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Rule-based exposure assessment versus case-by-case expert assessment using the same information in a community-based study

Susan Peters,[1] Deborah C. Glass,[2] Elizabeth Milne,[3] Lin Fritschi,[1] and the Aus-ALL consortium

1. Centre for Medical Research, University of Western Australia, Perth, WA, Australia

2. Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC, Australia

3. Telethon Institute for Child Health Research, Centre for Child Health Research, University of Western Australia, Perth, WA, Australia

Corresponding author: Susan Peters, PhD

susan.peters@uwa.edu.au

ABSTRACT

Background Retrospective exposure assessment in community-based studies is largely reliant on questionnaire information. Expert assessment is often used to assess lifetime occupational exposures, but these assessments generally lack transparency and are very time-consuming. We explored the agreement between a rule-based assessment approach and case-by-case expert assessment of occupational exposures in a community-based study.

Methods We used data from a case-control study of childhood acute lymphoblastic leukaemia in which parental occupational exposures were originally assigned by expert assessment. Key questions were identified from the completed parent questionnaires and, based on these, rules were written to assign exposure levels to diesel exhaust, pesticides, and solvents. We estimated exposure prevalence separately for fathers and mothers, and used Kappa statistics to assess the agreement between the two exposure assessment methods.

Results Exposures were assigned to 5829 jobs among 1079 men and 6189 jobs among 1234 women. For both sexes, agreement was good for the two assessment methods of exposure to diesel exhaust at a job level (κ=0.70 for men and κ=0.71 for women) and at a person level (κ=0.74 and κ=0.75). The agreement was good to excellent for pesticide exposure among men (κ=0.74 for jobs and κ=0.84 at a person level) and women (κ=0.68 and κ=0.71 at a job and person level, respectively). Moderate to good agreement was observed for assessment of solvent exposure, which was better for women than men.

Conclusion The rule-based assessment approach appeared to be an efficient alternative for assigning occupational exposures in a community-based study for a selection of occupational exposures.

Keywords: exposure assessment; community-based study; algorithm

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What this paper adds

- Retrospective exposure assessment in community-based studies is often performed by experts on a case-by-case basis, but these assessments generally lack transparency and are very time-consuming.
- We explored the agreement between a standardised rule-based assessment approach and case-by-case expert assessment of three occupational exposures that are different in occurrence and distribution over workplaces.
- The rule-based approach appeared to be an efficient alternative to assign occupational exposures to diesel exhaust and pesticides, and to a lesser extent for solvents, in a community-based case-control study. This method will be particularly useful for risk identification.

INTRODUCTION

Retrospective exposure assessment in community-based studies is largely reliant on questionnaire information. Case-by-case expert assessment is often used to assess lifetime occupational exposures and is considered to be a reliable method.[1] [2] However, these assessments generally lack transparency and are very time-consuming.

Recently, several developments to structure expert assessment in community-based studies have been described. Fritschi and colleagues developed a web-based application (OccIDEAS) to automate part of the expert assessment process.[3] This application uses pre-defined exposure assignment rules and makes the process more transparent and objective, and, although experts still need to make some of the final decisions, improves the efficiency.[3] Pronk *et al.* (2012) applied algorithms to assign decision rules to assess occupational exposure to diesel exhaust in a US case-control study of bladder cancer.[4] Moderately high agreement was observed between the algorithm and expert assessment, showing that such a framework may improve the efficiency, consistency and transparency of the exposure assessment process. However, the authors advised caution because assessment of diesel exhaust exposure is relatively straightforward, and therefore the observed advantages might not be generalizable to other occupational exposures.[4] OccIDEAS and the algorithm approach both provided an instrument to replicate exposure decisions in other studies.[3] [4]

The Aus-ALL study was a case-control study that used case-by-case expert assessment to investigate the association between parental occupational exposures and childhood acute lymphoblastic leukaemia (ALL). Results have been published previously.[5-7] The questionnaire information became available for exposure assessment in six batches as they were collected. It was a time-consuming process to individually assess the thousands of job histories, which also made consistency over time difficult. Another study on childhood brain tumours (Australian childhood brain tumour study, Aus-CBT), was recently conducted with the same study design and data collection instruments.[8] In a

quest to identify a more standardized and, above all, efficient way to accurately assess occupational exposures in Aus-CBT, we explored the possibility of applying a 'rule-based assessment' to replace the case-by-case expert assessment.[9] [10] The Aus-ALL study provided us with the opportunity to compare the two methods and to investigate the feasibility of a rule-based approach among both men and women in a community-based study.

For the current comparison of assessment methods we have selected three occupational exposures that are different in occurrence and distribution over workplaces. The first is diesel exhaust, which is a combustion product affecting workers in a wide range of jobs. Second is pesticide exposure, which is related to a relatively limited number of specific tasks in a limited number of occupations. Lastly, we assessed exposure to solvents, as these include aromatic, aliphatic and chlorinated solvents occurring in a variety of workplaces.

METHODS

Aus-ALL was a nation-wide Australian case-control study of risk factors for childhood acute lymphoblastic leukaemia. Full details of the study have been published elsewhere.[11] Three controls, frequency matched by age, sex and state of residence, were recruited for each case by random digit dialling. In total, 416 cases and 1361 controls aged under 15 years were recruited from mid-2003 to 2006.

Both parents were asked to complete a written questionnaire requesting demographic and lifestyle details and a lifetime occupational history up to the birth of the child for the father and up to one year after the birth for the mother. Information requested about each job included the year started and finished, job title, employer, main tasks, and hours worked each week. If the mother or father reported ever having worked in any of certain jobs (carpenter/cabinet maker, chemist, office

worker, drycleaner, driver, engineering technician, farmer, fisherman, gas station attendant, hairdresser, health professional, labourer, mechanic, miner, metal worker, painter, printer, radio operator, railway worker, shoemaker, store man, or teacher) or working in particular industries (aluminium, forestry, military, leather, oil refining, rubber, or textile), they were telephoned and trained interviewers used job-specific modules (JSM) to ask them further detailed questions about tasks they undertook in that job. The relevant JSMs were assigned by members of the Aus-ALL research team before contacting the subjects by telephone.

An occupational hygienist (DG, 2005-2008) reviewed all job histories to assess exposure to solvents, exhausts, paints and pigments, glues, pesticides, lead, ionizing and non-ionizing radiation, and extremely low frequency electromagnetic fields. Blinded to case status she determined the likelihood of exposure (no, possible or probable exposure), level of exposure (low, medium, high), and frequency of exposure (hours per week and weeks per year). These assessments have been used in previous reports from the Aus-ALL study.[5-7] Occupational histories and corresponding case-by-case expert assessments were available for 1079 men (328 case and 751 control fathers) and 1234 women (379 case and 855 control mothers). For the current analyses, only likelihood of exposure was taken into account, where jobs were considered exposed when classified by the expert as 'probable' exposed. Jobs with 'no' or 'possible' exposure were considered non-exposed.

For the 'rule-based assessment', one of the authors (SP, 2012) selected key questions that indicated exposure from the JSM interviews. Based on the answers to these questions, rules were written to assign exposures (yes/no) to diesel exhaust, pesticides, and solvents (benzene, other aromatics, aliphatics and chlorinated solvents). The preliminary rules were discussed with the exposure expert who performed the original exposures (DG) and modified where necessary to finalise the rules to be used in the current comparison study.

The rules we developed were based on the questionnaire used for this study. For the different exposures, different numbers of questions were selected: for pesticides the assessment was based on 11 specific questions from 6 JSMs; diesel exhaust was based on 26 questions from 11 JSMs; benzene was based on 16 questions from 14 JSMs; other aromatic solvents based on 31 questions from 16 JSMs; aliphatic solvents was based on 30 questions from 16 JSMs; and chlorinated solvents was based on 20 questions from 11 JSMs. Rules that lead to assignment of exposure to an agent were either based on the response to one question only (*e.g.* exposure to diesel exhaust when the answer to *"What kind of vehicle did you usually drive?"* was 'a bus' or 'a truck'), or based on the combination of responses to two or three questions. An example of the latter is assigning exposure to diesel exhaust when 'Yes' was answered to both the questions *"Were trucks being loaded or unloaded in the area where you worked?"* and *"Were their engines usually running?"*. Time period was taken into account for use of chlorinated solvents in the printing industry, for which exposure was only assigned when the job was before 1990.

9.5% (n=103) of the fathers and 18.7% (n=231) of the mothers did not report working in any of the relevant jobs or industries and were therefore not assigned an interview. JSM interviews were conducted with 97.9% (n=955) of the fathers and 96.8% (n=970) of the mothers who had reported working in at least one of the relevant jobs or industries. Not all JSMs of the relevant jobs were included in the interview, however, due to the burden on the respondent. If more than five JSMs were assigned to a subject, a selection of five JSMs was made by the research team prior to the interview; these represented the longest held, or most different from other jobs. In total, interviews were available for 62.1% (n=2416) of the JSMs for relevant jobs of the fathers and for 60.8% (n=2053) of those of the mothers. If no JSM was available for a parent, the original exposure assessment was based on information from similar JSMs answered by that parent. If no similar JSMs were completed, a generic assessment was assigned based on typical answers from other parents with that job. The rule-based approach used the originally assigned JSM to assess the exposures. A

JSM without interview was then assessed as 'exposed' if, based on the interviews held in the rest of the study population, an exposure was assigned to more than 50% of that particular JSM.

We compared the original case-by-case expert assessment with the rule-based assessment. Both methods were reliant on the same digitised information as extracted from the telephone interviews using JSMs. We calculated Kappa statistics (κ) as a measure of inter-method agreement.[12] Assignments using the original case-by-case expert assessment were compared with those using the rule-based approach, based on exposed versus non-exposed jobs and persons. The κ was interpreted using the following arbitrary cut points: <0.4 poor; 0.4-0.75 moderate to good; and >0.75 as excellent.[12] Statistical analyses were conducted using SAS v.9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Exposures were assessed for 5829 jobs among 1079 men and 6189 jobs among 1234 women from the Aus-ALL study. Overall, exposure prevalence was lower among women than men (Table 1). For both sexes, agreement was good for the two assessment methods of exposure to diesel exhaust at a job level (κ=0.70 for men and κ=0.71 for women) and at a person level (κ=0.74 and κ=0.75). The agreement was good to excellent for pesticide exposure among men (κ=0.74 for jobs and κ=0.84 at a person level) and assessments for pesticide exposure among women showed good agreement (κ=0.68 and κ=0.71 at a job and person level, respectively).

Overall, better agreement was observed for assessments of solvent exposure for women than men. Agreements between the two assessment methods for the specific solvents were moderate to good for benzene, other aromatics and aliphatics in both men and women (Table 2). The agreement was lowest for chlorinated solvents (κ=0.26 at a job level for men, and κ=0.46 for women).

Table 3 shows the agreement between the two methods separately for jobs where interview data was available and for jobs without an interview. The latter group also included jobs where no JSM was assigned. Better agreement was observed for jobs with interview data (ranging from κ=0.56 to κ=0.80) compared with jobs for which no interview was performed (κ=0.31-0.54).

DISCUSSION

Rule-based exposure assessment has the potential to replace case-by-case expert assessment of occupational exposures in community-based studies that have to rely on questionnaire data. The main advantages of a rule-based approach are: (a) full standardization of the exposure assessment process; (b) documentation of all decisions made in the assessment which increases the transparency; and (c) a less labour-intensive method that will save time and costs.

Overall agreement between the exposures assessed by algorithm and by expert was good at both a job and a person level. Neither of the two methods appeared to assign systematically a higher or lower prevalence of exposure than the other. We collected occupational histories from both parents so we were able to compare the results among men and women. Since men are generally more often employed in jobs with exposures to hazardous substances, it was not surprising that exposure prevalence was higher for men for all agents assessed. Agreements between the two assessment methods were comparable between men and women. Only the agreements for exposure to solvents were somewhat higher among women.

So far, the rule-based approach has only been described and evaluated for diesel exhaust exposure in a US case-control study of bladder cancer.[4] They observed high agreement ($\kappa_{weighted}$=0.81) between the algorithm and expert assessment method for probability of diesel exhaust exposure at a job level, which they defined in four categories.[4] This agreement is comparable to our findings: κ=0.70

for men and κ=0.71 for women. Assessment of exposure to diesel exhaust is considered relative straightforward: diesel exhaust has an offensive odour and the source (diesel engines in vehicles or other equipment) is clear. The accuracy of assessment of diesel exhaust exposure may therefore be greater than for other agents.[4]

In our study, however, exposure to pesticides showed the highest agreement (Kappa=0.74 at a job level for men). This high agreement is probably due to the clear tasks related to pesticide exposure. Agreements for solvent exposures were somewhat lower, but still moderate to good in most cases, except for chlorinated solvents (κ=0.26 for men and κ=0.46 for women on a job level). Chlorinated solvents appear to be particularly difficult to assess. For example, a study comparing the assessments by experts from different study centres showed poor agreement for chlorinated solvents (κ=0.11), while agreement was excellent for diesel exhaust (κ=0.80).[13] A recent study on trichloroethylene exposure and non-Hodgkin lymphoma used a comprehensive exposure assessment method, combining occupational histories, job- and industry-specific modules with specific focus on solvents, and task-, job-, industry-, and decade-specific exposure matrices developed based on an extensive literature review.[14] The industrial hygiene expert considered all these data when assigning potential exposure to trichloroethylene. The use of more detailed information for exposure assessment of trichloroethylene enabled the detection of significantly increased risks of non-Hodgkin lymphomas, which were not detected using less detailed exposure assessment methods.[14]

The aim of the rule-based assessment was to standardise the exposure assessment process. Although the approach is different from the case-by-case expert assessment, their starting points are the same. Both methods rely on the same information from the subjects (*i.e.* the responses to the questionnaires) and expert knowledge; although in the case-by-case assessment an expert is able to take into account free text fields as well. On the one hand, differences between the rule-

based approach and the expert assessment may reveal the lack of flexibility of the rules in cases where additional information leads to the classification of exposure by the expert. OccIDEAS, for example, therefore uses expert views as a complement to the rules for complex decisions.[3] Agreement between the two methods in our study was higher when we limited the comparison to the jobs for which interview data were available (Table 3). This observation may indicate that, in situations where interview data are not available, individual assessments based on free-text fields on job, employer and tasks may be required. On the other hand, differences between the methods may reflect the main weakness of case-by-case expert assessment, namely that there is inevitably a degree of subjectivity. The process of assessing thousands of job histories, assessing exposures to numerous agents, takes several months, which makes it nearly impossible to be perfectly consistent.

In the US study, statistical learning techniques (*i.e.* classification and regression tree (CART) and random forest models) were applied to identify the underlying rules of the expert's exposure assignments to diesel exhaust.[15] In that study two exhaust-specific questions were available for each job of each participant (*i.e. 'While at this job, did you ever work near diesel engines or other types of engines?'* and *'While at this job, did you ever smell diesel exhaust or other types of engine exhaust?')*.[4] The variable constructed from these two questions appeared to be the most predictive.[15] However, this type of information is generally not available for all subjects in community-based studies. This was also not the case in our study, where there was a wide range of questions asked in the different JSMs. Therefore, we identified the key questions for each exposure manually. Identification of the most important information for an exposure decision will help in refining questionnaires in future studies.[15] This can reduce the respondent burden, which may improve the feasibility of data collection in case-control studies, as time needed for occupational data collection can be shortened by asking only essential questions.

We have only compared the assessment of exposed versus non-exposed, which is sufficient for risk identification. For risk quantification, however, more detailed information is required. Measurement data would be preferred as quantitative exposure assessment is the ultimate goal in all occupational studies.[16-18] Unfortunately, measurements are not always available, particularly not in community-based case-control studies which are the most efficient type of study to investigate risk factors for rare diseases or rare exposures. In those situations input from experts can be used to assign exposure levels.[19] Besides a rule-based approach, the use of job-exposure matrixes (JEMs) is another standardised and transparent method that is often applied in community-based studies.[20 21] Unlike JEMs, however, rule-based assessment based on questionnaire information allows account to be taken of individual differences between workers within the same job title.[22] The main limitation of the rule-based approach, as well as of case-by-case expert assessment, is that it is dependent on the questions selected for the respondents and their answers. This might lead to misclassification due to missing information or recall bias.

To determine the implications of the differences between methods, resulting risk estimates should be compared. Ideally this would be done within a study with an established association between occupational exposure and disease outcome, as for example has been done for several lung carcinogens.[21] The ability of the method to detect a known association gives an indication of its effectiveness. No external exposure has yet been established as a cause of childhood ALL, so we were not able to test the effectiveness of the methods in this way. Nevertheless, the Kappa's presented in this paper show a moderate to good agreement between the rule-based approach and the conventional method.

Overall, the rule-based exposure assessment approach appeared to be an efficient way to assign occupational exposures to diesel exhaust and pesticides, and to a lesser extent for solvents, in a community-based case-control study. This method may therefore be applicable as a substitute for

case-by-case expert assessment, particularly for risk identification. While both methods use the same information, the rule-based approach is more standardised and transparent, and is less time-consuming.

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Table 1. Comparison between exposure assessment methods for three occupational exposures

			Original case-by-case expert assessment		Rule-based assessment		Agreement
			% exposed[a]	N	% exposed[a]	N	Kappa[b] (95% CI[c])
Diesel exhaust	Job level	Men	17.5%	1021	14.0%	817	0.70 (0.67 to 0.72)
		Women	1.2%	74	1.2%	72	0.71 (0.62 to 0.79)
	Person level	Men	38.6%	416	34.1%	368	0.74 (0.70 to 0.79)
		Women	4.4%	54	4.1%	51	0.75 (0.66 to 0.85)
Pesticides	Job level	Men	4.3%	248	4.1%	241	0.74 (0.69 to 0.78)
		Women	0.3%	20	0.5%	30	0.68 (0.53 to 0.83)
	Person level	Men	12.4%	134	12.1%	130	0.84 (0.79 to 0.89)
		Women	1.0%	12	1.3%	16	0.71 (0.52 to 0.90)
Solvents combined	Job level	Men	20.7%	1205	11.7%	682	0.51 (0.48 to 0.54)
		Women	4.4%	271	3.3%	203	0.71 (0.66 to 0.75)
	Person level	Men	47.7%	514	30.2%	325	0.57 (0.52 to 0.62)
		Women	11.5%	142	8.4%	104	0.71 (0.65 to 0.78)

[a] Percentage exposed by applying the respective exposure assessment method; [b] Kappa statistic comparing the two exposure assessment methods; [c] Confidence Interval

Table 2. Comparison between exposure assessment methods for occupational exposures to specific solvents

			Original case-by-case expert assessment		Rule-based assessment		Agreement
			% exposed[a]	N	% exposed[a]	N	Kappa[b] (95% CI[c])
Benzene	Job level	Men	3.3%	156	2.7%	194	0.60 (0.54 to 0.66)
		Women	0.7%	41	0.7%	45	0.63 (0.51 to 0.75)
	Person level	Men	12.4%	134	11.0%	119	0.71 (0.64 to 0.78)
		Women	2.8%	34	3.1%	38	0.71 (0.59 to 0.83)
Other aromatic solvents	Job level	Men	9.7%	563	9.7%	566	0.51 (0.47 to 0.55)
		Women	1.3%	78	1.1%	66	0.55 (0.45 to 0.65)
	Person level	Men	28.3%	305	26.6%	287	0.57 (0.51 to 0.62)
		Women	4.3%	53	4.1%	50	0.67 (0.59 to 0.77)
Aliphatic solvents	Job level	Men	19.9%	1158	11.4%	666	0.52 (0.49 to 0.55)
		Women	4.3%	263	3.0%	186	0.70 (0.65 to 0.75)
	Person level	Men	46.5%	501	29.4%	317	0.58 (0.53 to 0.62)
		Women	11.0%	135	7.4%	91	0.71 (0.64 to 0.78)
Chlorinated solvents	Job level	Men	1.6%	94	1.3%	76	0.26 (0.17 to 0.35)
		Women	0.2%	10	0.4%	25	0.46 (0.25 to 0.66)
	Person level	Men	5.5%	59	3.5%	38	0.36 (0.24 to 0.49)
		Women	0.7%	9	1.5%	18	0.51 (0.28 to 0.74)

[a] Percentage exposed by applying the respective exposure assessment method; [b] Kappa statistic comparing the two exposure assessment methods; [c] Confidence Interval

Table 3. Agreement on job level between the two exposure assessment methods for three occupational exposures, stratified by availability of interview data

		All jobs	**Jobs without interview data[a]**	**Jobs with interview data**
Number of jobs	Men	5829	3396	2433
	Women	6189	4125	2064
Agreement		*Kappa[b]*	*Kappa[b]*	*Kappa[b]*
Diesel exhaust	Men	0.70	0.52	0.74
	Women	0.71	0.38	0.76
Pesticides	Men	0.74	0.54	0.80
	Women	0.68	0.53	0.77
Solvents combined	Men	0.51	0.31	0.56
	Women	0.71	0.52	0.79

[a]Including the jobs where no job-specific module (JSM) was assigned; [b]Kappa statistic comparing the rule-based assessment with the original case-by-case expert assessment