

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

TABLE 1. QUALITY SCORING OF PAPERS WITH CANCER AS HEALTH OUTCOME

1A. Cohort Studies

Study	Response rate	Exposure assessment	Confounders	Bias	Disease characterisation	Dose-response data	Conclusions of study	Quality score
Alavanja (2005)	32,347 spouses of applicators were enrolled in the study, and 13,760 (42.5%) did not personally apply pesticides (“unexposed”); less than 1% of the whole cohort (N=319) was lost to mortality or cancer incidence follow-up in 7.2 years of follow-up	self-administered questionnaire; no detailed exposure information:- estimate of days/ years of personal application of pesticides, or no personal application. SIRs cover the whole group of spouses, regardless of exposure	smoking status, frequency of alcohol consumption and education level noted	1) small loss to follow-up of cohort as a whole 2) missing data on use of pesticides for 16.6% of spouses 3) exposure misclassification likely	cancer incidence ascertained from population-based cancer registries in Iowa and North Carolina	not applicable	the incidence of several types of cancer among spouses of farmers/private applicators was observed to be lower than expected, but there was an unexpected finding of excess of melanoma	3 based on lack of detail in the exposure assessment, missing data for spouses, and SIRs reported for whole group of spouses, regardless of use/non-use of pesticides
Engel (2005)	74% of eligible wives enrolled in the cohort; 61% of those enrolled completed 2 questionnaires, one of which elicited information on exposure and general health, and the other on	take-home questionnaire completed by wives about farm exposures; for specific pesticides, the exposure of wives who never used pesticides is based only on their husbands’	age, race, state of residence (Iowa/ North Carolina)	1) missing data: numbers of cases and non-cases included in the analyses differ across the individual 50 pesticides and the classes of pesticides because of missing data 2) inaccurate recall	incident breast cancer cases identified through population-based cancer registries	no exposure-response trend observed for general measures of possible indirect exposure, such as frequency of washing work clothes worn during pesticide	some evidence of an increased breast cancer risk in women who did not use pesticides themselves is presented for the husbands’ use of the fungicide captan, but is not significant for chlorpyrifos	3 study clearly identifies a para-occupationally exposed group, “wives who never used pesticides”; however, there is a low response rate, incomplete data, and inaccuracy surrounding the

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	reproductive health history; 39% completed only the exposure and general health questionnaire	cumulative use, but study authors lacked information on how long each woman had been married to her current partner		3) possible misclassification of exposure		application (days/year); for specific pesticides, an exposure-response trend is reported for cumulative husbands' use of certain pesticides, but insufficient information was available to evaluate trends for captan		exposure assessment
Flower (2004)	about 82% of eligible private pesticide applicators enrolled	self-report on take-home questionnaire; applicators and spouses reported on personal mixing and application of pesticides, and frequency of mixing and application; exposure to individual pesticides and pesticide classes is shown when the number of cases was at least 5	parental age at child's birth, child's sex and birth weight, ever/never parental smoking, paternal history of cancer, maternal history of miscarriage examined but are reported not to be significant, so are excluded; child's age at parent's enrolment in study was included as a confounder in final models	1) missing exposure data for 5-6% of children in most analyses 2) exposure misclassification possible 3) inaccurate recall of frequency of exposure or of specific pesticides used 4) small numbers of cases for most types of exposure, often less than 10	Iowa Cancer Registry used to identify cases of childhood cancer	no dose-response relationships observed	study suggests small increase in risk of all childhood cancers combined, and lymphoma specifically; also suggests a modest increase in risk among children of men who apply pesticides without using chemically resistant gloves	2 limited power for many of the detailed exposure analyses because of small numbers

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Kristensen (1996)	out of 323,359 children born between 1952 - 1991 who were followed up for incident cancer in the Cancer Registry, 67 did not contribute person-time to the study (0.02%)	information taken from agricultural censuses; crude indicators of exposure were used:- horticulture; orchards or greenhouses on holding; pesticide purchase; horticulture and pesticide purchase; orchards or greenhouses and pesticide purchase.	Rate Ratios in the Poisson regression adjusted for year of birth and calendar year	1) missing data: information on pesticide purchase only in 1969 census, 24.9% missing; information on pesticide spraying equipment only in 1979 census, 7.1% missing; 2) exposure misclassification; 3) misclassification due to criteria used for definition of "farmer"	cancer classification based on information on cancer site and morphology in the Cancer Registry of Norway	there is some evidence for a dose-response relationship for the association between non-Hodgkin's lymphoma and different levels of pesticide purchase (test for trend $p=0.04$), but the exposure indicator "pesticide purchase" is restricted to subjects covered in the 1969 census, which had 24.9% missing data	no significant differences in SIRs for cancer at all sites were observed in the study; significantly elevated RRs for a few specific types of cancer are reported	3 based on the nature of the exposure assessment, with use of crude indicators of exposure, and the possible bias indicated

1B. Case-Control Studies

Study	Response rate	Exposure assessment	Confounders	Bias	Disease characterisation	Dose-response data	Conclusions of study	Quality score
Alderton (2006)	75% of mothers of cases, 81% of controls (but only 51% of the primary care clinics contacted were able to provide lists of children with Down's syndrome and no leukaemia)	telephone questionnaire to mothers; mother's report of exposure to professional pest exterminations around time of pregnancy, and mother's report of child's exposure to professional pest exterminations	child's race, gestational age, birth weight; maternal age at delivery, mother's educational level, smoking during pregnancy	1) potential recall bias between mothers of cases and mothers of controls; 2) selection bias likely among the controls, since approximately one third of primary care clinics declined to provide lists of potential controls, and contact information was not available for a further one third of children selected; 3) some indication of selection by socioeconomic status – mothers of controls had significantly more years of education than mothers of cases	cases of acute leukaemia identified through registration files of the Children's Oncology Group	categories of "any", "low" (frequency of exposure below the median) and "high" exposure (frequency of exposure above the median) were determined; no dose-response trend was seen for either maternal or child exposure	some evidence presented for a positive association between maternal exposure to professional pest control applications around the time of pregnancy and childhood ALL in a sample of children with Down's syndrome	2 based on the reported response rate, and possible areas of bias noted
Buckley (2000)	86% of eligible cases	telephone interview with mother: mother's report of exposure during pregnancy to professional insect extermination, and report of either parent being occupationally	cases and controls were matched for age, race and gender	1) selective recall bias likely, over-reporting of pesticide exposure by case parents; 2) validation of exposure difficult, especially since some exposures occurred many years previously;	81% of cases were classified histopathologically	some evidence for a dose-response trend for the pesticide exposure score, but the "score" is an arbitrary scoring system based on answers to all the pesticide-	some associations reported between exposure of the mother during pregnancy to professional pest control, and occupational exposure of the parents, and the risk of NHL in children	3 good participation rate and histopathological classification of 81% of cases, but several areas of possible bias, and for the dose-response evaluation, para-

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		exposed to unspecified pesticides		3) misclassification of exposure likely, both in terms of the agent of interest and the dose		related questions; all exposure information is combined together, so para-occupational exposure is not differentiated		occupational exposure is not reported separately
Carreon (2005)	90.2% of cases (only 57% were direct respondents, 43% were proxies), and 71.6% of controls (98% were direct respondents, 2% were proxies)	interview to complete a questionnaire; self-report of residence on a farm and performance of household tasks involving possible pesticide exposure; also self-reported exposure to classes of pesticides and to 12 specific pesticides	adjustments made for age, 10-year age group, and education	1) large number of proxy respondents for the cases – 43%; proxy responses for only 2% of controls, so possibility of differential misclassification bias; 2) retrospective assessment of exposure relied on participants' and proxies' memory, so exposure misclassification is likely; 3) differential recall between cases and controls is likely; 4) authors comment that reliability of proxy responses on details of agricultural practices was poor	histologically confirmed primary intracranial gliomas, identified through medical facilities and neurosurgeon offices	not applicable	study does not find evidence to support the hypothesis that farm residence or specific types of para-occupational exposure increase the risk of glioma in women	3 possibility of a large amount of bias affecting the results due to large number of proxy respondents for cases, and exposure is assessed partly through the surrogate of residence on a farm

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Colt (2006)	76% of potentially eligible cases and 52% of potentially eligible controls	1) self-administered questionnaire and computer-assisted interview; 2) carpet dust sample analysis for 18 specific pesticides; to estimate risk, individuals with detectable levels of an analyte were grouped into quartiles; 3) participants were asked about pesticide treatment for 8 specific types of insects, not products used; 4) application of insecticides by the respondents themselves, or by professional applicator, was not treated separately	adjustments for study centre, sex, education, age and race	1) missing data: dust samples were analysed only for approximately half of the samples:- 682 out of 1321 cases, and 513 out of 1057 controls; further missing data because some analytes contained interfering compounds, and values were assigned based on estimates; 2) a “large number” of people had incomplete information on the number of treatments of their homes	cases identified through the National Cancer Institute Surveillance Program; pathology reports were classified according to the International Classification of Diseases for Oncology, 3 rd edition	no evidence of a dose-response trend for levels of propoxur, carbaryl, chlorpyrifos, diazinon, <i>cis</i> -permethrin or <i>trans</i> -permethrin measured in carpet dust	the evidence presented in the study does not suggest an association between NHL risk and carpet dust levels of some major insecticides	3 although the study has actual measurements of insecticide residues in carpet dust, there is an appreciable amount of missing data and incomplete information for the participants, and the response rate was relatively low, especially for controls
Cooney (2007)	80% of case mothers and 76% of control mothers completed interviews	telephone interview with mother; mother's report of application of pesticides in the house by a professional applicator	household income, maternal education, breast feeding, maternal age, child's age at reference date, geographic region of residence	1) possibility of inaccurate recall, because mothers were asked to remember exposure details from several years before; 2) only mother's report of exposure was used because of poor response from fathers –	cases were newly diagnosed patients registered with the National Wilms' Tumour Study (NWTS), a North American collaborative clinical trial study of the treatment and biology of Wilms tumour	not analysed	study does not provide evidence of increased risk of developing Wilms Tumour from exposure to pesticides applied by a professional applicator	2 based on the response rate, the nature of the exposure assessment and the possible kinds of bias

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				mothers and fathers may differentially recall the use of pesticides around the home				
Daniels (2001)	73% of eligible case mothers and 76% of eligible case fathers provided interviews; for controls, 72% of eligible mothers and 61% of eligible fathers provided interviews	telephone interviews with mothers and fathers of children; parents' report of professional insect extermination in the house	child's age, race, household income, maternal age, education	1) differential recall of use of pesticides in the home between mothers and fathers - Odds Ratios were different when both parents reported use of professional extermination or when either parent reported use; 2) 35% of couples in the study disagreed about whether/when pesticides were used; 3) it is not known if recall bias was greater when both parents reported on exposure than when exposure was reported by only one parent; 4) inaccurate recall – parents asked to remember events from 1 to 5 years earlier; 5) missing data due to low response rate, especially among control fathers	diagnosis of neuroblastoma was confirmed by two collaborative clinical trial groups, the Children's Cancer Group and the Pediatric Oncology Group	not analysed	study reports some elevated Odds Ratios for use of professional pest control in the home or garden and neuroblastoma in children, but all Confidence Intervals include 1.0	3 based on the large amount of possible bias indicated, relatively low response rates and the lack of objective exposure assessment

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Hartge (2005)	59% of presumed eligible cases, 44% of presumed eligible controls	1) computer-assisted personal interview, report by participants of number of applications of herbicides by a lawn care professional; 2) levels in house dust of 2,4-dichlorophenoxy-acetic acid and dicamba	education, family history of lymphoma, whether currently or previously working as a farmer, insecticide use	1) missing data: only 679 out of 1,321 cases had carpet dust samples analysed, and 510 out of 1,057 controls; 2) some degree of misclassification due to inaccuracy in reporting pesticide use, and measurement errors in environmental pesticide samples	cases identified from SEER (Surveillance Epidemiology and End Results) registries for 4 states	no evidence of a dose-response trend with increasing levels of 2,4-dichlorophenoxy-acetic acid or dicamba in carpet dust samples, or with increasing number of applications of herbicides by lawn care professional	study suggests no increased risk of NHL from residential exposures to herbicides by professional application	1 despite the low response rate, the use of dust sampling is an objective measure, and avoids recall bias. The two exposure assessments, personal interviews and carpet dust samples, are in agreement (both suggest no increased risk of NHL)
Infante-Rivard (1999)	96.3% of parents of eligible cases gave an interview, and 83.8% of parents of eligible controls (491 cases and 491 controls analysed)	telephone interview; mother's report of house treatment by professional applicator during pregnancy and/or during childhood of the index child	adjustments for maternal age and maternal level of schooling; cases and controls matched for age, sex, and geographical region	1) controls were population-based, chosen from family allowance files, instead of selection by random-digit dialling, which could lead to the selection of controls with spuriously high socioeconomic level; 2) however, interviewers were not blind to the case or control status; 3) cases may have over-reported exposure in comparison with controls	acute lymphoblastic leukaemia (ALL) was classified according to the International Classification of Diseases on the basis of a clinical diagnosis by an oncologist or haematologist in a tertiary care centre	higher Odds Ratio for >5 professional treatments of home than for 1-5 treatments of home	risks of childhood ALL were not seen to be significantly increased by exposure to professional treatment of homes against insects	1 despite the telephone interview and mother's report of house treatment by professional applicator, the classification of ALL was done by experts, and there was a good response rate and relatively large number of cases and controls. Some evidence of a dose-response supports the reliability of the findings, although the CIs do not suggest significance

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Kato (2004)	56% of cases, and 30% and 67% among 2 sets of controls	telephone interview; self-reported exposure to application of fungicides and/or herbicides by others	adjustments for age at index date, family history of haematologic cancer, college education, surrogate status and year of interview, frequency of use of pain-relieving drugs and cortisone injections, history of eczema/hives, history of antihistamine use	1) relatively low overall participation rate raises issues of selection bias and generalisability of the results; 2) surrogates were interviewed for 20.5% of the cases, and using information from surrogates can bias the results; 3) poor recall of exposures from a long time back in the past may have affected the results	copies of medical records of cases; pathology slides reviewed by expert haematopathologist for 71% of cases; 26% of these slides were reviewed by second expert haematopathologist to resolve discrepancies with original diagnoses	there is a evidence of a dose-response trend for outdoor application of insecticides by others; however, there is no evidence of a trend for indoor application of insecticides by others	one statistically significant result is reported for outdoor application of insecticides by others and the risk of NHL in women	3 based on the low response rate and likely bias. The evidence for a dose-response trend for outdoor application may be anomalous, since there is no evidence of a trend for indoor application.
Ma (2002)	83% of eligible cases and 69% of eligible controls	personal interview with mother; mother's report of exposure to professional pest control and/or lawn service around the time of pregnancy, and during years 1, 2 and 3 of the child's life	annual household income	1) potential recall bias among mothers of cases and mothers of controls; 2) potential misclassification of exposure, because exposure is based on mother's report	hospital diagnosis of leukaemia	exposure to professional pest control was not analysed for dose-response	the authors suggest that exposure of the mother during pregnancy, and of young children in the first 3 years of life, to insecticides applied indoors by pest control operators may be associated with an increased risk of childhood leukaemia	2 based on the type of exposure assessment and potential bias
McDuffie (2001)	67.1% of cases, 48.0% of controls	postal questionnaire and telephone interview; indirect estimate of exposure of "residence on a farm at any time"	potential confounders considered were: history of measles, mumps, cancer, allergy desensitisation	1) potential misclassification of exposure 2) potential recall bias 3) low response rate, especially among controls	cases ascertained from provincial Cancer Registries or from hospitals; 84% of NHL tumours were validated by reference	only analysed for individuals who mixed or applied pesticides, not analysed for number of years of	the evidence in this study does not suggest a significant association between farm residence and risk of NHL in men	3 evidence for para-occupational exposure in this study is limited, since exposure is estimated only by the indirect indicator

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			treatment, positive history of cancer in first-degree relatives		pathologist	residence on a farm		of residence on a farm
Meinert (1996)	82% of parents of cases and 71% of the contacted control families	self-administered questionnaire and telephone interview, including self-reported occupation as farmer, gardener or florist, self-reported use of pesticides on farm or of classes of pesticides, and report if pest control operator applied pesticides in the home	analysis for leukaemia cases and local controls adjusted for social status; analysis for leukaemia cases and state controls adjusted for degree of urbanisation and social status; analysis for group with solid tumours compared to local and state controls adjusted for age, sex, degree of urbanisation and social status	1) misclassification of exposure, because parents' occupations and parents' self-reported exposures were used as the basis of exposure assessment; some parents appeared to be unsure which substances were pesticides; 2) interpretation of results made difficult by use of two different control groups, local and state controls: ORs were consistently higher than 1 if cases were compared to local controls, and less than 1 for most comparisons with state controls; 3) Confidence Intervals are not reported for most of the Ors	cases identified through German Childhood Cancer Registry	not analysed	the study suggests a possible association between leukaemia in children and parental occupational exposure to pesticides, an increased risk with use on farms, and increased risk from applications by pest control operator	3 based on the limitations of the exposure assessment, problems with the use of 2 control groups, and the fact that Confidence Intervals are not reported for most of the Odds Ratios

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Meinert (2000)	84.4% of cases and 70.7% of controls	self-administered questionnaire and telephone interview; self-reported exposure to classes of pesticides and whether either parent had carried out farming; report if pest control operator applied pesticides in the home	adjustments for degree of urbanisation (urban, mixed, rural), and for socio-economic status	1) possible recall bias, with more sensitive recall among parents of cases; 2) misclassification of exposure due to crude assessment based on job title and report of involvement in farming	cases identified through German Childhood Cancer Registry	not analysed	the study suggests an association between childhood lymphoma and pesticides applied indoors by a pest control operator, and an association with leukaemia and occupational exposure of the father or mother	2 based on the limitations of the exposure assessment and likely bias
Monge (2007)	90% of cases and 90.5% of controls	interview with either or both parent/s; self-reported exposure by mother and/or father of use of 25 specific pesticides, and reported exposure of child in 5 time periods	urban or rural residence	1) possible misclassification of exposure because agricultural tasks were classified according to estimated hazard, with a score of 0 – 4; 2) the correlation coefficient between mothers' and fathers' exposures, calculated for ORs for insecticides, herbicides, and fungicides, was low (0.32), and it is uncertain whether case mothers and fathers recalled their job details better than control mothers and fathers	cases identified through the Cancer Registry and Children's Hospital of Costa Rica	authors report the "suggestion" of an exposure-response gradient (low versus high exposure) for fathers' exposure to picloram during child's first year of life, but this is based on very small numbers (10 cases of total leukaemia, 10 cases of acute lymphocytic leukaemia)	study suggests that the father's exposure to certain pesticides (e.g. picloram) during the child's first year of life may increase the risk of ALL in the child, and that the mother's exposure to certain pesticides during the child's first year of life may also increase the child's risk of developing ALL	3 although the response rate is high, the exposure assessment is uncertain: reported exposure by fathers and mothers is not in good agreement

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Ruder (2004)	93% of eligible cases and 70% of eligible controls (457 cases, 648 controls)	interview with participant or proxy, including report of ever having lived on farm, years on farm, whether laundered pesticide-applicator clothes, and whether pesticides stored in house	age, 10-year age group, education, farm residence	1) large number of proxy interviews for case participants: 47% were interviewed by proxy only, while around 3% of controls had proxy interviews, so there is possibility of differential misclassification bias; 2) there may be problems with the accuracy and completeness of information given by surrogate respondents; 3) attempt to compensate for the high proportion of proxy interviews by conducting all analyses with and without the proxy responses, and reporting both sets of results	cases identified through participating medical facilities and neurosurgeon offices; cases had to have a histologically confirmed intracranial glioma, and the tumour had to be primary	no evidence from the ORs of a dose-response with increasing number of years of residence on a farm	study does not suggest an increased risk of glioma among men who reported having been exposed to pesticides by living on a farm	3 precise characterisation of the disease outcome, but almost 50% of case participants were interviewed by proxy, which makes the reported exposure uncertain
Ruder (2006)	92% of eligible cases and 70% of eligible controls; there were larger numbers of cases and controls (798 cases, 1175 controls) than in the previous study above	interview with participant or proxy, including respondent's report of ever having lived or worked on a farm, and age of first living on a farm	adjustments made for age, 10-year age groups, education, gender, state	1) use of large number of proxy respondents, >40%, is a source of bias; 2) accuracy and completeness of information provided by proxies is variable; 3) non-participation	potential glioma case participants identified by ascertaining physicians, group practices and other medical facilities; two of the study authors re-reviewed	not analysed	farm residence in general was not seen to be associated with an increased risk of glioma, but some evidence suggests that moving to a farm as an adolescent (age 11	3 accurate characterisation of disease, but as in the previous Ruder(2004) study, exposure assessment relies heavily on proxy respondents

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				by never-farming eligible controls could have affected results	pathology reports		to20), as opposed to as an adult, was associated with a greater risk of glioma	
Teitelbaum (2007)	82.1% of eligible cases interviewed, and 62.8% of eligible controls	interview, including report of application of lawn and garden pesticide products by professional only	adjustments for age and education in the final model; characteristics assessed as possible confounders included race, age at menarche, oral contraceptive use, hormone replacement therapy use, first-degree family history of breast cancer, body mass index, alcohol use, smoking status	1) possibility of inaccurate recall, because self-reported lifetime exposure is used; 2) authors report that response rates varied by age, so either differential or non-differential misclassification is possible; 3) possible recall bias between cases and controls	cases of breast cancer confirmed by physician and medical record	no dose-response relationship observed for increasing use of pesticides; not analysed for application by professional only	study suggests there may be an association between increased risk of breast cancer and residential professional application of pesticides, but authors caution about uncertainty in this observation	2 based on self-reported lifetime exposure as the basis of exposure assessment, and other possible bias
Van Wijn-gaarden (2003)	82% of eligible cases, 74% of controls	telephone interview of fathers and mothers; probability and intensity of exposure was estimated based on industrial hygiene literature review and job-exposure matrix; 2 raters were used	maternal age, household income, maternal education	1) misclassification because exposure assessment relies on job characteristics reported by study subjects, and on a job-exposure matrix; 2) the inter-rater agreement between the two raters was only moderate	cases identified through the Children's Cancer Group	no exposure-response patterns were observed	the evidence in the study does not suggest that parental occupational exposure to pesticides increases the risk of childhood brain cancer	3 based on inaccuracy of exposure assessment – a job-exposure matrix is used - and the possible sources of bias indicated

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		to classify exposure to classes of pesticides in different jobs; self-report by farmers of which pesticides they used		(kappa coefficient 0.5-0.6), which adds to the possibility of misclassification of exposure; 3) a large proportion of mothers provided a proxy interview for fathers (e.g. 18% of fathers of astrocytoma cases and 32% of fathers of astrocytoma controls)				

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TABLE 2. QUALITY SCORING CRITERIA FOR CANCER OUTCOME PAPERS

The quality score was awarded on the basis whereby two or more criteria in a score category applied to the paper:

Quality score	Criteria
1	<ul style="list-style-type: none">• clearly identified para-occupational exposure• objective measure of exposure• expert classification of disease outcome• response rate of >90% for cases or controls, or cohort subjects
2	<ul style="list-style-type: none">• exposure assessment by questionnaire or interview, self-reported• response rate of around 80% for cases or controls, or cohort subjects• identified areas of bias likely to affect quality of study
3	<ul style="list-style-type: none">• exposure assessment by questionnaire or interview, self-reported where the information is poorer than category 2• response rate of 60% or lower for cases or controls, or cohort subjects• several kinds of bias likely to affect quality of study and the information is poorer than category 2• para-occupational exposure not reported separately