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

Table 7. REFERENCES RELEVANT TO PARA-OCCUPATIONAL EXPOSURE AND CANCER

7(A) Cancer References

Author	Year	Reference	Title	Health outcome studied	Study type
Cohort studies					
Alavanja,M.C.; Sandler,D.P.; Lynch,C.F.; Knott,C.; Lubin,J.H.; Tarone,R.; Thomas,K.; Dosemeci,M.; Barker,J.; Hoppin,J.A.; Blair,A.	2005	Scan.J. Work Environ. Health 31 suppl 1: 39-45	Cancer incidence in the Agricultural Health Study	cancer	prospective cohort
Engel,L.S.; Hill,D.A.; Hoppin,J.A.; Lubin,J.H.; Lynch,C.F.; Pierce,J.; Samanic,C.; Sandler,D.P.; Blair,A.; Alavanja,M.C.	2005	Am J Epidemiol 161 (2): 121-135	Pesticide use and breast cancer risk among farmers' wives in the agricultural health study	breast cancer incidence in farmers' wives	prospective cohort
Flower,K.B.; Hoppin,J.A.; Lynch,C.F.; Blair,A.; Knott,C.; Shore,D.L.; Sandler,D.P.	2004	Environ. Health Perspect.112 (5): 631-635	Cancer risk and parental pesticide application in children of Agricultural Health Study participants	childhood cancer	cohort, hybrid study design – retrospective and prospective identification of child cancer cases after parental enrollment
Kristensen,P.; Andersen,A.; Irgens,L.M.; Bye,A.S.; Sundheim,L.	1996	Int. J. Cancer 65 (1): 39-50	Cancer in offspring of parents engaged in agricultural activities in Norway: Incidence and risk factors in the farm environment	cancer incidence	prospective cohort
Case-control studies					
Alderton,L.E.;Spector,L.G.; Blair,C.K.; Roesler,M.; Olshan,A.F.; Robison,L.L.; Ross,J.A.	2006	Am J Epidemiol 164(3): 212-221	Child and maternal household chemical exposure and the risk of acute leukemia in children with Down's syndrome: A report from the children's oncology group	Acute lymphoblastic leukaemia and acute myeloid leukaemia in children with Down's syndrome	case-control

Author	Year	Reference	Title	Health outcome studied	Study type
Buckley,J.D.; Meadows,A.T.; Kadin,M.E.; Beau M.M.le; Siegel,S.; Robison,L.L.	2000	Cancer 89 (11): 2315-21	Pesticide exposures in children with non-Hodgkin lymphoma	Non-Hodgkin's Lymphoma and lymphomatous leukaemia in children and adolescents ≤20 years of age	case-control
Carreon,T.; Butler,M.A.; Ruder,A.M.; Waters,M.A.;Davis-King,K.E.; Calvert,G.M.; Schulte,P.A.; Connally,B.; Ward,E.M.; Sanderson,W.T.; Heineman,E.F.; Mandel,J.S.; Morton,R.F.; Reding,D.J.; Rosenman,K.D.; Talaska,G.; Cancer,B.	2005	Environ Health Perspect 113 (5): 546-551	Gliomas and farm pesticide exposure in women: the Upper Midwest Health Study	intracranial gliomas in women living in non-metropolitan areas	case-control
Colt,J.S.; Davis,S.; Severson,R.K.; Lynch,C.F.; Cozen,W.; Camann,D.; Engels,E.A.; Blair,A.; Hartge,P	2006	Cancer Epidemiol Biomarkers Prev 15 (2): 251-257	Residential insecticide use and risk of non-Hodgkin's lymphoma	Non-Hodgkin's Lymphoma in adults	population-based case-control
Cooney,M.A.; Daniels,J.L.; Ross,J.A.; Breslow,N.E.; Pollock,B.H.; Olshani,A.F.	2007	Environ Health Perspect 115 (1): 134-137	Household pesticides and the risk of Wilms tumor	Wilms Tumour in children <16 years of age	case-control
Daniels,J.L.; Olshan,A.F.; Teschke,K.; Hertz-Picciotto,I.; Savitz,D.A.; Blatt,J.; Bondy,M.L.; Neglia,J.P.; Pollock,B.H.; Cohn,S.L.; Look,A.T.; Seeger,R.C.; Castleberry,R.P.	2001	Epidemiology 12 (1): 20-27	Residential pesticide exposure and neuroblastoma	neuroblastoma in children <15 years of age	case-control
Hartge,P.; Colt,J.S.; Severson,R.K.; Cerhan,J.R.; Cozen,W.; Camann,D.; Zahm,S.H.; Davis,S.	2005	Cancer Epidemiol Biomarkers Prev 14 (4): 934-7	Residential herbicide use and risk of non-Hodgkin lymphoma	Non-Hodgkin's Lymphoma in adults	population-based case-control
Infante-Rivard,C.; Labuda,D.; Krajinovic,M.; Sinnett,D.	1999	Epidemiology 10 (5): 481-487	Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms	childhood acute lymphoblastic leukaemia	case-control
Kato,I.; Watanabe-Meserve,H.; Koenig,K.L.; Baptiste,M.S.; Lillquist,P.P.; Frizzera,G.; Burke,J.S.; Moseson,M.; Shore,R.E.	2004	Environ Health Perspect 112 (13): 1275-1281	Pesticide product use and risk of non-Hodgkin lymphoma in women	Non-Hodgkin's Lymphoma in women	population-based case-control

Author	Year	Reference	Title	Health outcome studied	Study type
Ma,X.; Buffler,P.A.; Gunier,R.B.; Dahl,G.; Smith,M.T.; Reinier,K.; Reynolds,P.	2002	Environ Health Perspect 110 (9): 955-960	Critical windows of exposure to household pesticides and risk of childhood leukemia	overall leukaemia and acute lymphoblastic leukaemia (ALL) in children 0-14 years	case-control
McDuffie,H.H.; Pahwa,P.; McLaughlin,J.R.; Spinelli,J.J.; Fincham,S.; Dosman,J.A.; Robson,D.; Skinnider,L.F.; Choi,N.W.	2001	Cancer Epidemiol Biomarkers Prev. 10(11): 1155-1163	Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health	Non-Hodgkin's lymphoma in men >19 years of age	case-control
Meinert,R.; Kaatsch,P.; Kaletsch,U.; Krummenauer,F.; Miesner,A.; Michaelis,J.	1996	Eur J Cancer 32A(11): 1943-1948	Childhood leukaemia and exposure to pesticides: results of a case-control study in northern Germany	leukaemia and solid tumours (central nervous system tumours, neuroblastomas, Wilms' tumours and rhabdomyosarcomas) in children <15 years of age	case-control
Meinert,R.; Schuz,J.; Kaletsch,U.; Kaatsch,P.; Michaelis,J.	2000	Am J Epidemiol 151(7): 639-646	Leukemia and non-Hodgkin's lymphoma in childhood and exposure to pesticides: results of a register-based case-control study in Germany	leukaemia and Non-Hodgkin's Lymphoma in children <15 years of age	case-control
Monge,P.; Wesseling,C.; Guardado,J.; Lundberg,I.; Ahlbom,A.; Cantor,K.P.; Weiderpass,E.; Partanen,T.	2007	Scand. J Work Environ Health 33(4): 293-303	Parental occupational exposure to pesticides and the risk of childhood leukemia in Costa Rica	leukaemia in children aged 0-14 years	population-based case-control
Ruder,A.M.; Waters,M.A.; Butler,M.A.; Carreon,T.; Calvert,G.M.; vis-King,K.E.; Schulte,P.A.; Sanderson,W.T.; Ward,E.M.; Connally,L.B.; Heineman,E.F.; Mandel,J.S.; Morton,R.F.; Reding,D.J.; Rosenman,K.D.; Talaska,G.	2004	Arch Environ Health 59 (12): 650-657	Gliomas and farm pesticide exposure in men: The upper midwest health study	primary intracranial gliomas in men	case-control
Ruder,A.M.; Waters,M.A.; Carreon,T.; Butler,M.A.; vis-	2006	J Agric Saf Health 12(4); 255-274	The Upper Midwest Health Study: a case-control study of	primary intracranial gliomas in adults	case-control

Author	Year	Reference	Title	Health outcome studied	Study type
King,K.E.; Calvert,G.M.; Schulte,P.A.; Ward,E.M.; Connally,L.B.; Lu,J.; Wall,D.; Zivkovich,Z.; Heineman,E.F.; Mandel,J.S.; Morton,R.F.; Reding,D.J.; Rosenman,K.D.			primary intracranial gliomas in farm and rural residents		
Teitelbaum,S.L.; Gammon,M.D.; Britton,J.A.; Neugut,A.I.; Levin,B.; Stellman,S.D.	2007	Am J Epidemiol 165 (6): 643-651	Reported residential pesticide use and breast cancer risk on Long Island, New York	breast cancer	case control
Van,Wijngaarden E.; Stewart,P.A.; Olshan,A.F.; Savitz,D.A.; Bunin,G.R.	2003	Am J Epidemiol 157 (11): 989-997	Parental occupational exposure to pesticides and childhood brain cancer	brain cancer - astrocytoma and primitive neuroectodermal tumours (PNET) - in children	community-based case control

7(B) Cancer Study Design Details

First author	Date published	Country	Study subjects	Reference populations	Health assessment method	Health outcomes investigated	Exposure assessment	Statistical analysis	Other risk factors evaluated/ confounders
Cohort studies									
Alavanja	2005	USA	spouses of private applicators n = 32,347; 13,760 spouses (42.5%) were "unexposed" to pesticides – did not personally apply pesticides	total population of Iowa and North Carolina; cohort members matched to cancer registry files in Iowa and North Carolina and to state death registries and National Death Index	self- administered questionnaire; additional questionnaire about reproductive histories and children	cancer incidence	status as spouse of private applicator/ farmer; self-reported exposure on questionnaire. Since this is a study at the ecological level, detailed exposure information is not given	Standardized Incidence Ratios(SIRs); chi-square test used to evaluate statistical significance of SIR values	smoking, alcohol consumption; education level noted
Engel	2005	USA	30,454 women who were wives of private pesticide applicators (mostly farmers) from Iowa and North Carolina and enrolled in the Agricultural Health Study between 1993-1997. Participants had no history of breast cancer prior to cohort enrolment	expected numbers of cases estimated from cancer registries for each state's population, using 5-year age and calendar-time, race-specific cancer incidence rates	self-administered questionnaire; breast cancer cases identified through population-based cancer registries	breast cancer	self-reported use/never use of 50 specific pesticides by farmers and spouses; performance of household tasks involving possible pesticide exposure, e.g. frequency of washing clothes worn during pesticide application; number of years participant lived on farm	Standardised Incidence Ratios (SIRs) for breast cancer calculated for study participants who reported any prior pesticide use and those who reported no prior use. Poisson regression used to calculate rate ratios and 95% Confidence Intervals (CIs) for exposure to various agricultural and non-agricultural risk factors among all 30,454 participants.	each pesticide exposure was examined in a separate model with adjustment for age, race, and state of residence (Iowa/North Carolina)
Flower	2004	USA	identifying information for 17, 357 children of Iowa pesticide applicators was provided by parents enrolled in the Agricultural Health Study (AHS) between 1993-1997; cancer cases among children	the Iowa Cancer Registry; cancer rates for Iowa 1975-1998 were used as reference standard in calculating Standardised Incidence Ratios (SIRs)	self-administered questionnaire; identifying information for children in Iowa was matched against the Iowa Cancer Registry to identify cases of childhood cancer	cancer diagnosed from birth – 19 years of age, to examine childhood cancer risk and associations with parental pesticide application	self-report by applicators and spouses on personal mixing and application of pesticides, and frequency of mixing and application (decade of first use, frequency and duration of use); ever use of 50 specific pesticides; individual pesticides were	SIRs were generated to compare the observed number of childhood cancer cases among children of AHS participants and the expected number of cancer cases from Iowa SEER (Surveillance	parental age at child's birth, child's sex, child's birth weight, history of parental smoking, paternal history of cancer, maternal history of miscarriage. These factors were not

First author	Date published	Country	Study subjects	Reference populations	Health assessment method	Health outcomes investigated	Exposure assessment	Statistical analysis	Other risk factors evaluated/ confounders
			were both retrospectively and prospectively identified after parental enrolment. 50 cases of childhood cancer arising between 1975-1998 were identified among AHS participants.				treated in the analysis when there were 5 or more exposed cases	Epidemiology and End Results) data; logistic regression analyses used to obtain Odds Ratios (ORs) to examine association between pesticide exposure variables and childhood cancer; multiple logistic regression models used to examine potential confounders of cancer risk	found to be significant in bivariate analyses and were excluded from final models. Child's age at parent's enrolment in study was related to cancer risk (β coefficient 0.06, p=0.02) and was included in final models
Kristensen	1996	Norway	323,292 offspring born in 1952-1991 to parents identifed as farm holders in agricultural censuses in Norway; 1,275 incident cases of cancer identified. A sub-set of the cohort was termed "farmers' offspring", and these were offspring from holdings where either parent worked for at least 500 hours annually on a farm, n=188,680; this group had 739 incident cancer cases	for standardisation, the expected numbers of cancer cases were estimated from the total rural population of Norway for each year from 1965 to 1991	data from Cancer Registry of Norway; information from agricultural censuses	incidence of all cancers and some specific types of cancer	exposure indicators were used, such as, "Orchards or greenhouses on holding; pesticide purchase; horticulture and pesticide purchase; orchards or greenhouses and pesticide purchase".	Standardised Incidence Ratios (SIRs) calculated for all cancers and for specific cancer types; Poisson regression for associations between exposure indicators and specific cancers; "Epicure" statistical software program used	Rate Ratios (RRs) in the Poisson regression were adjusted for year of birth and calendar year
Case-control studies									
Alderton	2006	USA and Canada	To assess associations with maternal exposure, 158 children with Down's syndrome and acute leukaemia: 97 acute lymphoblastic	To assess associations with maternal exposure, 173 children with Down's syndrome but no leukaemia,	telephone questionnaire to mothers; cases of acute leukaemia identified through the registration	ALL and AML and association with child and maternal exposure to household chemicals	study considers mother's exposure around time of pregnancy to chemicals used in the household, including insecticides, insect repellants, and	t test for 2 proportions or χ^2 test; unconditional logistic regression using SAS version 9.1 software	child's race, gestational age, birth weight; maternal age at delivery, mother's educational level

First author	Date published	Country	Study subjects	Reference populations	Health assessment method	Health outcomes investigated	Exposure assessment	Statistical analysis	Other risk factors evaluated/ confounders
			leukaemia (ALL), 61 acute myeloid leukaemia (AML). For child exposure, 136 Down's syndrome leukaemia cases.	randomly selected from primary care physicians' lists, frequency matched to cases by age at diagnosis of leukaemia. For child exposure, 118 Down's syndrome controls.	files of the Children's Oncology Group		herbicides; for para-occupational exposure, the mother's report of exposure to professional pest exterminations around time of pregnancy was considered		and smoking during pregnancy
Buckley	2000	USA	268 children and adolescents age≤20y identified by the Children's Cancer Group who were newly diagnosed between Feb 1986 and June 1990 with non-Hodgkin's lymphoma (NHL) or lymphomatous leukaemia	268 children matched individually; 252 controls (94%) were race matched, 254 (95%) were matched based on gender, and 243 (91%) differed in age from the case by <2 years	telephone interview with mother; pathology slides requested for central review	NHL or lymphomatous leukaemia in children	report by mother to 5 exposure-related questions; for para-occupational exposure, the relevant characteristics were exposure of the mother during pregnancy to professional insect extermination, and either parent being occupationally exposed to unspecified pesticides	conditional logistic regression to estimate relative risks of NHL/lymphomatous leukaemia for each covariate	cases and controls matched for age, race and gender; ORs for the pesticide-related questions within subgroups of cases were adjusted for maternal education and race
Carreon	2005	USA	341 cases from women aged 18-80 living in 4 states: Iowa, Michigan, Minnesota and Wisconsin.	527 women with no diagnosis of glioma, randomly selected within 10-year age-group strata. Women aged 18-64 selected from state driver's license/non-driver identification records, and women aged 65-80 from Medicare data	interviews; histologically confirmed primary intracranial gliomas diagnosed from 1 January 1995 to 31 January 1997 and identified through medical facilities and neurosurgeon offices	primary intracranial gliomas among female rural residents	self-report of residence on a farm, and performance of household task "laundered pesticide applicator clothes", which involves possible pesticide exposure; self-reported exposure to functional classes of pesticides (fungicides, herbicides, insecticides) and to chemical classes (e.g. organophosphates), and to 12 specific pesticides	unconditional logistic regression using SAS software version 8.0	adjustments for age, 10-year age group and education
Colt	2006	USA	1321 men and women aged 20-74 years, diagnosed with non-Hodgkin's lymphoma (NHL) between 1998-	1057 men and women from general population of the same state and metropolitan areas;	self-administered questionnaire, then home interview	NHL in adults	collection of blood or saliva sample, carpet dust sample analysis for 18 specific insecticides, and drinking water sample	multiple logistic regression models using SAS version 8.2	models included study centre, sex, education, age and race

First author	Date published	Country	Study subjects	Reference populations	Health assessment method	Health outcomes investigated	Exposure assessment	Statistical analysis	Other risk factors evaluated/ confounders
			2000, from Iowa and metropolitan areas of Los Angeles, Detroit and Seattle	controls under age 65 identified by random digit dialling, age >65 from Medicare files.					
Cooney	2007	USA and Canada	523 children newly diagnosed with Wilms tumour <16 years of age and treated at one of 128 participating hospitals in the USA and Canada from 1999 to 2002.	517 children identified through random digit dialling and frequency matched to cases according to age at diagnosis and geographic region of residence	telephone interview with mother	Wilms Tumour in children <16 years of age	for para-occupational exposure, report by mother of application by professional applicator in the house; pesticides not specified	unconditional logistic regression	household income, maternal education, breast feeding, maternal age, child's age at reference date, geographic region of residence
Daniels	2001	USA and Canada	538 children diagnosed with neuroblastoma between May 1, 1992 and April 30, 1994 at one of 139 participating hospitals in the USA and Canada	504 children identified through telephone random digit dialing and individually matched to cases by telephone number (area code and exchange) and date of birth	telephone interviews with mothers and fathers; confirmation of diagnosis of neuroblastoma and confirmation on the clinical stage at diagnosis by the Children's Cancer Group and Pediatric Oncology Group, and MYCN oncogene amplification status for case children	neuroblastoma in children	for para-occupational exposure, report by mothers and fathers of the use of professional insect extermination in the house; pesticides are not specified	relation between pesticide exposures and neuroblastoma evaluated by estimating odds ratios (ORs) for both parents reporting use (OR_B) and either parent reporting use (OR_E), and calculating 95% Confidence Intervals using unconditional logistic regression	race, household income, maternal age, education
Hartge	2005	USA	1,321 cases identified from 4 SEER (Surveillance Epidemiology and End Results) registries (Iowa, Los Angeles County, metropolitan Detroit, metropolitan Seattle) of residents	1,057 controls of unaffected residents identified by random digit dialling and Medicare files	computer-assisted personal interview	NHL in adults	1) for para-occupational exposure, report of total applications of herbicides by lawn care professional; 2) duration of exposure to herbicides was assessed by asking about number of years of treatment of lawn or garden for weeds;	multiple unconditional logistic regression models to estimate Relative Risk (RR) of developing NHL, using SAS version 8.2	education, family history of lymphoma, whether currently or previously working as a farmer, insecticide use

First author	Date published	Country	Study subjects	Reference populations	Health assessment method	Health outcomes investigated	Exposure assessment	Statistical analysis	Other risk factors evaluated/ confounders
			aged 20-74 years with a first primary diagnosis of non-Hodgkin's lymphoma (NHL) between July 1998 and June 2000				3) levels of the specific herbicides 2,4-dichloro-phenoxyacetic acid and dicamba were measured in dust taken from used vacuum cleaner bags in the current home for 679 cases and 510 controls		
Infante-Rivard	1999	Canada	491 cases diagnosed with acute lymphoblastic leukaemia (ALL) between 1980-1993 in the Province of Québec, aged 0-9 years, recruited from tertiary care centres which treat and hospitalise children with cancer in the province	491 population-based controls chosen from family allowance files, matched on age within 24 months, sex and region of residence at time of diagnosis	telephone interview; clinical diagnosis by oncologist or haematologist in a tertiary care centre	childhood ALL in children aged 0-9 years	for para-occupational exposure, report by mother whether home was professionally treated with insecticides against ants or cockroaches during mother's pregnancy and/or during childhood of the index child	conditional logistic regression	adjustments for maternal age and maternal level of schooling
Kato	2004	USA	376 cases identified through the State Cancer Registry and resident in the upstate counties of New York State; women were 20-79 years of age and newly diagnosed with non-Hodgkin's lymphoma (NHL) during the 3 year period of 1 October 1995- 30 September 1998	463 controls selected from Medicare beneficiary files and state driver's license records	telephone interview; copies of medical records of cases; pathology slides obtained and reviewed by a haematopatholo-gist	NHL in women	self-report of exposure to types of home pesticides (e.g. "fungicides/plant pesticides"), and "application type" – applied by self, indoor application by others, outdoor application by others.	unconditional logistic regression using SAS software	Odds Ratios (ORs) for NHL associated with selected home pesticides and by application type were adjusted for age at index date (1 year before diagnosis), family history of haematologic cancer, college education, surrogate status and year of interview, frequency of use of pain-relieveing drugs and

First author	Date published	Country	Study subjects	Reference populations	Health assessment method	Health outcomes investigated	Exposure assessment	Statistical analysis	Other risk factors evaluated/ confounders
									cortisone injections, history of eczema/hives, history of antihistamine use
Ma	2002	USA	162 cases from the first phase (1995-1999) of the Northern California Childhood Leukaemia Study. Cases were newly diagnosed leukaemia, rapidly ascertained from major clinical centres, usually within 24 hours of diagnosis; 135/162 patients had diagnosis of acute lymphoblastic leukaemia (ALL)	162 controls randomly selected from the California birth registry, matched 1:1 to cases on date of birth, sex, mother's race, Hispanicity and mother's county of residence at time of child's birth	case ascertainment by hospital	leukaemia in children aged 0-14 years	for para-occupational exposure, report by mother in interview of use of professional pest control services and professional lawn service, during the time windows of 3 months before pregnancy, pregnancy, and years 1, 2 and 3 of the child's life	conditional logistic regression analyses for overall leukaemia and ALL separately	adjusting for annual household income in some of the conditional logistic regression models. Exposure history was separated by specific periods of interest, so patients diagnosed during year 1 and their controls were excluded from the analysis of exposures during year 1 because of the difficulty of deciding whether exposure occurred before diagnosis; similar exclusions made for exposures during years 2 and 3 .
McDuffie	2001	Canada	cases were 517 men aged >19 years or over with a first diagnosis of non-Hodgkin's lymphoma (NHL) between 1 September 1991 and 31 December 1994 and resident in one of six Canadian provinces; cases ascertained from	1506 controls selected at random from provincial Health Insurance records, telephone listings or voters' lists. Stratified by age ± 2 years to be comparable with age distribution of the case group within	information from Cancer Registries and hospitals, including pathology reports, to confirm diagnosis. Pathological material reviewed and classified by reference	NHL in men aged >19 years	only one characteristic in this study could be considered for para-occupational exposure: residence on a farm at any time; self-report by questionnaire and telephone interview	conditional logisitic regression	ORs calculated with strata for the variables of age and province of residence; potential confounders considered were history of measles, mumps, cancer, allergy desensi-

First author	Date published	Country	Study subjects	Reference populations	Health assessment method	Health outcomes investigated	Exposure assessment	Statistical analysis	Other risk factors evaluated/ confounders
			provincial Cancer Registries, or hospital ascertained in Quebec	each province	pathologist				tisation treatment, positive history of cancer in first-degree relatives
Meinert	1996	Germany	173 cases of leukaemia diagnosed between 1 July 1988 and 30 June 1993 with age at time of diagnosis <15 years, and resident in state of Lower Saxony. Additional study group of 175 solid tumours (75 central nervous system tumours, 30 neuroblastomas, 43 Wilms' tumours, 27 rhabdomyosarcomas). Total 348 cases; 161 leukaemia cases were 1:1 matched with 161 local controls.	220 "local" controls, that is, for each leukaemia case, 1 control was selected from the same place of residence; 213 "state" controls, that is, a second control was selected from another commumity in Lower Saxony. Controls were matched by sex and date of birth ±1 year. Total 433 controls.	recruitment of cases through the German Childrens Cancer Registry	leukaemia and some solid tumours in children <15 years of age	self-administered questionnaire and telephone interview; self-reported occupation as farmer, gardener or florist within the time interval of 2 years prior to child's birth and the diagnosis or reference date, or whether engaged in farming (agriculture or cattle breeding) during the same time interval; self-reported used of pesticides "on farm", and of "direct occupational exposure to insecticides, herbicides or fungicides"; report if extermination was carried out by a pest control operator at home	conditional logistic regression using SAS for leukaemia cases with their 1:1 matched local controls and leukaemia cases with state controls; unconditional logistic regression for solid tumours compared with local and state controls	analysis for leukaemia cases and local controls was adjusted for social status ("high" versus "other"); analysis for leukaemia cases and state controls was adjusted for degree of urbanisation (urban, mixed, rural) and social status; analysis for group with solid tumours compared to local and state controls was adjusted for age, sex, degree of urbanisation and social status
Meinert	2000	Germany	2,358 cases identified from the German Childhood Cancer Registry, diagnosed when >15 years of age between October 1992 and September 1994, and resident in West Germany on date of diagnosis; out of the total number of cases, 1,184 were diagnosed with leukaemia, 234	2,588 controls from files of local resident registration offices; one control was matched to each case, and matched on gender, date of brith within 1 year, and on community of residence	cases were identified through the German Childhood Cancer Registry	acute leukaemia and NHL in children <15 years of age	self-administered questionnaire and telephone interview of both parents; self-reported exposure to insecticides, herbicides or fungicides, whether either parent had carried out farming and if/when they had used pesticides, and whether they had used a professional pest control operator at home	conditional logistic regression using SAS software version 6.12, and LogXact software program for sparse data	adjustments made for degree of urbanisation (urban, mixed, rural), and for socio-economic status (high, other), estimated on the basis of family income and level of parental education

First author	Date published	Country	Study subjects	Reference populations	Health assessment method	Health outcomes investigated	Exposure assessment	Statistical analysis	Other risk factors evaluated/ confounders
			with non-Hodgkin's lymphoma (NHL), and 940 with a solid tumour						
Monge	2007	Costa Rica	334 cases of childhood leukaemia in children aged 0-14 years at diagnosis, diagnosed in Costa Rica in 1995-2000, and identified at the Cancer Registry and the Children's Hospital of Costa Rica	579 population controls drawn from the National Birth Registry, frequency matched to cases by birth year	case diagnoses extracted from Cancer Registry data and confirmed from files of the Children's Hospital	acute lymphocytic leukaemia and total leukaemia in children aged 0-14	interviews with both parents (most cases and controls) or mother or father only; self-reported exposure by mother and father of use of 25 specific pesticides; report of agricultural tasks performed, which were classified according to their estimated hazard from 0=no exposure to 4=very high exposure; reported exposure of child in 5 time periods: the year before conception, first trimester of pregnancy, second trimester, third trimester, and first year of life	unconditional crude and adjusted logistic regression, using STATA Release 8.0	urban or rural residence
Ruder	2004	USA	457 men aged 18-80, nonmetropolitan residents of 4 states: Iowa, Michigan, Minnesota and Wisconsin (n=457 including proxy respondents, n=242 excluding proxy respondents), diagnosed between 1 January 1995 and 31 January 1997	648 controls with with no diagnosis of glioma, resident in the eligible counties on 1 January 1995. Controls aged 18-64 were selected from state driver's license or state ID card records, and individuals aged 65-80 from Medicare data (n=648 including proxy respondents, n=625 excluding proxy respondents)	histologically confirmed primary glioma cases were identified through participating medical facilities and offices of neurosurgeon	primary intracranial glioma in men	interview with participant or proxy; for para-occupational exposure, respondent's report of ever having lived or worked on a farm (distinct from personal direct use of pesticides), years on farm, whether on farm as an adult (age 18+), whether laundered pesticide-applicator clothes, and whether pesticides stored in house (the latter only asked of participants on farm age 18+)	unconditional multiple logistic regression models; analyses done using SAS 8.0 software	age, 10-year age group, education

First author	Date published	Country	Study subjects	Reference populations	Health assessment method	Health outcomes investigated	Exposure assessment	Statistical analysis	Other risk factors evaluated/ confounders
Ruder	2006	USA	798 men and women aged 18-80 living in 4 states: Iowa, Michigan, Minnesota and Wisconsin, in rural areas or on farms (n=798 including proxy respondents, n=438 excluding proxy respondents), diagnosed between 1 January 1995 and 31 January 1997	1175 controls with no diagnosis of glioma, resident in the eligible counties on 1 January 1995. Controls aged 18-64 were selected from state driver's license or state ID card records, and individuals aged 65-80 from Medicare data (n=1175 including proxy respondents, n=1141 excluding proxy respondents)	cases identified by ascertaining physicians, group practices and medical facilities in the 4 study states, and border-city facilities and practices in Illinois, Nebraska, North Dakota and South Dakota; two of the study authors re-reviewed pathology reports; release of a brain tissue specimen requested from cases if one had been collected during previous surgery or biopsy	primary intracranial glioma in adults	interview with participant or proxy; for para-occupational exposure, respondent's report of ever having lived or worked on a farm (distinct from personal direct use of pesticides), and age of first living on a farm	multiple logistic regression models; analyses done using SAS 8.0 software	age, 10-year age groups, education, gender, state
Teitelbaum	2007	USA	1,505 cases of invasive or in situ breast cancer newly diagnosed between 1 August, 1996 and 31 July, 1997, among women who were residents of either Nassau or Suffolk Counties in New York State	1,553 controls from women residents in the same 2 counties during the same time period who had not been diagnosed with breast cancer, selected by random digit dialling if <65 years of age, and from Medicare records if >65 years of age	cases of breast cancer confirmed by physician and medical record	*in situ* or invasive breast cancer	interview; for para-occupational exposure, report of application of lawn and garden pesticide products by professional only	unconditional logistic regression	age, education
Van Wijn-gaarden	2003	USA and Canada	154 children diagnosed with astrocytoma and 158 children diagnosed with primitive	312 controls selected by random digit dialling, matched individually to cases	cases diagnosed according to the *International Classification of*	astrocytoma and primitive neuroectodermal tumours (PNET) in	telephone interview, in which occupational history obtained for fathers and mothers;	conditional logistic regression using SAS version 8.1	maternal age, household income, maternal education

First author	Date published	Country	Study subjects	Reference populations	Health assessment method	Health outcomes investigated	Exposure assessment	Statistical analysis	Other risk factors evaluated/ confounders
			neuroectodermal tumours (PNET) in the USA and Canada between 1986 and 1989, identified through the Children's Cancer Group; cases were children diagnosed before 6 years of age	by race, age and geographic area	*Diseases for Oncology* code 191, and identified through the Children's Cancer Group	children diagnosed before 6 years of age	for each job probability and intensity of exposure was estimated, based on an industrial hygiene literature review of determinants and levels of pesticide exposure, and a job-exposure matrix; 4 classes of pesticides (insecticides, herbicides, agricultural and non-agricultural fungicides) evaluated, and farmers were asked which pesticides they used		

7(C) Cancer Results and Conclusions

First author	Date published	Major findings	Strengths/Limitations	Conclusions
Cohort studies				
Alavanja	2005	1) after 5.3 years of follow-up the overall cancer incidence among spouses of farmers was significantly lower than expected: Standardised Incidence Ratio (SIR) 0.84, 95% Confidence Interval (CI) 0.80-0.90; 2) cancer incidence of the respiratory tract was significantly lower than expected among spouses: SIR 0.41, 95% CI 0.32-0.51; cancer of the buccal cavity was close to the expected value: SIR 0.73, 95% CI 0.40-1.22. 3) cancer incidence of the digestive system was significantly lower than expected for spouses of private applicators (mostly farmers): SIR 0.85, 95% CI 0.72-0.99, and a significant deficit was also observed for rectal cancer: SIR 0.59, 95% CI 0.38-0.89; a significantly lower than expected frequency of ovarian cancer was also seen among spouses of private applicators: SIR 0.55, 95% CI 0.38-0.78; 4) spouses of private applicators were found to have a significant excess of melanoma: SIR 1.64, 95% CI 1.27-2.09, which was not observed among either the private or commercial applicators, and which was an unexpected finding.	Strengths: 1) large size of cohort – 32,347 spouses. Limitations: 1) since this is a population-level study there is no direct measure of exposure, only self-reported duration of exposure to unspecified pesticides ("Years personally applied pesticides", "Days per year personally applied"); the characteristic "unexposed" covers para-occupational exposure in both the above categories; 2) the observed cancer incidence cases among the spouses are not separated according to occupational or para-occupational exposure; 3) some sample sizes were very small, e.g. observed number of cases of cancer of the rectum, n=23; cancer of the lip, n=2.	The incidence of several types of cancer among spouses of farmers/private applicators was observed to be lower than expected, although there was an unexpected finding of excess of melanoma; however, this is a population-level study which does not focus on exposure details.
Engel	2005	1) the Standardised Incidence Ratio (SIR) for breast cancer for all of the women was 0.9, 95% CI 0.8-1.1. In Iowa the SIR was 1.3, 95% CI 1.0-1.6 for women who never applied unspecified pesticides, and in North Carolina the SIR was 0.8, 95% CI 0.6-1.1, for this category; 2) the characteristic, "grew up on a farm", was not related to breast cancer risk: Rate Ratio (RR) 0.9, 95% CI 0.7-1.3; 3) no significant association was found with frequency of washing work clothes worn during unspecified pesticide application among wives who never used pesticides: RR 1.4, 95% CI 0.8-2.7 for >20 days/year of washing work clothes worn during pesticide application; 4) exposure to 50 specific pesticides was also considered; there was an increased risk in relation to the husbands' use among wives who never used pesticides for the fungicide captan, RR 2.7, 95% CI 1.7-4.3, but not for chlorpyrifos: RR 1.3, 95% CI 0.9-1.8; 5) some findings in the study are inconsistent and appear difficult to interpret: e.g., increased risk was found for husband's use among wives who never used pesticides for the fungicide captan (Rate	Strengths: 1) study clearly identified a group that was para-occupationally exposed: "Wives who never used pesticides", "Husbands' pesticide use among wives who never used pesticides"; 2)large cohort size – 152 cases and 13,297 non-cases among wives who never used pesticides. Limitations: 1) no direct measure of exposure, information on pesticide use was based on self-reporting; 2) because of the large number of pesticide exposures investigated, some associations may have occurred by chance; 3) inaccurate recall may have occurred because pesticide use covered participants' lifetime use; 4) some numbers of cases were small – e.g. 17 cases in postmenopausal women exposed to husband's use of captan.	For para-occupational exposure, 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; some findings are difficult to interpret.

First author	Date published	Major findings	Strengths/Limitations	Conclusions
		Ratio, RR 2.7, 95% CI 1.7-4.3), but no elevation of risk was seen for women who applied this pesticide themselves (RR 0.5, 95% CI 0.2-1.2); 6) findings stratified by menopausal status are difficult to interpret: significant increased risks related to the women's own pesticide use occurred among premenopausal women for chlorpyrifos, RR 2.2, 95% CI 1.0-4.9, but lower risks associated with women's own use and increased risks associated with the husbands' use were found among postmenopausal women: for chlorpyrifos, women's own use RR 1.0, 95% CI 0.5-2.2, and husband's use RR 1.6, 95% CI 1.1-2.4; for captan, data are not available for women's own use, but for husband's use among post-menopausal women, RR 3.6, 95% CI 2.1-6.1.	5) some findings are inconsistent and difficult to interpret: e.g.increased risk was found for husband's use among wives who never used pesticides for captan, but no elevation of risk was seen for women who applied these pesticides themselves 6) patterns of risk were generally inconsistent between Iowa and North Carolina	
Flower	2004	1) study reports on childhood cancer among children para-occupationally exposed because one or both parents apply pesticides; exposure is to unspecified pesticides, and to 16 specific pesticides and 3 pesticide classes, but the exposures to specific compounds did not give statistically significant results; 2) Standardised Incidence Ratios (SIRs) for Iowa (n=50 cases) showed more cases than expected: expected total number of cancer cases in Iowa was 37, SIR 1.36, 95% CI 1.03-1.79. For tumour-specific SIRs, there was an increased incidence of lymphoma: SIR 2.18, 95% CI 1.13-4.19. There was also an increased incidence of Hodgkin's lymphoma: SIR 2.56, 95% CI 1.06-6.14; 3) children of fathers who reported they generally did not wear chemically resistant gloves (16%), n=13 cases, had an increased risk of childhood cancer: Odds Ratio (OR) 1.98, 95% CI 1.05-3.76; 4) no increase in childhood cancer risk detected with increasing maternal or paternal frequency of pesticide exposure (frequency of mixing/application).	Strengths: 1) large cohort size – information for 17,357 children was provided. Limitations: 1) number of cases was small for most types of exposure, often less than 10; exposure to individual pesticides and pesticide classes is shown when the number of cases was at least 5; 2) no direct measure of exposure in the children.	The study suggests a small increase in risk of all childhood cancers combined, and lymphoma specifically; it also suggests a modest increase in risk among children of men who apply pesticides without using chemically resistant gloves, but the number of cases in this category was small.
Kristensen	1996	1) for the whole cohort, Standardised Incidence Ratios (SIRs) for cancer at all sites was close to that expected, and did not deviate significantly from unity for any site-specific cancers; for the sub-cohort of offspring of farmers, SIRs were significantly elevated only for testicular cancer: SIR 124, 95% CI 101-152; 2) in the Poisson regression analyses, the Rate Ratios (RRs) for all ages on holdings with orchards or greenhouses was 1.21, 95% CI 1.00-1.47, and for "Pesticide purchase" RR was 1.16, 95% CI 1.00-1.34. For "orchards or greenhouses and pesticide purchase" the RR was 1.38, 95% CI 1.09-1.76. For children aged 0-4 years, the RR for "orchards or greenhouses" was 1.86, 95% CI 1.18-2.92; 3) for specific types of cancers, significant results were seen for the	Strengths: 1) large size of cohort, analysed over a long period of time, 1965-1991. Limitations: 1) use of crude proxies (orchards or greenhouses on holding; pesticide purchase) for true exposure; 2) no precise exposure characterisation and no separation of occupational from para-occupational exposure, except where para-occupational exposure may be understood from age of cases (e.g. 0-4 years);	No significant differences in SIRs for cancer at all sites were observed in this study; significantly elevated RRs for a few specific types of cancer are reported, but results need to be interpreted with caution because of limitations of the study.

First author	Date published	Major findings	Strengths/Limitations	Conclusions
		following types of cancer: non-astrocytic neuroepithelial tumours and pesticide purchase of Norwegian Krone (NOK) 100-499 and >500, RR=2.93, 95% CI 1.54-5.60, and RR=3.28, 95% CI 1.39-7.76 respectively; RR for non-Hodgkin's lymphoma was 1.67 with dose-response relationship for different levels of expenditure – test for trend p=0.04; RR for Wilm's tumour and the exposure indicator," orchards or greenhouses and pesticide spraying equipment" was 8.87, 95% CI 2.67-29.5.	3) some sample sizes were very small, e.g. 4 cases of Wilm's tumour with the exposure indicator "orchards or greenhouses and pesticide spraying equipment".	
Case-control studies				
Alderton	2006	1) study considers mother and child exposure to unspecified pesticides, and for para-occupational exposure, professional pest control applications in the home were considered; 2) an association was found among the cases for maternal exposure around the time of pregnancy and acute lymphoblastic leukaemia (ALL) with exposure to professional pest control applications: Odds Ratio (OR) 2.25, 95% CI 1.13- 4.49: 3) exposure of the child to professional pest control applications and the risk of ALL is not found to be significant, OR 1.48, 95% CI 0.77-2.88.	Strengths: 1) study focuses on cases and controls from a group of children who are known to have a high risk of acute leukaemia. Limitations: 1) no direct measure of exposure; 2) number of cases is small: 21 cases of ALL.	The study presents some evidence 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, but is based on a small number of cases.
Buckley	2000	1) study considers para-occupational exposure of the mother during pregnancy to professional pest control using insecticides, and parental occupational exposure to unspecified pesticides, and the risk of cancer in children; 2) exposure of the mother around the time of pregnancy to professional insect treatment to the home was related significantly to non-Hodgkin's lymphoma (NHL) risk in the child: Odds Ratio (OR) 2.98, 95% CI 1.44-6.16, P = 0.002; 3) within subgroups of cases, the large cell and Burkitt lymphoma groups had the highest ORs of risk of NHL in the child for mother's exposure during pregnancy to professional pest control applications: large cell lymphoma, OR=6.7, 0.01<P<0.05; Burkitt lymphoma, OR=8.0, 0.01<P<0.05; 4) there was an increased risk of Burkitt lymphoma in children whose parents reported that they had been occupationally exposed to unspecified pesticides: OR=9.6, 0.01<P<0.05.	Strengths: 1) the study includes 2 definite categories of para-occupational exposure, that of the mother during pregnancy to professional pest control using insecticides in the home, and occupational exposure of either parent. Limitations: 1) no direct measure of pesticide exposure; 2) small sample size - for exposure of mother around time of pregnancy to professional insect treatment in the home, there were 31 cases and 12 controls; 3) authors caution that their measurement of parental occupational exposure to unspecified pesticides is likely to be subject to substantial misclassification.	Some associations are 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.
Carreon	2005	1) the characteristics "Ever lived/worked on farm" and "Living on farm as adult ≥18 years of age" were not significantly associated with increased risk of glioma: (Odds Ratio) OR= 1.0, 95% CI 0.7-1.3, and OR= 1.1, 95% CI 0.7-1.6, respectively;	Strengths: 1) relatively large number of cases (341) and controls (527), with focus on one type of brain tumour to increase homogeneity of the case	The study does not find evidence to support the hypothesis that farm residence or specific types of para-

First author	Date published	Major findings	Strengths/Limitations	Conclusions
		2) the characteristic, "laundered pesticide applicator clothes," was not found to be associated with increased risk of glioma: OR=0.7, 95% CI 0.4-1.3; 3) another characteristic, "Pesticides stored in house" was not significantly associated with increased risk of glioma: OR= 2.0, 95% CI 0.6-6.8; 4) participants were also asked about exposure to functional classes of pesticides (fungicides, herbicides, insecticides), to chemical classes (e.g. organophosphates), and to 12 specific pesticides, but none of these exposures were found to be significant.	group. Limitations: 1) no direct measure of exposure; 2) the characteristics, "Ever lived/worked on farm" and "Living on farm as adult ≥18 years of age" do not separate para-occupational from occupational exposure, although only 8% of women reported directly applying pesticides; 3) large number of cases had proxy respondents-43% of cases and 2% of controls, so possibility of bias in the reports; also reliability of proxy responses on details of agricultural practices was poor; 4) assessment of exposure retrospective, so difficulty for participants and proxies to remember precise details, particularly on details of specific pesticide exposure.	occupational exposure increase the risk of glioma in women.
Colt	2006	1) relevant to this review is the collection and analysis of carpet dust samples for 18 specific insecticides; non-Hodgkin's lymphoma (NHL) risk was assessed according to levels measured. Results for selected organophosphates/carbamates/pyrethrins do not show an increased risk: e.g. for chlorpyrifos, OR= 0.7, 95% CI 0.5-1.0, for levels of 41.8-91.7 ng/g in dust, and OR= 0.7, 95% CI 0.5-1.0 for levels of 799-38,200 ng/g in dust, P_{trend}= 0.20. The only positive results were found for the treatment of termites using chlordane, which is an organochlorine and not included in this review.	Strengths: 1) quantitative measure of insecticide levels in carpet dust. Limitations: 1) dust samples were analysed only for 682 cases and 513 controls, out of a total of 1321 cases and 1057 controls; 2) there is no report of analysis on the blood and saliva samples taken; 3) it is reported that there were a "large number of people" in the "no/unknown" category ("did not treat" and "don't know" if home treated) for most insect types, who were not included in the analysis; 4) exposure as a result of application of insecticides by respondents themselves, or through application by a professional applicator, is not reported separately in the paper.	The evidence presented in this study does not suggest an association between NHL risk and carpet dust levels of some major insecticides.
Cooney	2007	1) for para-occupational exposure of the pregnant mother or of the child, application of unspecified pesticides by a pest control operator was considered. The results are not significant: OR was 1.0, 95% CI 0.7-1.3.	Strengths: 1) relatively large number of cases (523) and controls (517). Limitations: 1) no direct measure of exposure of the mother during pregnancy or of the child.	The study does not provide evidence of increased risk of developing Wilms Tumour from exposure to pesticides applied by a professional applicator.
Daniels	2001	1) for para-occupational exposure, report by mothers and fathers of	Strengths:	Although the study reports

First author	Date published	Major findings	Strengths/Limitations	Conclusions
		the use of professional pest control in the house is considered; pesticides are not specified; 2) when both parents reported use of pesticides, professional pest control was associated with neuroblastoma: OR_B (Odds Ratio Both parents reporting) 1.4, 95% CI 0.9-2.1. The OR was lower when only one parent reported use: OR_E (Odds Ratio Either parent reporting) 1.1, 95% CI 0.8-1.7, but the Confidence Intervals do not suggest significance; 3) Odds Ratios were higher for effects of professional pest control among children diagnosed at <1 year of age: OR_B =1.5, 95% CI 0.7-3.0, OR_E =1.4, 95% CI 0.6-3.0. At age 1+, OR_B =1.3, 95% CI 0.7-2.3. However, all Confidence Intervals include 1.0.	1) relatively large number of cases and controls. Limitations; 1) no direct measure of exposure, only parents' reports; 35% of the couples in the study disagreed about whether pesticides were used; 2) it is not known whether the category that requires both parents to report is more or less sensitive to recall bias than exposures reported by only one parent; 3) problems of accurate recall – parents were asked to recall events from 1 to 5 years earlier; 4) although elevated odds ratios are reported, all the Confidence Intervals include 1.0.	some elevated Odds Ratios for the use of professional pest control in the home or garden and neuroblastoma in children, all the Confidence Intervals include 1.0 and do not suggest significance.
Hartge	2005	1) study reports on herbicide use in the home on lawn or garden and the risk of non-Hodgkin's lymphoma (NHL), and contains measurements of the specific herbicides 2,4-dichlorophenoxy-acetic acid (2,4-D) and dicamba in carpet dust samples; 2) para-occupational exposure was estimated by the characteristic, "total applications (treatment of lawn or garden for weeds) by lawn care professional". A Relative Risk (RR) of 1.20 was found for <10 applications by lawn care professional, 95% CI 0.78-1.85; for 20-49 applications by lawn care professional RR=1.14, 95% CI 0.78-1.66, but both sets of CIs include 1.0; for highest exposure of >50 applications by lawn care professional, RR= 0.94 , 95% CI 0.68-1.29, with a non-significant test for trend, P_{Trend}= 0.71; 3) for respondents with carpet dust samples (679 cases, 510 controls), neither 2,4-dichlorophenoxy-acetic acid (2,4-D) nor dicamba was consistently related to NHL risk. For example, for 2,4-D levels <500 ng/g, RR =1.10, 95% CI 0.78-1.55, and for the highest levels of >10,000 ng/g RR = 0.82, 95% CI 0.41-1.66. For dicamba, levels of 500-999 ng/g had RR = 1.16, 95% CI 0.44-3.09, and for the highest levels of >1,000 ng/g RR = 0.70, 95% CI 0.22-2.23.	Strengths: 1) large number of cases (1,321) and controls (1,057), although only approximately half of each group had carpet dust samples analysed (679 cases, 510 controls); 2) there is clearly identified para-occupational exposure to application of herbicides by lawn care professional. Limitations: 1) there was no direct measure of exposure to the applications by a lawn care professional, and sample sizes of exposed groups were small: e.g. 38 cases, 41 controls for exposure to <10 applications by lawn care professional, and 83 cases, 57 controls for exposure to 20-49 applications; 2) respondents with carpet dust samples were not separated into those who had applied herbicides themselves and those with para-occupational exposure. The numbers of respondents with carpet dust samples were in some cases very small: for example, 24 cases, 18 controls with levels of 2,4-D >10,000 ng/g, and 6 cases, 6 controls with levels of dicamba >1,000 ng/g.	The study suggests that residential exposures to herbicides by professional application do not increase the risk of NHL.
Infante-Rivard	1999	1) for para-occupational exposure and risk of acute lymphoblastic leukaemia (ALL), report of the mother as to whether the home was professionally treated with insecticides during mother's pregnancy and/or during childhood of the index child was considered; 2) for exposure to professional treatments of home, 65 case families	Strengths: 1) the study differentiates between para-occupational exposure to professional treatment of homes, and pesticide use by mothers/home owners themselves.	Risks of childhood ALL were not seen to be significantly increased by exposure to professional treatment of homes against insects.

First author	Date published	Major findings	Strengths/Limitations	Conclusions
		and 54 controls reported exposure to 1-5 professional treatments against ants and cockroaches, and for this group the Odds Ratio for childhood ALL was 1.26, 95% CI 0.84-1.90; 15 case families and 7 controls reported more than 5 treatments; for this group OR=2.35, 95% CI 0.89-6.17; 26 case families and 15 controls reported professional treatment against ants and cockroaches during pregnancy: OR=1.68, 95% CI 0.87-3.25. All Confidence Intervals include 1.0.	Limitations: 1) no direct measure of exposure in the children, or mothers during pregnancy; 2) possible over-reporting of exposure by cases compared to controls; 3) sample sizes were small; 4) although elevated odds ratios are reported, all the Confidence Intervals include 1.0.	
Kato	2004	1) study reports on risk of non-Hodgkin's lymphoma (NHL) in women and exposure to insecticides. Para-occupational exposure in this study is covered by application type: "indoor application by others" and "outdoor application by others". Cases and controls were ordered in quartiles; 2) no significant elevations in Odds Ratios (ORs) in any quartile for "indoor application by others" is seen, *p* value for trend=0.149; 3) for "outdoor application by others", for the pesticide type "insecticides for flying bugs or foggers", there was a significantly elevated OR for the fourth quartile, "applied ≥49 times": OR=2.37, 95% CI 1.32-4.24, and a significant *p*-value for trend: *p*=0.005.	Strengths: 1) study identifies 2 distinct para-occupational exposure categories. Limitations: 1) no direct measure of exposure; 2) the elevated ORs for outdoor application of insecticides for flying bugs seems anomalous, since indoor application might be presumed to be greater; 3) sample sizes were small – for the 4th quartile with significantly elevated ORs, there were 53 cases and 32 controls; 4) inaccuracy is likely in recalling exposure details from a long way back in the past; 5) overall low participation rate, 56%, raises questions of selection bias and generalisability of the results.	For para-occupational exposure to home pesticides applied by others and the risk of NHL in women, there is one statistically significant result reported for outdoor application of insecticides.
Ma	2002	1) study examines the possible association between para-occupational exposure of the mother during pregnancy to pro-fessional pest control using insecticides and leukaemia in the child; para-occupational exposure of the child in the first 3 years of life to professional pest control is also considered; 2) ORs associated with use of professional pest control service were >2 for all periods except for the 3 months before pregnancy: • 3 months before pregnancy, 16 cases/12 controls exposed, OR=1.7, 95% CI 0.7-3.9; • during pregnancy, 22 cases/14 controls exposed, OR=2.2, 95% CI 1.0-4.8; • Year 1, 25 cases/16 controls exposed, OR=2.3, 95% CI 1.1-4.9; • Year 2, 31 cases/15 controls exposed, OR=3.6, 95% CI 1.6-8.3; • Year 3, 23 cases/15 controls exposed, OR=2.2, 95% CI	Strengths: 1) study clearly identifies a para-occupational exposure category; 2) there was a good response rate among eligible cases in the study (83%), and also relatively good response from controls (69%). Limitations: 1) no direct measures of exposure; 2) numbers of cases and controls in the various time windows were small.	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.

First author	Date published	Major findings	Strengths/Limitations	Conclusions
		1.0-4.7; • overall, 3 months before pregnancy to 3 years old, 39 cases/25 controls exposed, OR=2.8, 95% CI 1.4-5.7; 3) pesticides were also grouped based on whether they were applied indoors or outdoors, although this category combines para-occupational exposure through application by pest control operators with personal application by household members; for all 5 time frames combined, children exposed to indoor pesticides had an increased risk of acute lymphoblastic leukaemia (ALL), OR=1.8, 95% CI 1.0-3.4, whereas for the risk of ALL and exposure to outdoor pesticides all 95% CIs of the ORs suggested non-significance; indoor pesticide exposures during pregnancy had OR=2.2, 95% CI 1.3-3.6.		
McDuffie	2001	1) the only para-occupational category in this study was "Residence on a farm at any time"; 235/517 cases answered "Yes" to this question, and 673/1506 controls (45.5% and 44.7% respectively). The calculated OR for risk of non-Hodgkin's lymphoma was 1.06, 95% CI 0.86-1.20; 2) for all remaining types of exposure, para-occupational, occupational and use of home/garden pesticides were not treated separately; subjects who reported 10 hours/year or more of cumulative exposure to any combination of compounds were included in the telephone interview, irrespective of how the exposure occurred.	Strengths: 1) relatively large number of cases and controls. Limitations: 1) indirect estimate of exposure of "residence on a farm at any time"; 2) type of exposure is not specified – people in a number of different occupations, and home and garden users, are treated as one group	For para-occupational exposure, the evidence from this study is limited and does not suggest a significant association between farm residence and risk of NHL in men.
Meinert	1996	1) for parental occupations with potential exposure to unspecified pesticides (farmer, gardener, florist), father: OR=1.23 for leukaemia cases versus local controls, mother: OR=1.93 for leukaemia cases versus local controls; the authors say the differences were not statistically significant, but no 95% CIs or *p* values are given; ORs for leukaemia cases versus state controls and ORs for solid tumours versus all controls were less than 1; 2) for parents' "direct occupational exposure" to insecticides, herbicides or fungicides, OR=1.19 for leukaemia cases versus local controls and "Ever" exposure of father; OR=1.58 for leukaemia cases versus local controls and "Ever" exposure of mother, and OR=1.16 for leukaemia cases versus state controls for "Ever" exposure of mother; OR=1.53 for leukaemia cases versus local controls and "Ever" exposure of father or mother; no CIs or *p* values are given; 3) for unspecified pesticide use on farm, OR=1.64 for leukaemia cases versus local controls, and less than 1 for the other compared groups; no CIs or *p* values given; 4) for extermination of insects by pest control operator, OR=1.03 for	Strengths: 1) good response rate: 82% of parents of children with cancer returned the questionnaire, and 71% of contacted control families. Limitations: 1) using 2 different comparison groups, local and state controls, makes interpretation of results difficult; results depend on the choice of the control group – ORs are consistently higher than 1 if leukaemia cases are compared to local controls, and less that 1 for most comparisons with state controls; 2) Confidence Intervals and p values are not given for the reported ORs; 3) no direct measure of exposure; 4) crude exposure assessments based on occupations and parents' self-reported exposures might give rise to misclassification of exposure; 5) for extermination of insects by pest control	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, but the limitations of the study must be taken into account.

First author	Date published	Major findings	Strengths/Limitations	Conclusions
		leukaemia cases versus local controls, OR=1.20 for leukaemia cases versus state controls, and OR=2.00 for solid tumours versus all controls, no CIs or *p* values given.	operator the number of cases and controls was very small: 3 leukaemia cases and 5 solid tumour cases, 4 local controls and 3 state controls.	
Meinert	2000	1) occupational exposure of the father to herbicides, insecticides and fungicides was associated with leukaemia in children, OR=1.6, 95% CI 1.1-2.3, but not with lymphoma; 2) occupational exposure of the mother to herbicides, insecticides and fungicides was associated with leukaemia, OR=2.5, 95% CI 1.3-4.7, and with lymphoma, OR=4.1, 95% CI 1.1-16 in children; 3) exposure of child to unspecified "pesticide use on farm" was weakly associated with leukaemia, OR=1.5, 95% CI 1.0-2.2, but not with lymphoma; 4) use of household insecticides by pest control operator was associated with lymphoma in children, OR=2.6, 95% CI 1.2-5.7.	Strengths: 1) large number of cases and controls included in study; 2) good response rate of 84.4% for cases and 70.7% for controls; 3) a clear para-occupational category is identified for domestic exposure to pesticides, "use of household insecticides by pest controller". Limitations: 1) misclassification of exposure possible due to crude exposure estimate of pesticide use on a farm, and occupational exposure of either parent – "occupation" was based on job title; 2) no measure of exposure in the children; 3) some sample sizes were small, e.g. there were only 10 lymphoma cases exposed to use of household insecticides by pest control operator.	The study suggests an association between childhood lymphoma and pesticides applied indoors by pest control operator, and an association with leukaemia and occupational exposure of the father or mother, but misclassification of exposure is possible, and would place some uncertainty on the study conclusions.
Monge	2007	1) to assess para-occupational exposure of the child, data for the father's or mother's occupational exposure during the time window of the first year of the child's life were considered; exposure of either parent in the year before conception or during the trimesters of pregnancy was considered to be occupational exposure of that parent, but not para-occupational exposure of the child; 2) for father's exposure to the herbicide picloram during the child's first year of life, there were 2 cases of child's acute lymphocytic leukaemia with low exposure of the father, and 8 cases with high exposure of the father; "low" and "high" are semi-quantitative measures. The OR is12.4, 95% CI=1.6-98.3; 3) for father's exposure to the fungicide benomyl during the child's first year of life, there were 3 cases of child's acute lymphocytic leukaemia with low exposure of the father, and 9 cases with high exposure of the father; OR=6.6, 95% CI=1.2-35.4; 4) for exposure of the mother to the category, "paraquat, chlorothalonil, glyphosate and others" during the child's first year of life, there were 9 cases of acute lymphocytic leukaemia, OR=2.5, 95% CI 1.0-6.5.	Strengths: 1) relatively large number of cases and controls (334 and 579, respectively); 2) good overall response rate of 90% for cases and 90.5% for controls. Limitations: 1) multiple comparisons – a large number of risk factors is studied, and positive associations might be a chance effect; 2) small numbers of cases in the various exposure categories -e.g. only 10 cases of acute lymphocytic leukaemia with father's exposure to picloram during the child's first year of life - so, although there is a suggestion of a dose-response effect for low/high exposure of fathers to picloram and benomyl, it is based on very small numbers; 3) benomyl and paraquat are not approved in the UK.	The study suggests that the father's exposure to certain pesticides (picloram, benomyl) during the child's first year of life may increase the risk of acute lymphocytic leukaemia in the offspring, 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 acute lymphocytic leukaemia.
Ruder	2004	1) for the characteristic, "Ever lived/worked on farm" and risk of	Strengths:	The study does not suggest an

First author	Date published	Major findings	Strengths/Limitations	Conclusions
		glioma, OR=0.86, 95% CI 0.66-1.11 for respondents including proxies, and OR=0.93, 95% CI 0.67-1.29 for respondents excluding proxies; 2) for the characteristic, "Years on farm, 11-20", OR=1.04, 95% CI 0.68-1.58 for respondents including proxies, and OR=1.08, 95% CI 0.63-1.86 for respondents excluding proxies; 3) for the characteristic, "On farm as an adult age 18+", OR=0.78, 95% CI 0.55-1.11 for respondents including proxies, and OR=1.11, 95% CI 0.69-1.81 for respondents excluding proxies; 4) for the characteristic, "laundered pesticide-applicator clothes", OR=0.79, 95% CI 0.36-1.73 for respondents including proxies, and OR=1.08, 95% CI 0.63-1.86 for respondents excluding proxies; 5) for "pesticides stored in house" OR=1.62, 95% CI 0.69-3.79 for respondents including proxies, and OR=0.66, 95% CI 0.40-1.10 for respondents excluding proxies; 6) chemical classes of pesticides (e.g. carbamates,organophosphates) were also considered, but none of the Confidence Intervals suggest significance.	1) large number of cases of histologically confirmed gliomas; 2) direct pesticide use by the participant and living or working on a farm where pesticides were used were differentiated. Limitations: 1) high proportion of proxy interviews for case participants, >40%, but the decision to conduct all analyses with and without proxy responses, and to report both, is an attempt to compensate; 2) some sample sizes were small – e.g. for the characteristic, "laundered pesticide-applicator clothes" there were 11 cases, and only 7 excluding proxy respondents.	increased risk of glioma among men who reported having been exposed to pesticides by living on a farm.
Ruder	2006	1) for the characteristic, "Ever lived/worked on farm" and risk of glioma, OR=0.89, 95% CI 0.74-1.09 for respondents including proxies, and OR=0.91, 95% CI 0.72-1.17 for respondents excluding proxies; 2) for the characteristic, "Age first on farm, Adolescent (11-20)" and risk of glioma, OR=1.96 95% CI 1.13-3.39 for respondents and proxies, and OR=2.21, 95% CI 1.13-4.34 for respondents excluding proxies; for children aged <11 years, Odds Ratios were slightly increased, but all Confidence Intervals included 1.0: "Age first on farm, Infant <1year", OR=1.06, 95% CI 0.79-1.43 for respondents and proxies, OR=1.19, 95% CI 0.81-1.76 for respondents excluding proxies; "Age first on farm, Child 1-10", OR=1.03, 95% CI 0.66-1.61 for respondents and proxies, OR=1.06, 95% CI 0.59-1.89 for respondents excluding proxies.	Strengths: 1) large number of histologically confirmed gliomas; 2) good response rate – 92% of cases, 70% of controls. Limitations: 1) large number of proxy interviews for case participants, >40%, although the decision to give results in two groups, including and excluding proxies, is an attempt to compensate for this; 2) the association observed between increased risk of glioma and first living on a farm during adolescence is contrary to the view that, for most toxicants, younger children are believed to be at higher risk; the increased risk for adolescents in this study may have occurred by chance.	Farm residence in general was not seen to be associated with an increased risk of glioma in this study, but some evidence suggests that moving to a farm as an adolescent (age 11 to 20), as opposed to as an adult, was associated with a greater risk of glioma.
Teitelbaum	2007	1) for application of unspecified pesticides by professional only to control the following garden pest problems, the risks of breast cancer are: to control weeds, OR=1.36, 95% CI 1.08-1.71; to control lawn insects, OR=1.41, 95% CI 1.13-1.77; to control insects or diseases of trees, OR=1.45, 95% CI 1.15-1.83; to control pests in vegetable or fruit gardens, OR=2.29, 95% CI 0.94-5.58;	Strengths: 1) large number of cases (1,505) and controls (1,553) overall; 2) there is a clearly identified para-occupational exposure category, where the "Person who applied the pesticides" is "Professional only". Limitations: 1) no direct measure of exposure;	The study suggests there may be an association between increased risk of breast cancer and residential professional application of pesticides, but authors caution that there is uncertainty in this observation due to limitations.

First author	Date published	Major findings	Strengths/Limitations	Conclusions
		to control insects or diseases of outdoor plants, OR=1.79, 95% CI 1.12-2.84.	2) some sample sizes were small – e.g. 14 cases reported, and 8 controls, for professional only application of pesticides for pests in vegetable or fruit gardens; 3) possibility of chance findings due to multiple comparisons; 4) no dose-response relation observed.	
Van Wijngaarden	2003	1) no increased risk of either astrocytoma or primitive neuroectodermal tumours (PNET) was found in children whose fathers or mothers worked as a farm manager or farm worker; 2) an increased risk of astrocytoma was found for children whose fathers had potential exposure to herbicides, OR=1.6, 95% CI 1.0-2.7, and potential exposure to fungicides, OR= 1.6, 95% CI 1.0-2.6, but both confidence intervals contain 1.0; 3)) an increased risk of astrocytoma was found for children whose mothers had potential exposure to insecticides, OR=1.9, 95% CI 1.1-3.3; 4) there was little indication of an association between cumulative parental exposure and either astrocytoma or PNET: a few sporadic increases in risk were found, but all 95% CIs contained 1.0; exposure-response gradient patterns were absent; 5) in evaluating the risk estimates for each class of pesticides individually after adjusting for the effects of the other 2 classes, there was the suggestion of an exposure-response trend to insecticides for mothers, but 95% CIs contain 1.0.	Strengths: 1) relatively large number of matched case-control pairs (312); 2) 82% response rate among eligible cases and 74% of eligible controls. Limitations: 1) exposure assessment relies on job characteristics reported by the study subjects, and the probability and intensity of exposure are based on literature review and a job-exposure matrix; 2) large proportion of mothers provided proxy interviews for fathers of both cases and controls (e.g. for 18% of fathers of astrocytoma cases and 32% of fathers of PNET controls); proxy respondents are less likely to recall or report details of work history information accurately.	Overall, the evidence in the study does not suggest that parental occupational exposure to pesticides increases the risk of childhood brain cancer.