Committee on
CARCINOGENICITY

CC/11/S1

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

STATEMENT ON THE SYSTEMATIC REVIEW OF EPIDEMIOLOGICAL LITERATURE ON PARA-OCCUPATIONAL EXPOSURE TO PESTICIDES AND HEALTH OUTCOMES

INTRODUCTION

1. In 2005, the Royal Commission on Environmental Pollution (RCEP) published a report following a request from Alun Michael, then Minister for Rural Affairs and Local Environmental Quality, on the assessment of human health risks associated with the use of agricultural pesticides.[1] The report set out the concerns of the RCEP over the exposure of residents and bystanders to pesticides.

2. Bystanders are persons located within or directly adjacent to an area where a plant protection application or treatment is in process or recently applied, and whose presence is incidental and unrelated to work involving pesticides, but whose position may put them at risk of exposure. Residents are persons who live, work or attend school or any other institution adjacent to an area that is being or has been treated with a plant protection product, and whose presence is incidental and unrelated to work involving pesticides but whose location may put them at risk of exposure. The scope and exposure scenarios considered in this statement are more fully explained in paragraph 8.

3. In paragraph 6.21 of the report, the RCEP recommended a '*systematic review of the literature on pesticide spraying and human health that takes account of the shortcomings of the Ontario Report*'.

4. The Committees on Toxicity (COT) and Carcinogenicity (COC) of Chemicals in Food, Consumer Products and the Environment were asked by the Department for Environment Food and Rural Affairs (Defra) and the Advisory Committee on Pesticides (ACP) to comment on the RCEP report. In 2006, the COT and COC published a joint statement.[2] As part of their response to the above-mentioned RCEP recommendation, the COT agreed

that an epidemiological review of para-occupational exposure should be undertaken.

5. In framing its response, the Government considered the evidence given in the RCEP report and advice published by the ACP, COT and COC on scientific issues raised by the report.[3]

6. The Government noted that the RCEP '…*did not undertake its own comprehensive critical review of the health based literature for either occupational or non-occupational exposure…'* and that the RCEP considered such a study '*…would take a large amount of resources.'* The Government noted that its independent advisory committees indicated doubts about the value of a comprehensive systematic review and favoured smaller and more directed reviews.[3]

Approach to COC Review

7. The Committee on Carcinogenicity undertook a comprehensive review based on a detailed discussion of the epidemiological literature on para-occupational exposure to pesticides and cancer that had been drafted jointly by HPA Toxicology Unit, Imperial College London and the HPA COT secretariat. In November 2009, the Committee evaluated a draft discussion paper detailing a narrative review of the epidemiological literature on para-occupational exposure to pesticides and cancer. An overview of literature searches and document acquisition was also provided in this document.[4] A summary of literature searches and reference selection is provided in Annex 1 to this statement (http://www.iacoc.org.uk/papers/documents/CC.09.11SystematicreviewonPara-OccupationalexposuretopesticidesandCancer.pdf) The COC considered that further analysis of these epidemiological data was needed before conclusions could be drawn.[5] Twenty-two papers with information relevant to para-occupational exposure to pesticides and cancer were identified from the narrative review.[6-27] Of these 22 papers, 4 reported cohort studies,[6-9] and the remainder case-control studies. Two types of analysis of the cancer studies were undertaken: quality scoring of all the cancer studies and meta-analysis of selected results. The COC considered the systematic review paper at its November 2010 meeting. http://www.iacoc.org.uk/papers/documents/CC1004FinaldiscussionpaperPara-OccupationalReviewandCancerPart2_000.pdf) A summary of the information presented in the narrative and systematic reviews is provided below.

Scope of COC Review

8. Para-occupational exposure, for the purposes of the COC review, was defined in terms of 3 exposure scenarios:

i. Scenario 1. Exposure of close family members who live with an occupationally exposed worker, but who are not themselves occupationally exposed.

ii. Scenario 2. Indirect domestic exposure in the home where the exposed persons did not apply pesticides themselves, but where professional exterminators applied the pesticides.

iii. Scenario 3. Exposure of children at school or nursery to pesticides applied by exterminators.

9. It should be noted that only the exposure scenario 1 is considered as the strict definition of para-occupational exposure, and there may be overlap between the Chemical Regulations Directorate (CRD) definitions of bystanders* and residents** in scenarios 2 and 3 above. The indirect exposure scenarios 2 and 3 were included as a comparison to scenario 1 and to broaden the scope of the COC review. The professional application of pesticides in scenarios 2 and 3 should involve recording the details of the substance used, its concentration and amount applied, and the dates of application.

[*Bystanders are defined by Chemical Regulations Directorate (CRD) as persons located within or directly adjacent to an area where a plant protection application or treatment is in process, and whose presence is incidental and unrelated to work involving pesticides, but whose position may put them at risk of potential exposure. **Residents are described by CRD as persons who live, work or attend school or any other institution adjacent to an area that has been treated with a plant protection product, and whose presence is incidental and unrelated to work involving pesticides but whose position may put them at risk of potential exposure.]

NARRATIVE REVIEW OF CANCER PAPERS

10. A brief summary of the papers considered for the narrative review is given below. A detailed tabulation summarising all of these studies can be found at
http://www.iacoc.org.uk/papers/documents/Annex2Referencesrelevanttopara-occupationalexposureandcancer.pdf

Cohort Studies

11. Alavanja et al (2005) undertook a prospective study of 32,347 spouses (13,760 with no occupational exposure to pesticides) from the Agricultural Health Study.[6] After 5.3 years of follow-up the overall cancer incidence among spouses was significantly lower than expected, Standardised Incident Ratio (SIR) 0.84, 95% Confidence Interval (CI) 0.80-0.90. Spouses of private applicators were found to have a statistically 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. There were no direct measures of exposures, only self-reported duration of exposure to unspecified pesticides, and the observed cancer incidence among the spouses was not separated according to occupational or para-occupational exposure. In addition, 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.

12. Engel et al (2005) investigated breast cancer incidence among 30,454 women who were wives of private pesticide applicators (mostly farmers) from Iowa and North Carolina enrolled in the Agricultural Health Study between 1993-1997.[7] Breast cancer cases and expected numbers of cases were estimated from cancer registries for each state. A questionnaire was administered to obtain details of reported use/never use of 50 specific pesticides by farmers and spouses and information on performance of household tasks involving possible pesticide exposure, e.g. frequency of washing clothes worn during pesticide application and also number of years participant lived on farm. The 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. After consideration of 50 specific pesticides, there was a statistically significant increased risk of breast cancer in relation to the husbands' use among wives 'who never used pesticides' for the fungicide captan (rate ratio (RR) 2.7, 95% CI 1.7-4.3). However, this result is difficult to interpret as there was no evidence for an elevation of risk seen for women who applied this pesticide themselves (RR 0.5, 95% CI 0.2-1.2).[7] This cohort study clearly identified a group that was para-occupationally exposed. However, information on pesticide use was based on self-reporting and, because of the large number of pesticide exposures investigated, some associations may have occurred by chance. In addition, some numbers of cases were small. For example, there were only 17 cases in postmenopausal women whose husbands used captan.

13. Flower et al (2004) undertook a cohort study of childhood cancer by identifying information for 17,357 children of Iowa pesticide applicators provided by parents enrolled in the Agricultural Health Study (AHS) between 1993-1997.[8] Cancer cases among children were both retrospectively and prospectively identified after parental enrolment. Fifty cases of childhood cancer arising between 1975-1998 were identified among AHS participants. Cancer rates for Iowa 1975-1998 from the Iowa Cancer Registry were used as reference standards in calculating SIRs (37 cases childhood cancer expected). The SIR for total cancer was 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 a statistically significant increased incidence of Hodgkin's lymphoma (SIR 2.56, 95% CI 1.06-6.14). Children of fathers who reported they generally did not wear chemically resistant gloves (16%), n=13 cases, had astatistically significant increased risk of childhood cancer (odds ratio (OR) 1.98, 95% CI 1.05-3.76). However, there was no increase in childhood cancer risk detected with increasing maternal or paternal frequency of pesticide exposure (frequency of mixing/application). There was no information on pesticide exposure and the number of cases was small for the exposure scenarios considered.[8]

14. Kristensen et al. (1996) investigated 323,292 offspring born in 1952-1991 to parents identified as farm holders in agricultural censuses in Norway; 1,275 incident cases of cancer were identified.[9] 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). Data from the Cancer Registry of Norway and estimates of the rural population of Norway were used to calculate SIRs For the whole cohort, 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 statistically significantly elevated only for testicular cancer (SIR 124, 95% CI 101-152). Some significant findings were reported for a number of crude proxies of possible exposure to pesticides (such as orchards or greenhouses on farm holding or pesticide purchase by farmer). Thus, the 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. A relationship between pesticide purchase and some specific tumours was also reported (non-astrocytic neuroepithelial tumours and non-Hodgkin's lymphoma). The 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.[9] This cohort study reported on a long period of follow-up. However, the use of crude proxies for exposure to pesticides and small numbers of cases in the exposure scenarios used and specific tumours investigated limit the conclusions that can be drawn from this study. For example, there were four cases of Wilm's tumour in the exposure category considered.

Case-Control Studies

15. A tabulation of the main findings from the 18 case-control studies considered in this review is appended at the end of this statement (Table 1).[10-27] A narrative summary of the main findings is provided below.

16. Alderton et al (2006) presented evidence for a statistically significant association between para-occupational exposure of the mother during pregnancy to unspecified pesticides through professional pest control applications and acute lymphocytic leukaemia in children with Down's syndrome (OR 2.25, 95% CI 1.13-4.49).[10] This was an exploratory study based on telephone interviews. Exposure of the child, instead of the mother during pregnancy, to professional pest control applications was not found to be significant (OR 1.48, 95% CI 0.77-2.88). Buckley et al (2000), a US study based on telephone interviews, suggested a statistically significant association between para-occupational exposure of the mother during pregnancy to applications of unspecified insecticides by professional pest control and non-Hodgkin's lymphoma in the child (OR 2.98, 95% CI 1.44-6.16, P=0.002). Numbers of exposed cases were small: 31 cases and 12 controls.[11] Ma et al (2002), a US study based in Northern California, suggested a statistically significant association between para-occupational exposure of the mother during pregnancy to insecticides, through applications of unspecified insecticides by professional pest control, and leukaemia in the child (OR 2.2, 95% CI 1.0-4.8), based on 22 cases and 14 controls,. Exposure of the child to insecticides through professional pest control in the first 3 years of life was also associated with a statistically significant increased risk of leukaemia, with the highest odds ratio for year 2 of the child's life (OR

3.6, 95% CI 1.6-8.3), based on 31 cases and 15 controls. Overall, for exposure of the mother 3 months before pregnancy to year 3 of the child's life, the OR was 2.8, with 95% CI 1.4-5.7, based on 39 cases and 25 controls.[19] However, the numbers of cases and controls in the various time windows were small.

17. Meinert et al (1996) was a German study that suggested an association between childhood leukaemia and exposure of the child to applications of unspecified pesticides by a pest control operator (OR 1.03 for leukaemia cases versus "local" control group, OR 1.20 for leukaemia cases versus "state" control group, OR 2.00 for solid tumours versus all controls).[21] However, the numbers of cases and controls were very small (3 leukaemia cases, 5 solid tumour cases, and 7 controls in total), and the study did not report confidence intervals or P values for the calculated odds ratios. Meinert et al (2000) was a larger German study with reported confidence intervals, and is discussed in more detail below (paragraph 20 and table 1).

18. Two studies (Teitelbaum et al (2007)[26], Kato et al (2004)[18]) presented evidence for an association between exposure of women from professional application of pesticides or professional pest control and cancer. Teitelbaum et al (2007) was a US study based in Long Island, New York in 1996-7. It reported an association between para-occupational exposure to professional application of unspecified pesticides to control garden pest problems and a statistically significant increased risk of breast cancer (for application of pesticides by professional to control weeds, OR 1.36, 95% CI 1.08-1.71; to control insects or diseases of outdoor plants, OR 1.79, 95% CI 1.12-2.84).[26] However, the study authors cautioned that there was uncertainty in the observed association, due to the absence of a dose response and the possibility of chance findings due to multiple comparisons.

19. Kato et al (2004), a US study based in New York State, reported one statistically significant result for non-Hodgkin's lymphoma in women and exposure by outdoor application of insecticides by others with some evidence for a dose-response relationship (OR 2.37 for 4th quartile, 'applied ≥49 times', 95% CI 1.32-4.24, P value for trend 0.005).[18] However, no dose-response trend was observed for indoor application of insecticides by others, where exposure might be presumed to be greater, and the positive association could have been a consequence of the multiple comparisons involved in the study. Furthermore, the authors stated that selection limitations and recall bias suggested caution in interpreting the results.

20. Three of the case-control studies (Buckley et al (2000)[11], Meinert et al (1996)[21] and (2000)[22]) also provided evidence for an association between parental occupational exposure to pesticides and cancer in children. Buckley et al (2000) suggested a statistically significant association with Burkitt lymphoma (OR 9.6, $0.01<P<0.05$) and unspecified pesticides. The authors cautioned that their measurement of exposure was likely to be subject to substantial misclassification.[11] Meinert et al (1996) found an association between parents' direct occupational exposure to insecticides, herbicides or fungicides and childhood leukaemia (OR 1.53 with direct occupational exposure of either father or mother, no confidence intervals given).[21] Meinert

et al (2000) found a number of statistically significant associations for para occupational exposure of children and leukaemia and non-Hodgkins lymphoma (see table 1 at the end of this statement).. Another study, Ruder et al (2006), presented evidence suggesting that moving to a farm as an adolescent aged 11 to 20 years, as opposed to as an adult, was associated with a greater risk of glioma (OR 1.96, 95% CI 1.13-3.39 for respondents including proxies).[24] However, there were no significant positive results for residence on a farm or for moving to a farm as a child aged 1 to 10 years or as an infant under 1 year, so this association may be due to statistical chance.

QUALITY SCORING

21. The 22 cancer papers were sub-divided into cohort and case-control studies and details from the papers were extracted for the following categories of information: response rate, exposure assessment, confounders, bias, disease characterisation, and any dose-response data. Exposure assessment and bias were considered key areas in assessing the quality of the studies. A list of criteria was drawn up to use as a basis for the quality scoring of the papers (,Annex 1 Table 1). The score (of 1,2 or 3 with a score of 1 for the highest quality studies) was awarded on the basis whereby two or more criteria in a score category in Annex 1 Table 1applied to the paper.

22. Using the quality criteria, a score of 1 was awarded to two papers, a score of 2 to six papers, and a score of 3 to fourteen papers. The two papers with a score of 1 were the Hartge et al (2005) and Infante-Rivard et al (1999) studies.[16,17] Both studies reported on exposure to professional treatment of the home, and both reported negative findings. Hartge et al (2005) found no evidence for a statistically significant increased risk of Non-Hodgkin's Lymphoma (NHL) in adults from exposure to professional application of herbicides, and Infante-Rivard et al found no evidence of a statistically significant increased risk of acute lymphocytic leukaemia (ALL) in children from exposure to professional treatment of the home with insecticides.

23. Of the studies awarded a score of 2, Flower et al (2004) and Meinert et al (2000) reported a possible association between children's exposure to parents' occupational use of pesticides and lymphoma and leukaemia, respectively.[8,22] Alderton et al (2006)[10], Ma et al (2002)[19] and Meinert et al (2000)[22] reported statistically significant associations between exposure to professional pest control and ALL, leukaemia or lymphoma in children. However, these studies had various limitations in design and possible areas of bias that cast some uncertainty on their conclusions. Study limitations and possible bias were even more applicable to studies awarded a score of 3.

24. Overall, a qualitative assessment of the cancer papers gave inconclusive results. The two more robust studies reported negative findings, while some of the remaining papers reported positive associations between exposure and risk of cancer, but with various limitations in the study design and conclusions.

META-ANALYSIS

25. Meta-analyses were undertaken using both fixed effects and random effects models, potential publication bias was assessed using funnel plots, and by performing Egger's test.[28] A meta-analysis of cohort studies was not undertaken, as data were only available for two cohorts of individuals. Accompanying relevant narrative information on each study can be found in the narrative review and tabled information at the end of this statement (table 1). The relevant figures summarising the meta-analyses performed are appended in Annex 2 to this statement. A detailed summary of the meta-analyses can be found in the COC discussion paper. http://www.iacoc.org.uk/papers/documents/CC1004FinaldiscussionpaperPara-OccupationalReviewandCancerPart2_000.pdf)

The following results and conclusions reached in the meta-analysis are accompanied by relevant Forest and Funnel plots in Annex 2 to this statement.

Fathers' Occupational Exposure to Pesticides and Haematopoietic Cancers in Children

26. The results of meta-analysis gave an OR 1.41, 95% CI 0.88-2.25 for combined haematopoietic cancers (Figures 1 and 2, Annex 2). The study by Meinert et al (2000)[22] on childhood leukaemia contributed the greatest weight to the analysis (40.1%) (OR 1.60, 95% CI 0.77-3.35). There was no evidence for publication bias based on Egger's test. Overall, no statistically significant association was found.

Mothers' Occupational Exposure to Pesticides and Haematopoietic Cancers in Children

27. The results of meta-analysis gave an OR 2.27, 95% CI 0.94-5.47 for combined haematopoietic cancers and might support a positive association between mothers' occupational exposure to pesticides and the occurrence of haematopoietic cancers in children (Figures 3 and 4, Annex 2). The study by Meinert et al (2000)[22] on childhood leukaemia contributed the greatest weight to the analysis (46.7%) (OR 2.50, 95% CI 0.69-9.04). There was no evidence for publication bias based on Egger's test. Overall, no statistically significant association was found.

Child's Exposure to Professional Pest Control Agents and Haematopoietic Cancers in Children

28. Analysis included a range of haematopoietic cancers (pooled OR 1.53, 95% CI 0.93-2.52 for 1-5 treatments (Figures 5 and 7, Annex 2), pooled OR 1.77, 95% CI 0.98-3.22 for >5 treatments (Figures 6 and 8, Annex 2)). The study by Infante-Rivard et al (1999)[17] on ALL contributed the greatest weight to the analysis (37.20%) for 1-5 treatments (OR 1.25, 95% CI 0.56-2.85), and the study by Meinert et al (2000)[22] on childhood leukaemia contributed the greatest weight to the analysis (32.0%) for >5 treatments (OR 1.30, 95% CI

0.45-3.74). There was no evidence for publication bias based on Egger's test. Overall no statistically significant association was found.

Mothers' Para-Occupational Exposure During Pregnancy to Professional Pest Control Agents and Haematopoietic Cancers in children

29. All studies considered ALL (pooled OR 2.01, 95% CI 0.87-4.66) (Figures 9 and 10, Annex 2). The study by Infante-Rivard et al (1999)[17] on ALL contributed the greatest weight to the analysis (40.8%) (OR 1.68, 95% CI 0.45-6.28). There was no evidence for publication bias based on Egger's test. Overall no statistically significant association was found

Adult Exposure and Disease Outcome

30. There were 8 case-control studies which reported on cancer outcomes in adults and various para-occupational exposures.[12,13,16,18,20,24,25,26] However, the studies were too dissimilar in terms of exposure scenario and disease outcome to allow comparison.

COC DISCUSSION

31. The Committee agreed that there was no significant heterogeneity in the analysis and funnel plots gave no evidence of publication bias, although the power to detect publication bias is low due to the small number of studies. Members agreed that it was not possible to perform a meaningful meta-analysis on the cohort studies as only two cohorts of individuals were involved in the studies and there were no readily comparable exposure conditions where a risk of disease was also reported.

32. The Committee considered that there was a diversity of cancer types and exposure scenarios reported in the case-control studies making comparison of these papers difficult in meta-analysis. Interpretation of these data is also complicated by the fact that the studies examine exposure to 'pesticides' as a whole which comprises many different active chemicals, each with potentially differing modes of action and target organs. This could dilute any genuine associations seen in the study or the observed associations could be due to confounding. It is possible that a high risk for a specific tumour type could be missed, although it was noted that, due to the extensive testing and toxicological evaluation of pesticides, high risk substances were unlikely to be in use today. A further complication is that a proportion of past pesticide exposure would have been to substances whose use had been discontinued, thus would not be relevant to a risk assessment of the present situation.

33. A meta-analysis was performed for a small group of studies reporting on 'haematopoietic cancers' in children. Although the pooled ORs were >1 in all of the meta-analyses performed, the confidence intervals suggested no statistically significant association between the exposure and the occurrence

of cancer. Members considered that, whilst confidence intervals which included the OR of 1 is a helpful tool for assessing the statistical significance of the findings, the fact that all results of the meta-analysis were above 1 did provide limited evidence of a weak effect. The two highest quality studies reported negative findings and the remaining studies had limitations in study design and possible bias that cast some uncertainty on the conclusions. Together, the lack of statistically significant effects, limitations in study design and limitations in the analysis of the studies mean that the strength of the findings is relatively weak; and the Committee concluded that , there is limited evidence of a weak positive association of para-occupational exposure of children to pesticides and haematopoietic cancers.

34. The Committee were aware that two recent meta-analyses of maternal prenatal occupational exposure also support an association between pesticides and childhood leukaemia.[29,30] Only 5 of the 25 studies included in the Van Maele-Fabry et al[29] analyses and 4 of the 35 studies used in the Wigle et al[30] analyses were also used in the COC review. This is a result of the different exposure scenarios considered in these separate analyses.

35. The Committee noted that a major limitation of the current analysis was the pooling of all leukaemias, since the aetiology of such cancers is not necessarily the same. Grouping haematopoietic cancers could dilute the effects for specific types of leukaemia. Also, there was relatively little information available for solid tumours; although some had been covered in the cohort studies. A further limitation of the available data was that no specific chemicals were identified with regard to haematopoietic cancers.

36. The meta-analyses undertaken for haematopoietic cancers was based on studies of both para-occupational exposure (i.e parental occupational use of pesticides) and professional pest control treatment of homes. It is not possible to extend the observations to residents and bystanders because the differences in magnitude and patterns of exposures are not yet known.

CONCLUSIONS

37. The Committee agreed the following conclusions:

i) There is limited evidence for a weak positive association between para-occupational exposure (as outlined in paragraphs 26-29 of this statement) of children to pesticides and haematopoietic cancer.

ii) The Committee also noted recent meta-analyses (paragraph 34) which support an association between maternal prenatal exposure to pesticides and childhood leukaemia.

iii) There is insufficient evidence to determine whether the observed association (paragraph 37 i) is causal, nor the likely candidate pesticides.

iv) The conclusion reached regarding para-occupational exposure to pesticides in this statement (paragraph 37 i) related to the exposures considered in the relevant studies and should not be extrapolated to current exposures of residents and bystanders.

i) No specific chemicals or populations were identified that would warrant further investigation by the ACP at this time.

July 2011

REFERENCES

1. Royal Commission on Environmental Pollution. The Royal Commission on Environmental Pollution report on crop spraying and the health of residents and bystanders. 2005.

2. Committees on Toxicity and Carcinogenicity of Chemicals in Food C.P.a.t.E. Joint statement on Royal Commission on Environmental Pollution report on crop spraying and the health of residents and bystanders. 2006.

3. Department for Environment F.a.R.A. The Royal Commission on Environmental Pollution report on crop spraying and the health of residents and bystanders Government response. 2006.

4. Committee on Carcinogenicity of Chemicals in Food C.P.a.t.E. Draft discussion paper on the systematic review of epidemiological literature of para-occupational exposure to pesticides and cancer. CC/09/11 . 2009.

5. Committee on Carcinogenicity of Chemicals in Food C.P.a.t.E. Draft Minutes of meeting held 19 November 2009. CC/MIN/2009/3. 2009.

6. 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., and Blair A. (2005) Cancer incidence in the agricultural health study. *Scand J Work Environ Health* 31 Suppl 1, 39-45; discussion 5-7.

7. Engel L.S., Hill D.A., Hoppin J.A., Lubin J.H., Lynch C.F., Pierce J., Samanic C., Sandler D.P., Blair A., and Alavanja M.C. (2005) Pesticide use and breast cancer risk among farmers' wives in the agricultural health study. *Am J Epidemiol* 161, 121-35.

8. Flower K.B., Hoppin J.A., Lynch C.F., Blair A., Knott C., Shore D.L., and Sandler D.P. (2004) Cancer risk and parental pesticide application in children of Agricultural Health Study participants. *Environ Health Perspect* 112, 631-5.

9. Kristensen P., Andersen A., Irgens L.M., Bye A.S., and Sundheim L. (1996) Cancer in offspring of parents engaged in agricultural activities in Norway: incidence and risk factors in the farm environment. *Int J Cancer* 65, 39-50.

10. Alderton L.E., Spector L.G., Blair C.K., Roesler M., Olshan A.F., Robison L.L., and Ross J.A. (2006) 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. *Am J Epidemiol* 164, 212-21.

11. Buckley J.D., Meadows A.T., Kadin M.E., Le Beau M.M., Siegel S., and Robison L.L. (2000) Pesticide exposures in children with non-Hodgkin lymphoma. *Cancer* 89, 2315-21.

12. 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., and Talaska G. (2005) Gliomas and farm pesticide exposure in women: the Upper Midwest Health Study. *Environ Health Perspect* 113, 546-51.
Notes: CORPORATE NAME: Brain Cancer Collaborative Study Group

13. Colt J.S., Davis S., Severson R.K., Lynch C.F., Cozen W., Camann D., Engels E.A., Blair A., and Hartge P. (2006) Residential insecticide use and risk of non-Hodgkin's lymphoma. *Cancer Epidemiol Biomarkers Prev* 15, 251-7.

14. Cooney M.A., Daniels J.L., Ross J.A., Breslow N.E., Pollock B.H., and Olshan A.F. (2007) Household pesticides and the risk of Wilms tumor. *Environ Health Perspect* 115, 134-7.

15. 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., and Castleberry R.P. (2001) Residential pesticide exposure and neuroblastoma. *Epidemiology* 12, 20-7.

16. Hartge P., Colt J.S., Severson R.K., Cerhan J.R., Cozen W., Camann D., Zahm S.H., and Davis S. (2005) Residential herbicide use and risk of non-Hodgkin lymphoma. *Cancer Epidemiol Biomarkers Prev* 14, 934-7.

17. Infante-Rivard C., Labuda D., Krajinovic M., and Sinnett D. (1999) Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms. *Epidemiology* 10, 481-7.

18. Kato I., Watanabe-Meserve H., Koenig K.L., Baptiste M.S., Lillquist P.P., Frizzera G., Burke J.S., Moseson M., and Shore R.E. (2004) Pesticide product use and risk of non-Hodgkin lymphoma in women. *Environ Health Perspect* 112, 1275-81.

19. Ma X., Buffler P.A., Gunier R.B., Dahl G., Smith M.T., Reinier K., and Reynolds P. (2002) Critical windows of exposure to household pesticides and risk of childhood leukemia. *Environ Health Perspect* 110, 955-60.

20. McDuffie H.H., Pahwa P., McLaughlin J.R., Spinelli J.J., Fincham S., Dosman J.A., Robson D., Skinnider L.F., and Choi N.W. (2001) Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. *Cancer Epidemiol Biomarkers Prev* 10, 1155-63.

21. Meinert R., Kaatsch P., Kaletsch U., Krummenauer F., Miesner A., and Michaelis J. (1996) Childhood leukaemia and exposure to pesticides: results of a case-control study in northern Germany. *Eur J Cancer* 32A, 1943-8.

22. Meinert R., Schuz J., Kaletsch U., Kaatsch P., and Michaelis J. (2000) Leukemia and non-Hodgkin's lymphoma in childhood and exposure to pesticides: results of a register-based case-control study in Germany. *Am J Epidemiol* 151, 639-46; discussion 647-50.

23. Monge P., Wesseling C., Guardado J., Lundberg I., Ahlbom A., Cantor K.P., Weiderpass E., and Partanen T. (2007) Parental occupational exposure to pesticides and the risk of childhood leukemia in Costa Rica. *Scand J Work Environ Health* 33, 293-303.

24. Ruder A.M., Waters M.A., Carreon T., Butler M.A., Davis-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., and Rosenman K.D. (2006) The Upper Midwest Health Study: a case-control study of primary intracranial gliomas in farm and rural residents. *J Agric Saf Health* 12, 255-74.
Notes: CORPORATE NAME: The Brain Cancer Collaborative Study Group

25. Ruder A.M., Waters M.A., Butler M.A., Carreon T., Calvert G.M., Davis-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., and Talaska G. (2004) Gliomas and farm pesticide exposure in men: the upper midwest health study. *Arch Environ Health* 59, 650-7.
Notes: CORPORATE NAME: Brain Cancer Collaborative Study Group

26. Teitelbaum S.L., Gammon M.D., Britton J.A., Neugut A.I., Levin B., and Stellman S.D. (2007) Reported residential pesticide use and breast cancer risk on Long Island, New York. *Am J Epidemiol* 165, 643-51.

27. van Wijngaarden E., Stewart P.A., Olshan A.F., Savitz D.A., and Bunin G.R. (2003) Parental occupational exposure to pesticides and childhood brain cancer. *Am J Epidemiol* 157, 989-97.

28. Egger M., Davey Smith G., Schneider M., and Minder C. (1997) Bias in meta-analysis detected by a simple graphical test. *BMJ* 315, 629-34.

29. Van Maele-Fabry G., Lantin AC., Hoett P., and Linson D. (2010) Childhood leukaemia and parental occupational exposure to pesticide: a systematic review and meta-analysis. *Cancer Causes Control*, 21, 787-809.

30. Wigle DI., Turner MC., Krewski D., (2009). A systematic review and meta-analysis of childhood leukaemia and parental occupational pesticide exposure. *Environ Health Perspect*, 117, 1505-13.

Table 1. Case-Control Para-Occupational Cancer Studies considered by COC

Reference/Study Groups	Health Outcomes	Exposure Assessment	Main Findings
Alderton et al 2006.[10] 97 acute lymphoblastic leukaemia (ALL), 61 acute myeloid leukaemia (AML). 173 control children Score 2	Acute lymphocytic leukaemia (ALL) and acute myeloid leukaemia (AML) and association with child and maternal exposure to household chemicals	Mother's report of exposure to professional pest exterminations around time of pregnancy	ALL; OR 2.25, 95% CI 1.13- 4.49 for professional pest control applications:
Buckley et al 2000[11] 268 cases age≤20y Feb 1986 and June 1990. 268 control children matched individually Score 3	Non-Hodgkins Lymphoma (NHL) or lymphomatous leukaemia in children	Mother's report concerning exposure of the mother during pregnancy to professional insect extermination, and either parent being occupationally exposed to unspecified pesticides	NHL OR 2.98, 95% CI 1.44-6.16, exposure of the mother around the time of pregnancy to professional insect treatment to the home
Carreon et al 2005[12] 341 female cases (aged 18-80y). 527 controls randomly selected using 10 year age strata. Score 3	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	No relevant statistically significant associations were reported in this study.
Colt et al 2006[13] 1321 cases (male/female) diagnosed1998-2000. 1057 controls Score 3	NHL in adults	Dust samples from 682 case and 513 control homes analysed for specific pesticides. Source of exposure not identified.	No association found for a range of organophosphates, carbamates, pyrethrins.
Cooney et al 2007[14] 523 cases (<16 years). 517 controls matched by age/region Score 2	Wilm's tumour in children <16 years.	Mothers report of professional application in the house; pesticides not specified	No relevant statistically significant associations were reported in this study.
Daniels et al 2001[15] 538 cases (children), 504 controls matched by age/region Score 3	Neuroblastoma in children	Mothers and/or fathers report of professional application in the house; pesticides not specified	Elevated ORs for the use of professional pest control in the home or garden and neuroblastoma in children, but all Confidence Intervals include 1.0 and do not suggest significance.
Hartge et al 2005[16] 1321 cases identified from SEER registries. 1057 controls. Score 1	NHL in adults	Report of total applications of herbicides by lawn care professional. levels of 2,4-dichloro-phenoxyacetic acid and dicamba measured in dust taken from used vacuum cleaner bags in the current home for 679 cases and 510 controls	No relevant statistically significant associations were reported in this study.
Infante-Rivard et al 1999[17] 491 cases , 491 population-based controls. Score 1	Childhood ALL (0-9 years)	Mother's report of professional treatment with insecticides against ants or cockroaches during mother's pregnancy and/or during childhood years.	No relevant statistically significant associations were reported in this study
Kato et al 2004[18] 376 female casesidentified from State Cancer Registry.	NHL in women.	Self-report of exposure to types of pesticides used in homes and application type – applied by self, indoor application by others, outdoor application by	No significant elevations in ORs in any quartile for "indoor application by others". However for "outdoor application by others", for the pesticide type "insecticides for flying bugs or

463 controls. Score3		others.	foggers", there was a significantly elevated OR for the fourth quartile, "applied ≥49 times": OR=2.37, 95% CI 1.32-4.24,
Ma et al 2002[19] 162 cases from North California Childhood Leukaemia study. 162 controls age, sex, race and residence matched Score 2	Leukaemia in children (0-14 years)	Mothers report professional pest control and lawn applications, during the time windows of 3 months before pregnancy, pregnancy, and years 1, 2 and 3 of the child's life	Overall, 3 months before pregnancy to 3 years old, 39 cases/25 controls exposed, OR=2.8, 95% CI 1.4-5.7; for all 5 time frames combined, children exposed to indoor pesticides had an increased risk of ALL, OR=1.8, 95% CI 1.0-3.4,
McDuffie et al 2001[20] 519 male cases (>19 years), 1506 controls matched for age and residence. Score 3	NHL in men	Self report of residence on farm	No relevant statistically significant associations were reported in this study
Meinert et al 1996.[21] 173 cases of leukaemia. 175 solid tumours. 220 controls matched for residence and 213 controls from another community. Score 3	Leukaemia and some solid tumours in children < 15 years.	Self report of occupation as farmer, gardener or florist and report of pesticides use within the time interval of 2 years prior to child's birth and the diagnosis or reference date	For leukaemia Ors consistently >1 (but 95% Cis not reported) for parental occupation, parents direct exposure and unspecified pesticide use on farm. OR for leukaemia and solid tumours >1 for extermination of insects by pest control operator.
Meinert et al 2000[22] 2358 cases (1184 leukaemia, 234 NHL, 940 with solid tumours). 2588 controls matched for age, gender, residence. Score 2	Acute leukaemia and NHL in children (<15 years)	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.	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.
Monge et al 2007[23] 334 cases, 579 population controls Score 3	ALL and total leukaemias in children 0-14 years	Self-reported exposure by mother and father of use of 25 specific pesticides; report of agricultural tasks performed, 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	For father's exposure to the herbicide picloram during the child's first year of life; OR 12.4, 95% CI=1.6-98.3. For father's exposure to the fungicide benomyl OR=6.6, 95% CI=1.2-35.4;
Ruder et al 2004[24] 457 male cases (257 excluding proxy respondents), 648 controls resident in eligible counties (625 excluding proxy respondents Score 3	Primary intracranial glioma in adults	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	No relevant statistically significant associations were reported in this study

Ruder et al 2006[25] 798 cases (male and female (438 excluding proxy respondents). 1175 controls (1141 excluding proxy respondents Score 3	Primary intracranial glioma in adults	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	No significant association for subjects who had 'ever lived/worked on farm' 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
Teitelbaum et al 2007[26] 1505 cases, 1553 controls matched for residence Score 2	*Iin situ* or invasive breast cancer	Interview; for para-occupational exposure, report of application of lawn and garden pesticide products by professional only	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; to control insects or diseases of outdoor plants, OR=1.79, 95% CI 1.12-2.84.
Van Wijn-gaarden Et al 2003[27] 154 children diagnosed with astrocytoma and 158 children diagnosed with PNET. 312 controls matched by race, age, and residence Score 3	Astrocytoma and primitive neuroectodermal tumours (PNET) in children diagnosed before 6 years of age	Fathers and mothers; job-exposure matrix determined by interview; 4 classes of pesticides (insecticides, herbicides, agricultural and non-agricultural fungicides) evaluated, and farmers were asked which pesticides they used	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. 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.

ANNEX 1

LITERATURE SEARCH AND REFERENCE SELECTION FOR SYSTEMATIC REVIEW

1. The Committees undertook a comprehensive review based on a detailed discussion paper of epidemiological literature of para-occupational exposure to pesticides and health outcomes drafted by DH Toxicology Unit, Imperial College and the HPA COT secretariat. The detailed discussion paper provides a summary of the approach taken to undertake the review including the literature search including search terms, references included and those excluded from the review. An overview of the review process is given below.

2. A systematic search of the epidemiological literature pertaining to para-occupational exposure to pesticides, fungicides, herbicides and insecticides was undertaken using the databases PubMed, EMBASE, Toxline, CAB Abstracts and Web of Science for the period January 1996 – January 2009 inclusive. In addition, the websites of two US studies, the Agricultural Health Study and the Farm Family Exposure Study were screened for references. Most of the retrieved papers were written in English, and a small number were written in French. The abstracts written in English were evaluated for the papers in French.

3. All the retrieved papers were screened individually and inclusion/exclusion criteria (see Table 1 below in Annex 1). Selection criteria were applied first to the titles of retrieved papers and, if the references were clearly unrelated or irrelevant, the reference was excluded at that stage. In practice, the selection criteria were applied to the abstracts for the majority of the retrieved papers. Any duplicate papers were omitted.

4. In total, 419 references reporting para-occupational exposure with and without health effects data were identified and the references reporting health effects (187 papers) were separated from those reporting exposure information only (232 papers). A list of the exposure references was supplied to the Health and Safety Executive Chemicals Regulatory Directorate (HSE CRD) for assessment. An overview of key exposure references was supplied and was appended to the detailed discussion paper cited in paragraph 7 above.

5. A decision was made to focus on health effects and all papers relating to this subject were obtained. The full papers were evaluated and those with no relevant information were excluded. A total of 54 papers were considered to be relevant to para-occupational exposure. These were summarised and then grouped into the following categories in line with the RCEP report: cancer, neurological and mental health, reproduction, respiratory, acute health effects, ocular effects and other health outcomes. The 54 summarised papers were cross-referenced to identify further references not retrieved through the searches. However, none of these additional identified references were considered relevant to para-occupational exposure and worthy of review. Twenty-two papers with information relevant to para-occupational exposure to pesticides and cancer were identified from the narrative review.[6-27]

6. Toxicological data on specific pesticides identified through the review process were extracted from the EU regulatory draft assessment reports by HSE CRD and provided for COC Members' information.

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	• 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	• 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	• 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

ANNEX 2

RELEVANT FUNNEL AND FOREST PLOTS

Child's Exposure to Parents' Occupational Use of Pesticides

Fathers' occupational exposure to pesticides and haematopoietic cancers in children

Figure 1. Forest plot of results for fathers' occupational exposure to pesticides

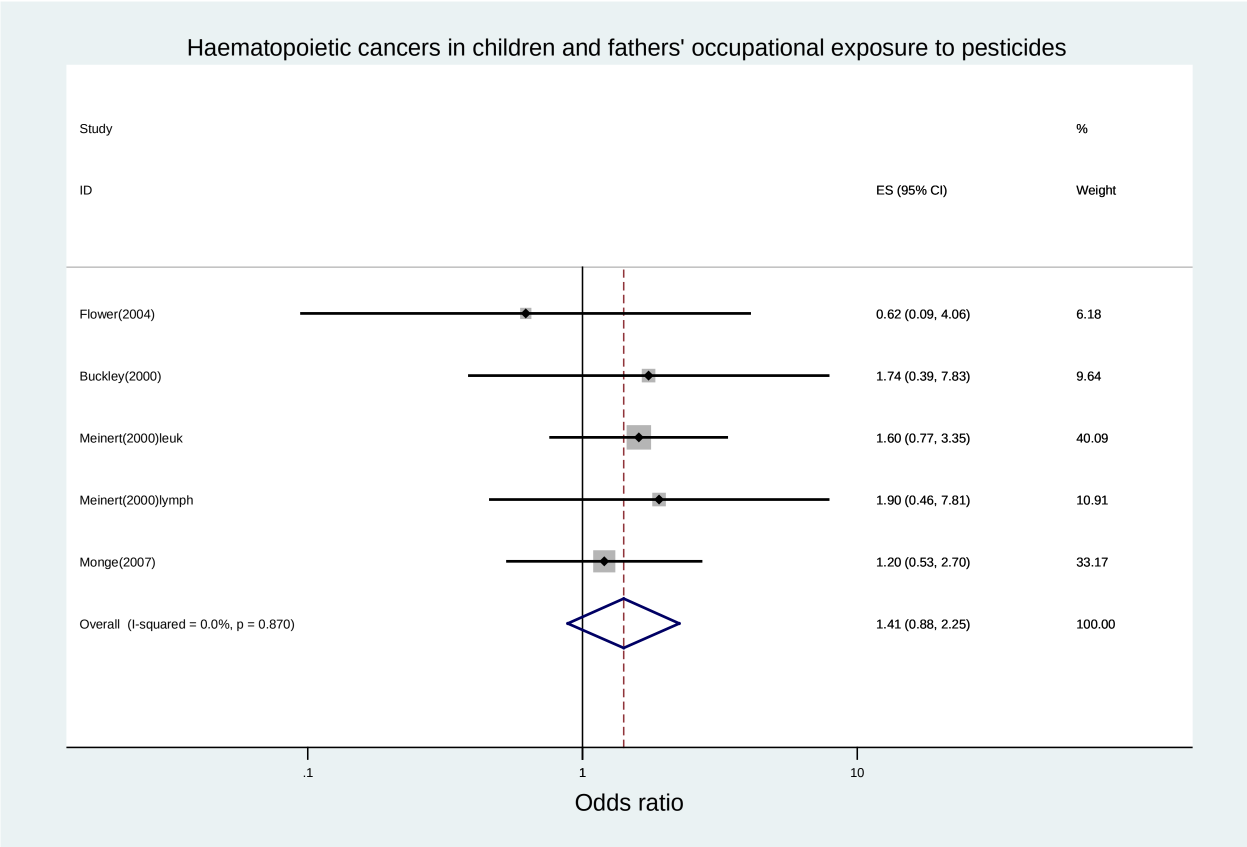
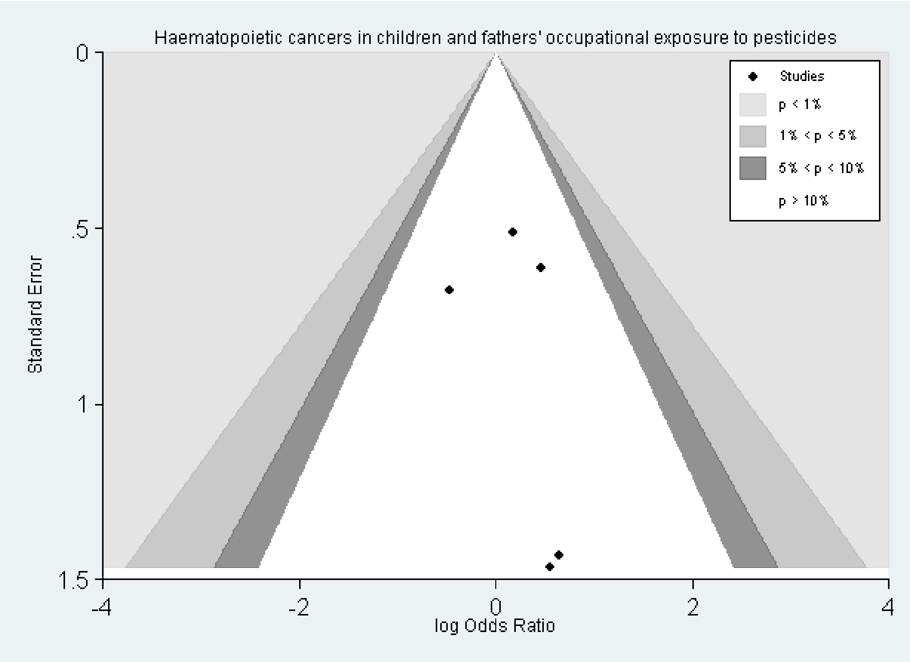


Figure 2. Funnel plot of results for fathers' occupational exposure to pesticides



Mothers' occupational exposure to pesticides and haematopoietic cancers in children

Figure 3. Haematopoietic cancers in children and mothers' occupational exposure to pesticides

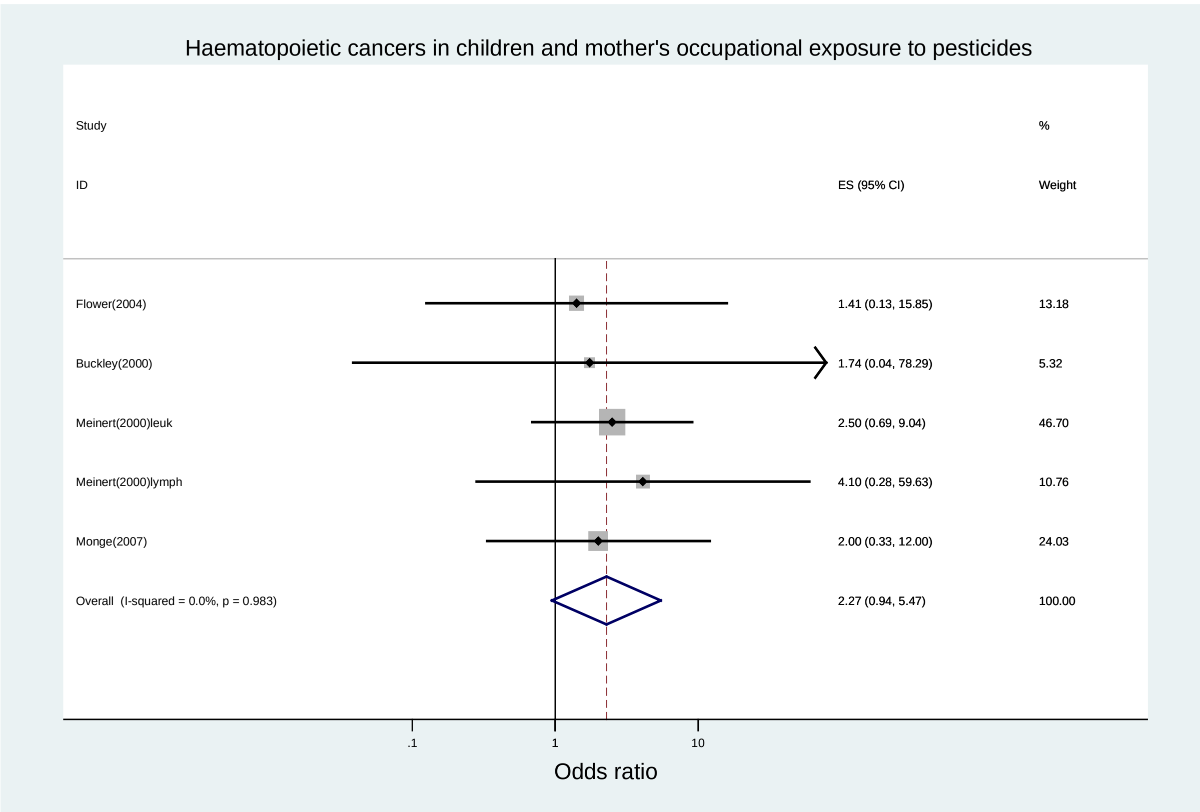
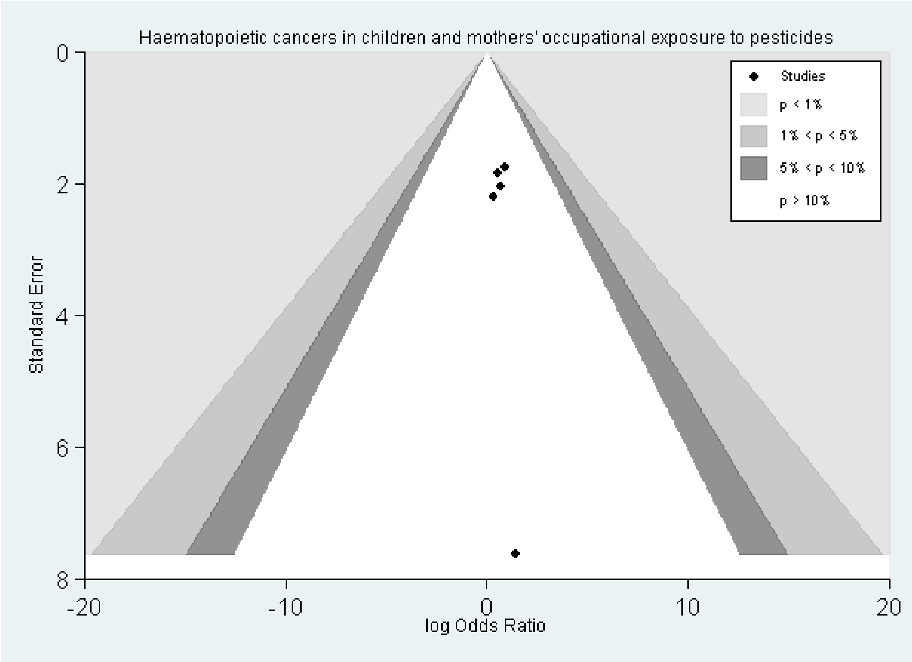


Figure 4. Haematopoietic cancers in children and mothers' occupational exposure to pesticides



Child's Exposure to Professional Pest Control Agents

Figure 5. Haematopoietic cancers in children and professional pest control (Analysis 1)

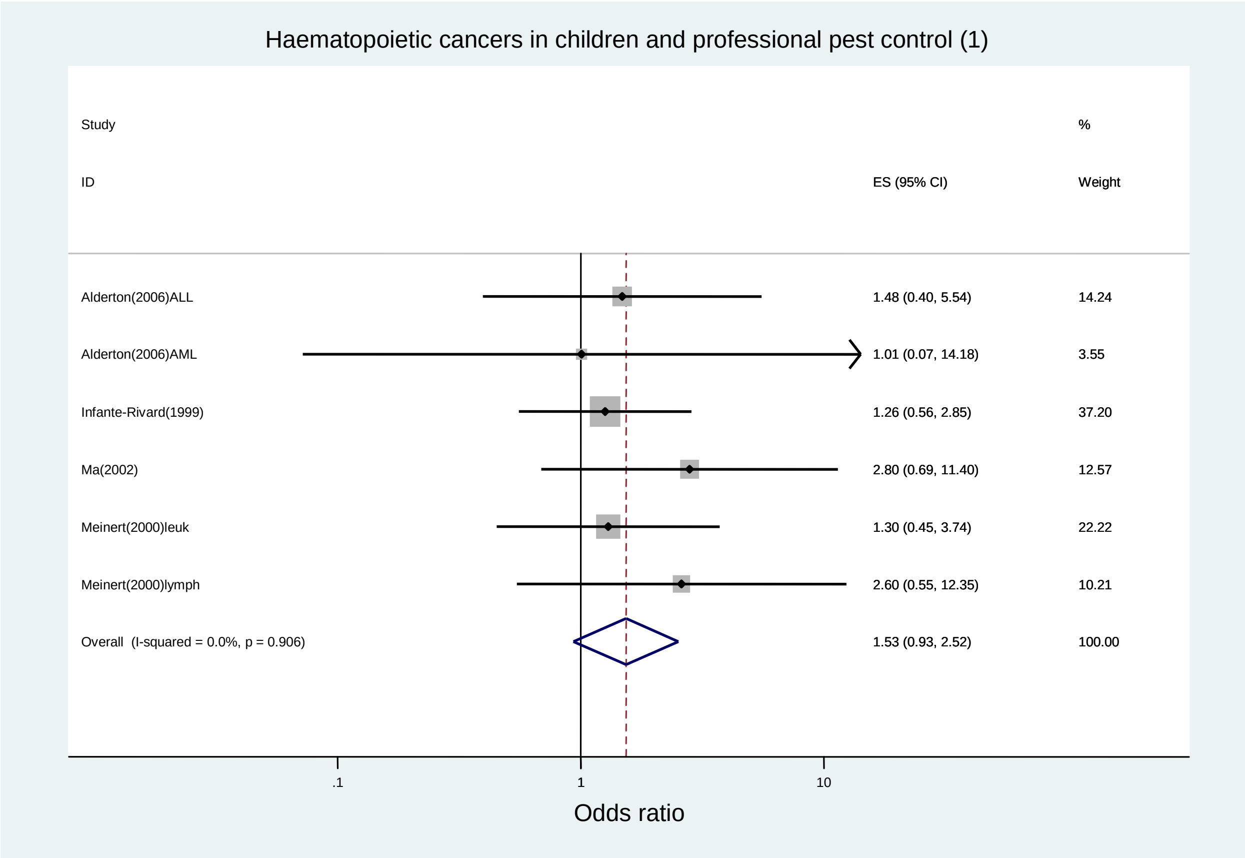


Figure 6. Haematopoietic cancers in children and professional pest control (Analysis 2)

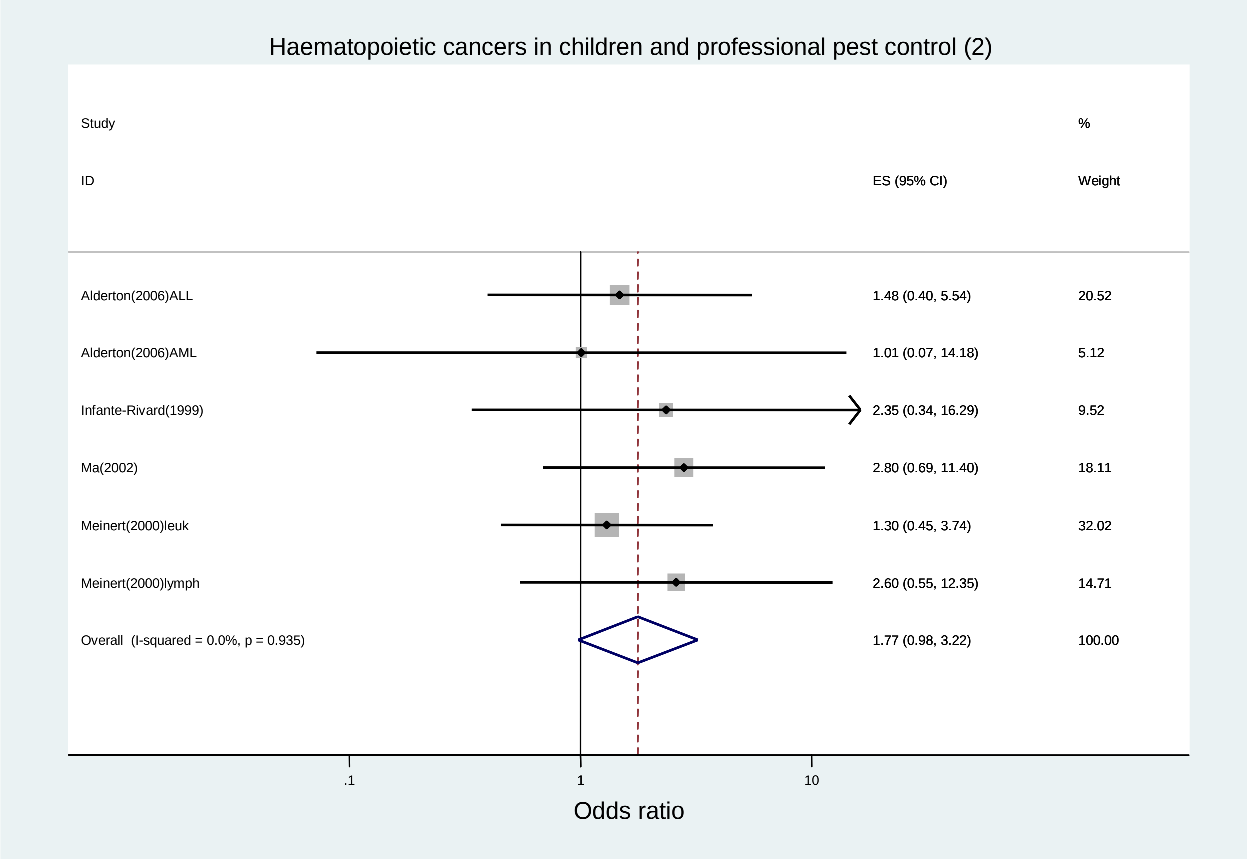


Figure 7. Haematopoietic cancers in children and professional pest control (Analysis 1)

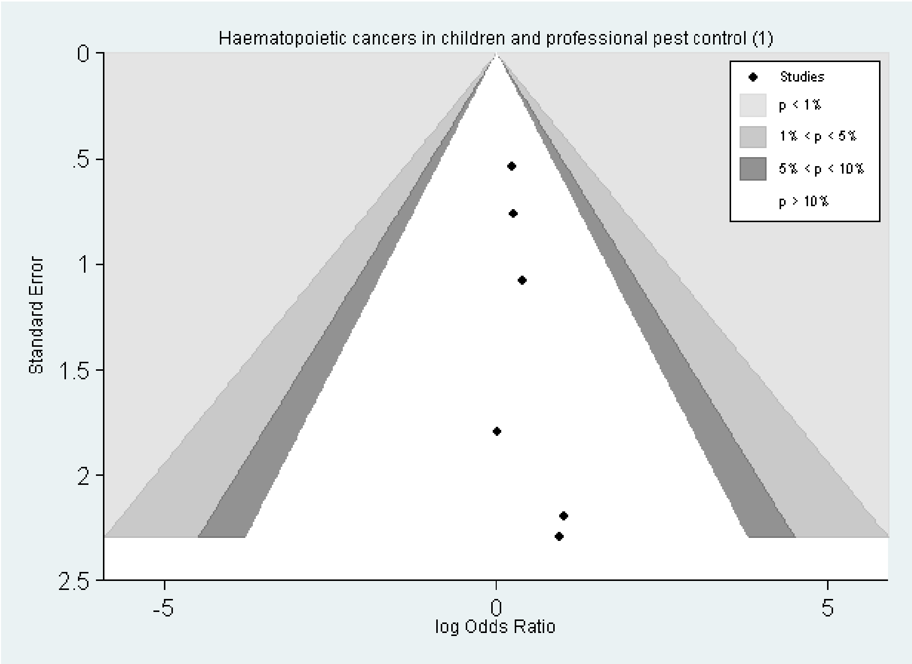
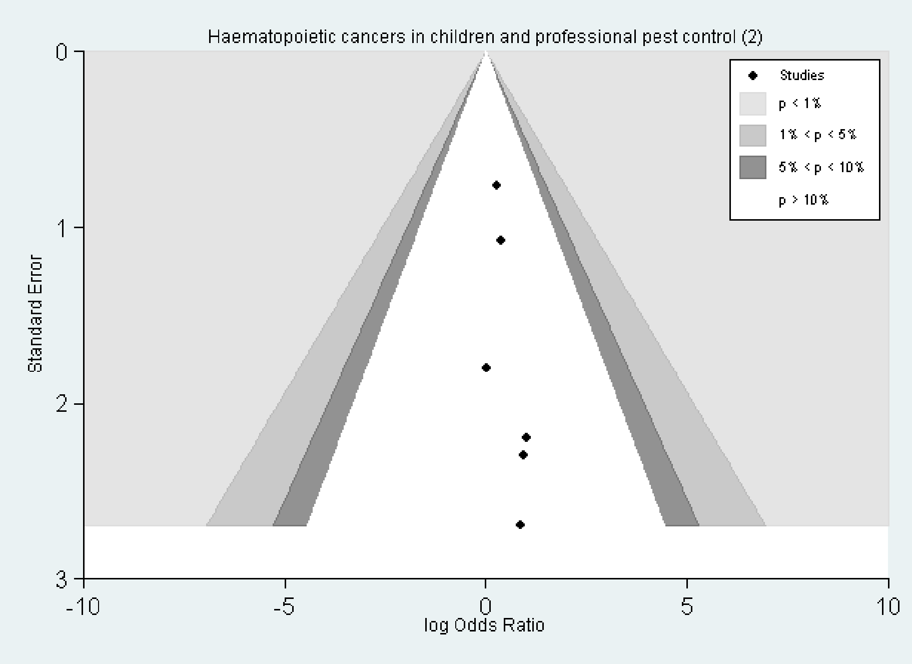


Figure 8. Haematopoietic cancers in children and professional pest control (Analysis 2)



Mothers' Para-Occupational Exposure During Pregnancy to Professional Pest Control Agents

Figure 9. Haematopoietic cancers in children and exposure of mother during pregnancy to professional pest control

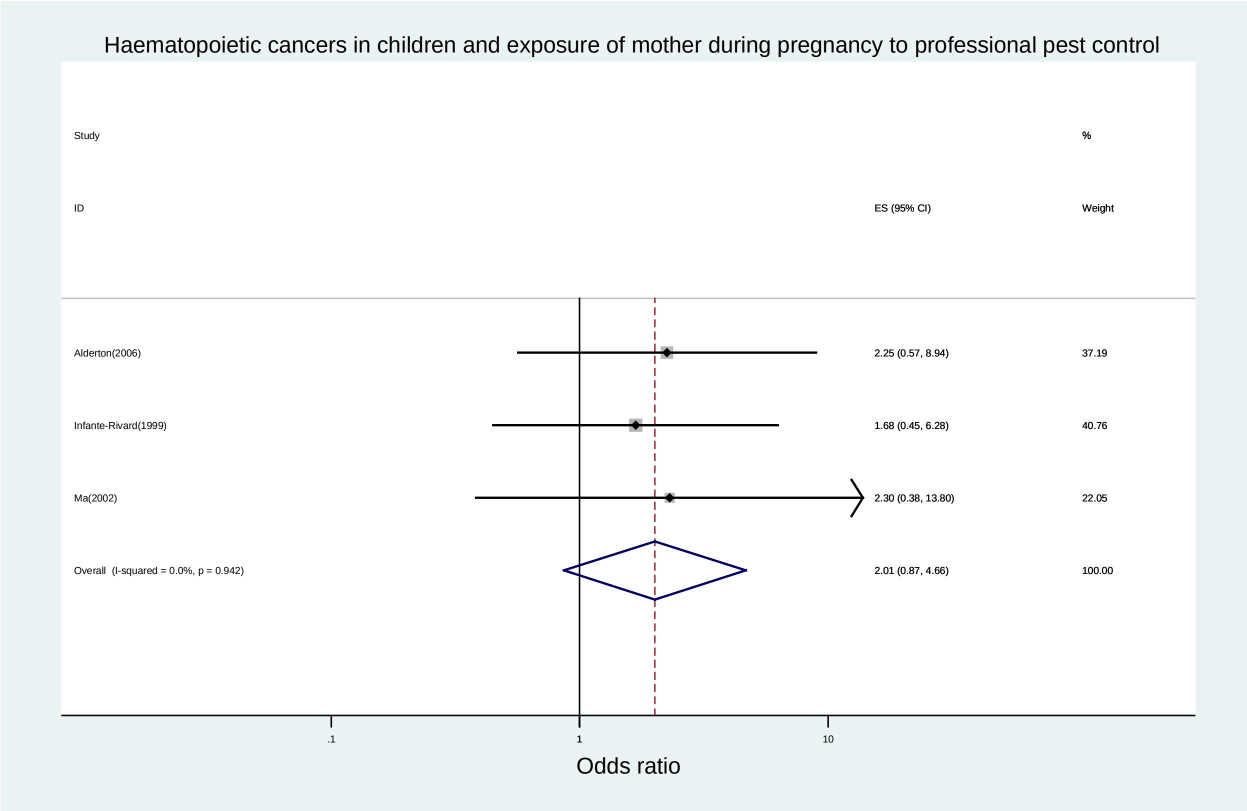


Figure 10. Haematopoietic cancers in children and exposure of mother during pregnancy to professional pest control