations averaged within a 30-fold range, and their mean concentrations averaged within a 300-fold range. In addition to these two sources of variability, it was shown that the main source of variability was due to differences in dermal exposure between parts of the body.

In table 1, an overview is presented of variance ratios estimated in large field studies in various sectors of agriculture. In all cases, the temporal (day-to-day) variability outweighs the variability between persons (even when they come from different farms). The picture is relatively similar whether we look at mineral dust, organic dusts (containing endotoxins), or pesticides. Farmers from California (5–6) farming outdoors had dust and endotoxin concentrations vary even more than predicted from the database of Kromhout et al (1). Dutch pig farmers (7–8), on the other hand, showed somewhat less variability than expected in their agricultural exposures. Most strikingly, the differences in mean exposures for more than 100 pig farmers were within a factor of 4. Given the large variability in agriculture, quite a few studies were able to show that determinants like tasks, machinery, control measures, stable characteristics, feeding systems, and the like could explain substantial amounts (35–80%) of the variability of exposures (4, 7, 9).

Table 1. Variance ratios of between- and within-worker distributions of some agricultural exposures [taken from de Cock et al (3, 4), Nieuwenhuijsen et al (5), Nieuwenhuijsen et al (6), and Preller et al (7, 8)]. (K = number of individuals, N = number of measurements, $_{BW}R_{.95}$ = ratio of the 97.5th and 2.5th percentiles of the between-worker exposure distribution, $_{WW}R_{.95}$ = ratio of the 97.5th and 2.5th percentiles of the within-worker (day-to-day) exposure distribution)

Type of exposure [a]	K	N	$_{BW}R_{.95}$	$_{WW}R_{.95}$
Dutch fruit growers (3–4)				
Inhalable captan	108	154	3.1	541
Dermal captan, wrist	133	188	17.3	143
Dermal captan, hands	128	182	45.1	65.3
Dutch pig farmers (7–8)				
Inhalable dust	131	262	3.7	8.6
Inhalable endotoxins	125	250	4.1	20.9
Californian livestock and arable farmers (5–6)				
Inhalable dust	73	142	62.4	62.6
Inhalable endotoxins	73	142	187	523
Respirable dust	63	144	21.6	144
Respirable endotoxins	63	144	38.5	57.9

[a] Reference numbers in parentheses.

Table 2. Regression coefficients (β) and standard errors (SE) between the baseline forced expiratory volume in 1 second (l) and the log-transformed average of the measured and modeled exposure to endotoxins for all pig farmers (N=121) and asymptomatic farmers (N=62) [taken from Preller et al (8)].

Endotoxins	All farmers		Asymptomatic farmers	
	β	SE	β	SE
Measured	–0.03	0.09	0.05	0.12
Predicted	–0.21	–0.16	–0.41 [a]	0.21

[a] P=0.03.

Given the nature of agricultural exposures and the potential for misclassification and measurement error, it is surprising that any exposure–response relation has been reported at all. Using individual measurements would, in most cases, lead to exposure–response relations that are largely biased to the null.

Consequences for epidemiologic studies within agriculture

In the study of Dutch pig farmers, the ratio between the day-to-day variability and the between-person variability for exposure to endotoxins was 4.7. With only two repeated measurements per farmer, it could be estimated that the exposure–response relation would be attenuated by 70% when the relation between exposure to endotoxins and lung function parameters is studied using simple formulas that describe the effect of measurement error in independent variables in regression models (7–8, 10). Therefore, a modeling approach was used by which the major determinants of exposure were identified (farm and task characteristics, where farm characteristics explained almost all between-worker variability and task characteristics explained a large part of the day-to-day variability) (7). These models were used to reduce the effect of day-to-day variability in exposure concentrations. For this purpose, information from diaries that the farmers kept for a week twice during the course of one year was fed into the models to arrive at more accurate estimates of these farmers' average exposures. As expected, in the exposure–response analyses, the estimates based on the information from the diaries outperformed estimates of exposure based on the actual measurements of 2 days (table 2). The increased amount of information used to estimate mean exposure had resulted in less misclassification. A positive relation between exposure to endotoxins and lung function parameters was apparent, the accurate data on determinants of exposure covering a longer period than the measurements. This relation was totally obscured when measurement data fraught with measurement error were used to predict average exposure (8).

While it may be difficult to estimate differences in exposure between agricultural workers, it is possible to use generic questions in studies of the general population (case–control), because they result in considerable contrast between persons exposed and unexposed to agricultural exposures. Studies within agriculture suffer, however, from a lack of contrast, accuracy, and precision. As has been shown, the use of quantitative measurement data does not necessarily result in more accurate exposure assessment, since we are dealing with mixed exposure situations with enormous variability in exposure (concentrations) and often we have only limited numbers of exposure measurements available (due to logistical problems). Good exposure modeling practices, combined with additional information collection, can remedy this problem to a large extent.

Evidence of the effect of measurement error

Is there any evidence of the consequences of a lack of contrast and variability in agricultural exposures? In the case of non-Hodgkin's lymphoma and agricultural exposures, most evidence, according to McDuffie et al (11), comes from community-based case–control studies. Several of these case–control studies have shown increased risks for farmers (12–15), farming practices (16), or specific groups of pesticides (17–20). Positive cohort studies within agriculture, focusing on non-Hodgkin's lymphoma, have been relatively few and have shown contradictory results (21–22). This situation is not surprising when methods of exposure assessment within agricultural cohorts do not address the variability in pesticide exposures well enough to create subgroups with real contrast in exposure.

Given what is known about agricultural exposures, one would have to put effort into identifying persons with high exposures, since their outcome determines the slope of the exposure–response relation (figure 1). With this in mind, one could ask why questions like "Were pesticide-contaminated clothes washed in the same washing machine as the regular family wash?" are used in community-based case–control studies. Such a question did not seem to be relevant for discriminating between medium and high pesticide exposure among Canadian male farm residents (11). On the contrary, without evidence that "washing pesticide contaminated clothes in the same washing machine as the regular family wash" actually leads to increased exposure, one can expect the specificity of the applied pesticide exposure assessment to go down. From the classical misclassification literature (23) and knowledge that pesticide exposure in the community will have a low prevalence, one should not be surprised to end up with a negative study for the relation with pesticide exposure (11).

Another example comes from a case–control study on neuroblastoma among children (24). In this community-based study, the prevalence of exposure to pesticides turned out to be (as expected) low, at 3.8% and 0.7% for fathers and mothers, respectively, when estimated by a comprehensive industrial hygiene review of their job history. For the fathers, an odds ratio (OR) of 1.5 [95% confidence interval (95% CI) 0.7–3.4] was found when exposure assessment was based on the expert review. Self-reported exposure to pesticides was, however, substantially higher, at 7.5% and 3.4% for fathers and mothers, respectively. According to the experts it was unlikely that 49% of the fathers and 80% of the mothers who considered themselves exposed were actually exposed to pesticides. No relation between self-reported exposures and neuroblastoma was found. The exposure classification, based on job title, showed opposite patterns from what was found with the expert assessment, namely, that mothers had an increased odds ratio of 3.2 (95% CI 0.9–11.7), while the fathers showed no increased odds ratio (OR 1.3, 95% CI 0.6–2.6). Given these very contradicting results, it is clear that the method used to assess exposure really makes a difference. Since the exposure assessment methods used in this study were not validated, no inferences can be made regarding which results were closest to the true association between pesticide exposure and neuroblastoma.

Methods using standardized and validated questions focusing on determinants of exposure to pesticides are needed. Epidemiologists should choose the exposure assessment method shown to yield the most accurate and precise estimates of exposure that will not lead to nondifferential bias or worse differential bias.

Algorithms for the quantitative assessment of exposure to pesticide

The largest prospective cohort study of agricultural workers, the Agricultural Health Study (25), focused

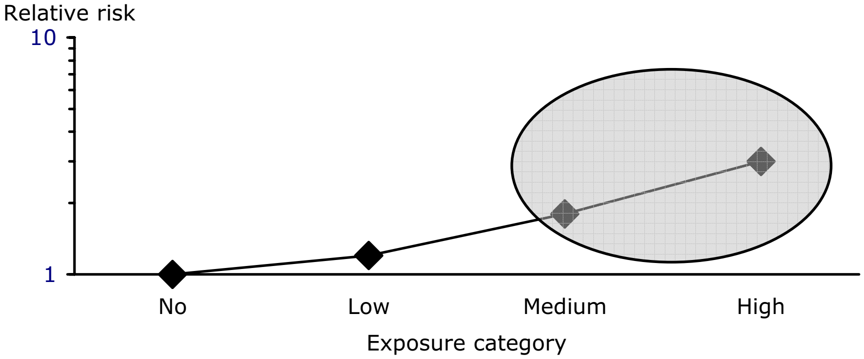

Figure 1. Slope of the exposure–response relation depending on our ability to assess medium and high exposure accurately.

primarily on cancer and exposure to pesticides among 58 000 pesticide applicators in North Carolina and Iowa in the United States. Recently the approach for estimating exposure in this cohort was published (26). The authors claimed that their approach yielded quantitative estimates of exposure to pesticides. Two algorithms were developed. A "basic algorithm" was based on information from the enrollment questionnaire on variables like mixing status, application method, repair status, and the use of personal protective equipment. The "detailed algorithm" also used the information on variables in the general algorithm, but, in addition, used more-detailed information from a take-home questionnaire, including variables such as the type of mixing system, the presence of a cabin on tractors, and the like. Weighting factors were based on published measurement data and professional judgment. Frequency and duration information was pesticide-specific; however, intensity-related information was collected for all the pesticides combined. No validation of the algorithms was presented. In table 3, mean scores of pesticide exposure are presented for 2,4-dichlorophenoxyacetic acid (2,4-D) and chlorpyrifos. The exact agreement between the two algorithms was low, being 28% for intensity and 50–57% for cumulative exposure. The authors reported that important differences were apparent between private and commercial applicators, the commercial applicators having a longer duration of exposure.

Will (semi-)quantitative methods as described by Dosemeci et al (26) work? Validation of the algorithms (especially the intensity part) will be needed before this question can be answered.

A recent study on semen quality and occupational exposure to pesticides and solvents validated the performance of several exposure assessment methods. This study showed that most methods based on questionnaires and interview data are only able to distinguish people with high exposures from the rest (medium, low and no exposures) (27–28).

Unfortunately, one cannot change anything about the mixed exposure environment of the applicator, and it may be important to include re-entry exposure with lower exposures but longer duration as well. For instance, de Cock et al (3) estimated slightly higher cumulative exposure to captan (a fungicide) during the harvesting season than during the growing season (when most pesticide applications occurred) for fruit growers and their collaborating sons. For their wives (partly participating in harvesting activities), cumulative exposure during the harvesting season was estimated to be 4–5 times higher than during the growing season (table 4). In both seasons however re-entry tasks were by far the major contributors to the cumulative exposure to captan.

Validation studies within the Agricultural Health Study are underway and some primary results have recently been published (29). This analysis suggested that pesticide applicators provided plausible information on the duration of pesticide use. Additional evidence that farmers are able to report accurately on commonly used pesticides and pesticide categories was reported by

Table 3. Mean scores for exposure to 2,4-dichlorophenoxyacetic acid (2,4-D) and chlorpyrifos using either the "basic" or "detailed" algorithm [taken from Docemeci et al (26)].

Pesticide	Number of observations	Intensity				Duration				Cumulative exposure			
		Basic		Detailed		Basic		Detailed		Basic		Detailed	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
2,4-D	16 077	6.5	3.8	5.9	4.0	164	284	164	284	1082	2341	1108	2303
Chlorpyrifos	8 565	6.2	3.6	7.3	5.7	79	176	65	124	395	853	492	1272

Table 4. Estimated relative contribution of the main tasks to the total cumulative exposure by inhalation and the dermal route for fruit growers, sons, and wives for each season [taken from de Cock et al (3)].

	Growing season				Harvesting season				Total (mg), both seasons
	Application (%)	Re-entry (%)	Home (%)	Total (mg)	Application (%)	Re-entry (%)	Home (%)	Total (mg)	
Inhalable exposure									
Farmer	4	95	1	37	2	97	<1	44	81
Son	1	98	1	35	<1	99	<1	52	87
Wife	0	91	9	6.4	0	98	2	26	33
Dermal exposure									
Farmer	6	84	10	202	3	89	7	238	440
Son	2	87	11	194	<1	93	5	274	468
Wife	0	47	53	60	0	84	17	151	211

Engel et al (30). These authors concluded that recall accuracy was probably high enough for analyses of broad categories of pesticides, but not high enough for detecting more specific relations. Going a step beyond use patterns and trying to estimate long-term exposure to pesticides accurately will fall or stand with the validity of the algorithms used for exposure intensity.

Concluding remarks

It should no longer be a surprise that, when the chronic effects of agricultural exposures are being studied, positive results are more often found in case–control studies within the general population than in studies within farmer populations. The contrast between farmers and the general population is large, especially if the agriculture-specific exposures of biological origin or exposures to pesticides are considered. Studies within the agricultural population suffer, to a large extent, from the enormous variability in exposure concentrations. This factor, along with logistical difficulties in obtaining large numbers of measurement data from the agricultural population, makes exposure–response relations often go unnoticed.

One will only find informative relations between agricultural exposures and chronic effects if one knows how to treat the inherent large temporal and spatial variability in exposures, for instance, by (i) focusing on proved determinants of exposure in the epidemiologic analysis or (ii) using predicted exposures based on exposure determinant models that diminish the effect of day-to-day variability in exposure.

Even with better exposure assessment methods available, not all problems will be solved. With a shift of agricultural production to less-developed countries (with less well-informed farmers and farm workers) and a less stable and less-informed workforce of migrant workers in western agriculture, studying health effects of agricultural exposure may well become even more complicated in the near future (31–32).

Acknowledgments

The authors would like to thank Dr Mark Nieuwenhuijsen for making his measurements of agricultural exposures of farmers in California available to the authors, enabling them to estimate variance components.

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