CC/10/04

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

ADDITIONAL EVALUATION OF DATA FROM THE SYSTEMATIC REVIEW OF EPIDEMIOLOGICAL LITERATURE OF PARA-OCCUPATIONAL EXPOSURE TO PESTICIDES AND CANCER

BACKGROUND

1. In November 2009, the Committee on Carcinogenicity (COC) evaluated a draft discussion paper detailing a systematic review of epidemiological literature of para-occupational exposure to pesticides and cancer.[1] Members considered that further analysis of this epidemiological data was needed before conclusions could be drawn.[2] To assist Members with their evaluation, an assessment of publication quality and bias and a sensitivity analyses where appropriate have been undertaken.

INTRODUCTION TO REVIEW

2. Twenty-two papers with information relevant to para-occupational exposure to pesticides and cancer were identified in the systematic literature review.[3-24] Of these 22 papers, 4 related to cohort studies,[3-6]and the remainder to case-control studies. Two types of analysis of the cancer studies have been undertaken: quality scoring of all the cancer studies and meta-analysis of selected results.

QUALITY SCORING OF CANCER PAPERS

3. 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 (Table 1, Annex 1). 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 (Table 2, Annex 1). The score was awarded on the basis whereby two or more criteria in a score category applied to the paper. The quality score of each study and the principal reasons for the score awarded are given in Table 1 (Annex 1).

4. Using the quality criteria, a score of 1 (highest quality) was awarded to two papers, a score of 2 to six papers, and a score of 3 (lowest quality) to fourteen papers. The two papers with a score of 1 were the Hartge (2005) and Infante-Rivard (1999) studies.[13,14] Both studies reported on exposure to professional treatment of the home, and both reported negative findings. Hartge (2005) found no evidence for increased risk of Non-Hodgkin's

Lymphoma (NHL) in adults from exposure to professional application of herbicides, and Infante-Rivard found no evidence of an increased risk of acute lymphocytic leukaemia (ALL) in children from exposure to professional treatment of the home with insecticides.

5. Of the studies awarded a score of 2, Flower (2004) and Meinert (2000) reported a possible association between children's exposure to parents' occupational use of pesticides and lymphoma and leukaemia, respectively.[5,19] Alderton (2006), Ma (2002) and Meinert (2000) suggested possible positive associations between exposure to professional pest control and ALL, leukaemia or lymphoma in children.[7,16,19] 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.

6. 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 possible positive associations between exposure and risk of cancer, but with various limitations in the study design and conclusions.

META-ANALYSIS AND PUBLICATION BIAS OF SELECTED CANCER PAPERS

7. All statistical analyses were performed using Stata SE version 11 software, and the meta-analyses used the random effects model. The meta-analyses are illustrated by forest plots in which the Confidence Interval for each study is represented by a horizontal line, the point estimate is represented by a black diamond and the pooled Odds Ratio (OR) is represented by a large diamond. The software also calculated and displayed the percentage weight of each individual measure on the forest plot, and reported the I^2 statistic as a measure of homogeneity between the studies. The I^2 statistic describes the total variation across the studies due to heterogeneity rather than chance. Negative values of I^2 were made equal to zero so that the range of I^2 was between 0 – 100% where no heterogeneity would have a value of 0%.

8. Potential publication bias was investigated by running the 'confunnel' command to produce funnel plots in Stata. This command produced a contour-enhanced funnel plot, adding contours to the graph to illustrate the statistical significance of the effect estimates. In the funnel plots, the logarithm of the Standard Error was plotted against the log of the OR. Funnel plot asymmetry was tested by performing Egger's test in Stata, a test that used the linear regression method suggested by Egger and collaborators.[25]

Meta-Analysis of Selected Cancer Cohort Studies

9. A summary of the information reported in the cohort studies is given in Table 3 (Annex 2). Table 3A indicates which cohorts were involved in the

studies. In reality, the 4 cohort study papers only concerned 2 groups of subjects since 3 papers, (Alavanja (2005), Engel (2005), Flower (2004), arose from the US Agricultural Health Study.[3-5] Alavanja (2005) reported on cancer incidence in spouses of private pesticide applicators from Iowa and North Carolina, Engel (2005) reported on breast cancer in the same group of subjects, and Flower (2004) reported on cancer in children of those spouses. There was only one other cohort study, Kristensen (1996).[6]

10. The incidence outcomes for a range of different types of cancer are given in Table 3B. Performing a meta-analysis of only 2 cohorts of individuals would give meaningless information and so such a comparison of the incidence outcomes was not undertaken. Table 3C contains an indication of the exposure conditions for which the Rate Ratios or ORs were reported in 3 of the cohort study papers. For a meaningful comparison to be drawn, it would be necessary to analyse studies investigating the same exposure scenarios and disease/condition. Table 3C shows that there are no readily comparable exposure conditions in the 3 cohort studies where risk of disease was also reported and so a meaningful comparison could not be made. However, some of the information on risk of disease could be analysed using ORs from the case-control studies, as discussed below.

Meta-Analysis of Cancer Case-Control Studies

11. Information from 17 case-control studies was extracted into the categories of person exposed (child or adult), type of disease and type of exposure (Table 4 (Annex 2). There were 18 case-control studies in total, but one study, Meinert (1996)[18], did not state Confidence Intervals for the ORs reported and so was removed from the meta-analysis. Furthermore, Meinert (2000) reported the findings of the 1996 study in greater detail, and so the ORs and Confidence Intervals were extracted from this study.

Child's Exposure to Parents' Occupational Use of Pesticides

12. Table 4A (Annex 2) shows that there were 5 studies reporting on the child's exposure to parents' occupational use of pesticides.[5,8,19,20,24] Three of the case-control studies concerned leukaemia, lymphoma or specific types of leukaemia or lymphoma. [8,19,20] The Flower (2004) cohort study also reported ORs for father or mother mixing and/or applying pesticides and the risk of childhood cancer, including haematopoietic cancers.[5] The one remaining case-control study in this group, Van Wijngaarden (2003),[24] reported on astrocytoma and could not be readily compared in terms of disease outcome with the other four studies. It was decided, therefore, that 3 case-control studies and one cohort study might be compared if considered in the category 'haematopoietic cancers'.

13. The four studies relating to 'haematopoietic cancers' and children's exposure to parents' occupational use of pesticides reported multiple ORs. A decision was made to select the OR for either father or mother being 'ever occupationally exposed to pesticides' and, if a study reported ORs for both

leukaemia and lymphoma, then both measures were taken. The extracted ORs are shown in Table 5 below.

Table 5. Haematopoietic cancers in children and parents' occupational exposure to pesticides

Study	Disease	Exposure	Effect measure	Lower limit	Upper limit
Flower (2004)	childhood cancer, including haematopoietic cancers and brain tumours	father mixed and/or applied pesticides >19 days/year	OR 0.62	0.24	1.57
Flower (2004)	childhood cancer, including haematopoietic cancers and brain tumours	mother mixed and/or applied pesticides >19 days/year	OR 1.41	0.42	4.72
Buckley (2000)	NHL	parents occupationally exposed to pesticides	OR 1.74	0.82	3.69
Meinert (2000)	leukaemia	father ever occupationally exposed to pesticides	OR 1.6	1.1	2.3
Meinert (2000)	lymphoma	father ever occupationally exposed to pesticides	OR 1.9	0.9	3.7
Meinert (2000)	leukaemia	mother ever occupationally exposed to pesticides	OR 2.5	1.3	4.7
Meinert (2000)	lymphoma	mother ever occupationally exposed to pesticides	OR 4.1	1.1	16
Monge (2007)	leukaemia	father ever occupationally exposed to pesticides	OR 1.2	0.8	1.8
Monge (2007)	leukaemia	mother ever occupationally exposed to pesticides	OR 2.0	0.8	4.8

14. Because results were given separately for fathers' and mothers' occupational exposure in all studies except Buckley (2000), it was decided to run two meta-analyses, one using the data for fathers and the other for mothers, and including the Buckley study results in both.

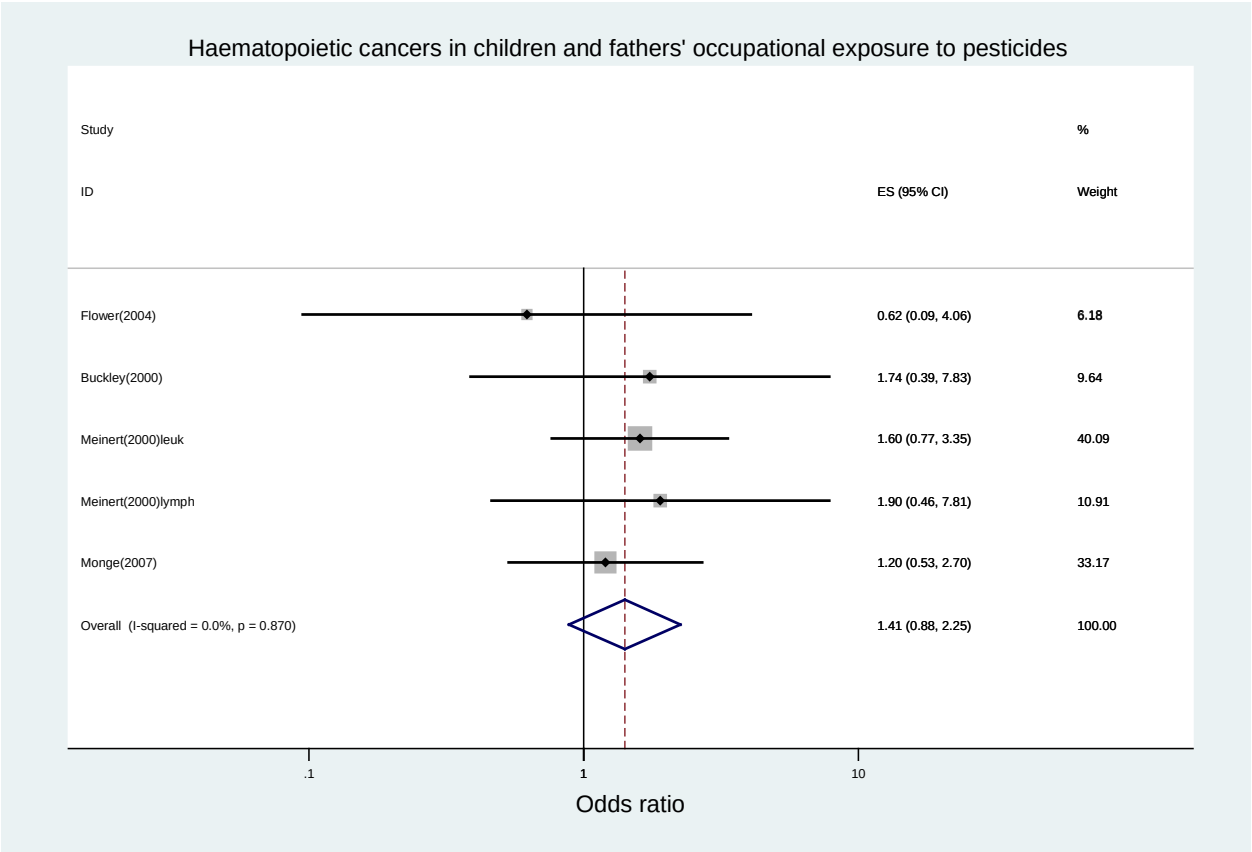
<u>Fathers' occupational exposure to pesticides and haematopoietic cancers in children</u>

15. Table 6 below shows the effect measures from the 5 studies that reported results on haematopoietic cancers in children and fathers' occupational exposure to pesticides. [5,8,19,20] Figure 1 below shows a forest plot of the results, giving the pooled OR and its 95% Confidence Intervals.

Table 6. Haematopoietic cancers in children and fathers' occupational exposure to pesticides

Study	Disease	Exposure	Effect measure	Lower limit	Upper limit
Flower (2004)	childhood cancer, including haematopoietic cancers and brain tumours	father mixed and/or applied pesticides >19 days/year	OR 0.62	0.24	1.57
Buckley (2000)	NHL	parents occupationally exposed to pesticides	OR 1.74	0.82	3.69
Meinert (2000)	leukaemia	father ever occupationally exposed to pesticides	OR 1.6	1.1	2.3
Meinert (2000)	lymphoma	father ever occupationally exposed to pesticides	OR 1.9	0.9	3.7
Monge (2007)	leukaemia	father ever occupationally exposed to pesticides	OR 1.2	0.8	1.8

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

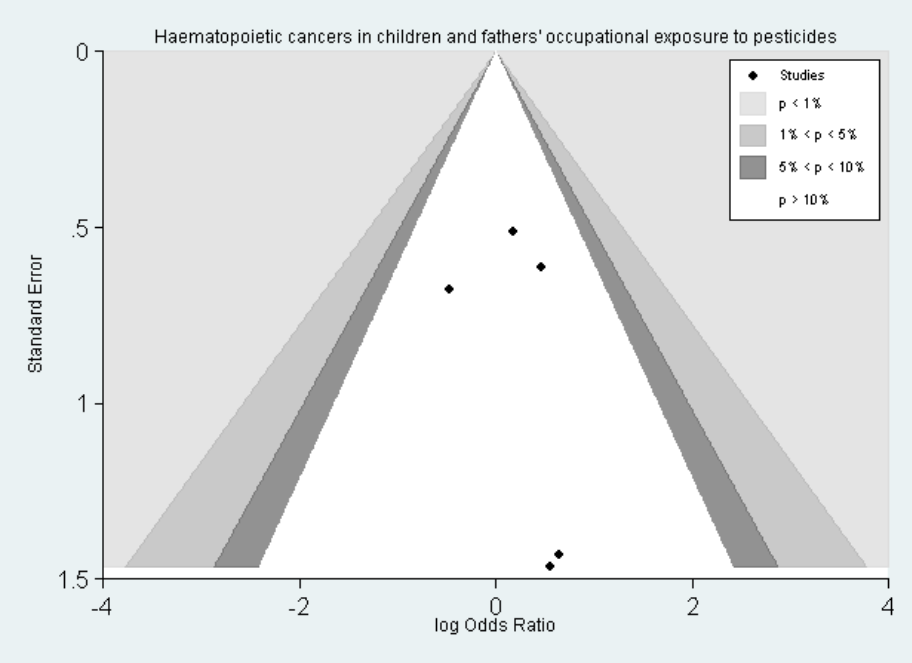


16. The forest plot showed that the Meinert (2000) leukaemia results contributed the greatest weight to the results (40.09%). The pooled OR was 1.41, but the 95% Confidence Interval ranged from 0.88 to 2.25, suggesting no significant association between fathers' occupational exposure to

pesticides and the occurrence of haematopoietic cancers in children. Tests for heterogeneity indicated no significant heterogeneity between the studies.

17. A funnel plot was produced for the results of haematopoietic cancers in children and fathers' occupational exposure to pesticides to investigate potential publication bias (Figure 2).

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



18. The position of the data points on the funnel plot could suggest possible publication bias, since 4 of the 5 studies appeared on the right-hand side of the plot. However, given the small number of studies, it was difficult to determine whether there was an area on the plot where studies appeared to be 'missing'. Furthermore, the contours on the plot suggested that all the study results appeared in the area where p>10%, an area of non-significance with regard to possible publication bias. A further test, Egger's test, was performed on the data which indicated that there were no small-study (publication bias) effects in this data (P=0.668).

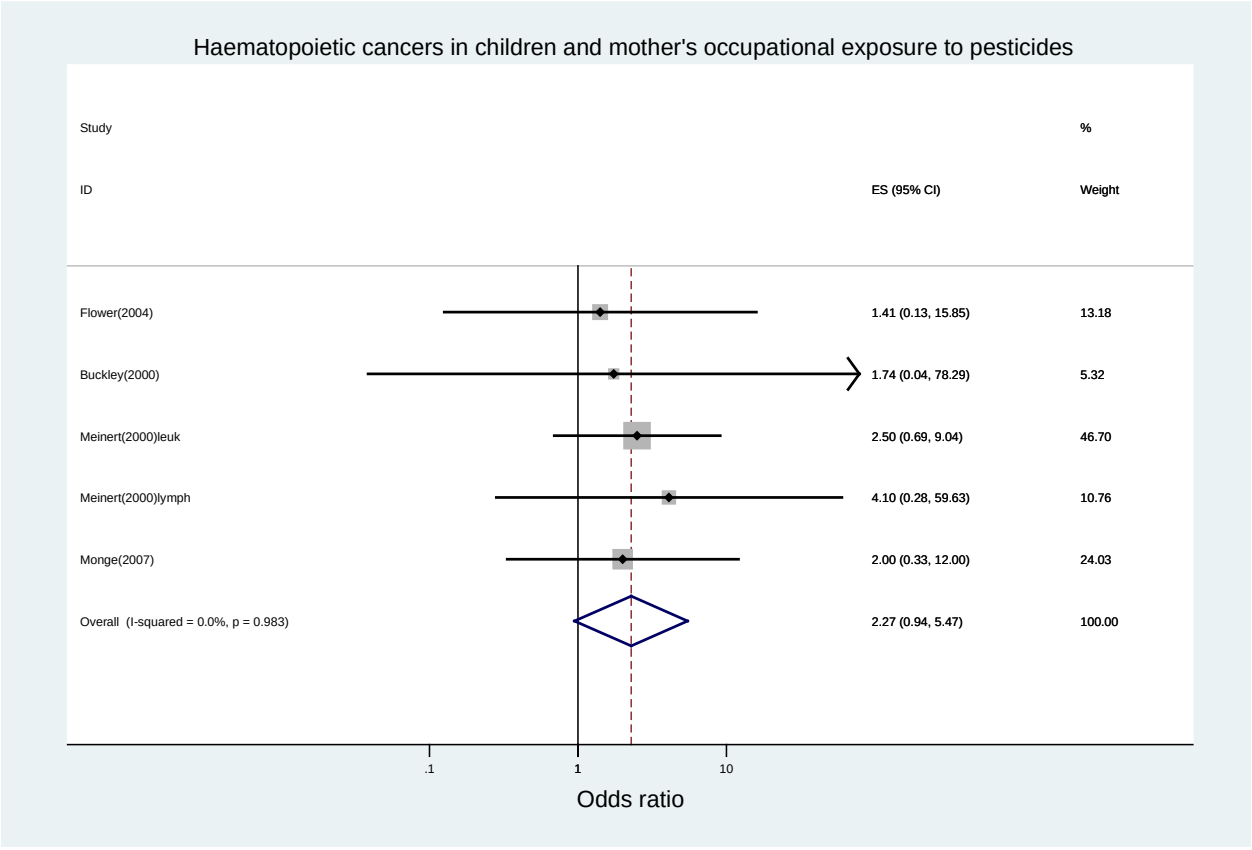
<u>Mothers' occupational exposure to pesticides and haematopoietic cancers in children</u>

19. Table 7 below shows the effect measures from the 5 studies reporting results on haematopoietic cancers in children and parents' occupational exposure to pesticides, this time focussing on mothers' occupational exposure. Figure 3 below shows a forest plot of the results, giving the pooled OR and its 95% Confidence Intervals.

Table 7. Haematopoietic cancers in children and mothers' occupational exposure to pesticides

Study	Disease	Exposure	Effect measure	Lower limit	Upper limit
Flower (2004)	childhood cancer, including haemato-poietic cancers and brain tumours	mother mixed and/or applied pesticides >19 days/year	OR 1.41	0.42	4.72
Buckley (2000)	NHL	parents occupationally exposed to pesticides	OR 1.74	0.82	3.69
Meinert (2000)	leukaemia	mother ever occupationally exposed to pesticides	OR 2.5	1.3	4.7
Meinert (2000)	lymphoma	mother ever occupationally exposed to pesticides	OR 4.1	1.1	16
Monge (2007)	leukaemia	mother ever occupationally exposed to pesticides	OR 2.0	0.8	4.8

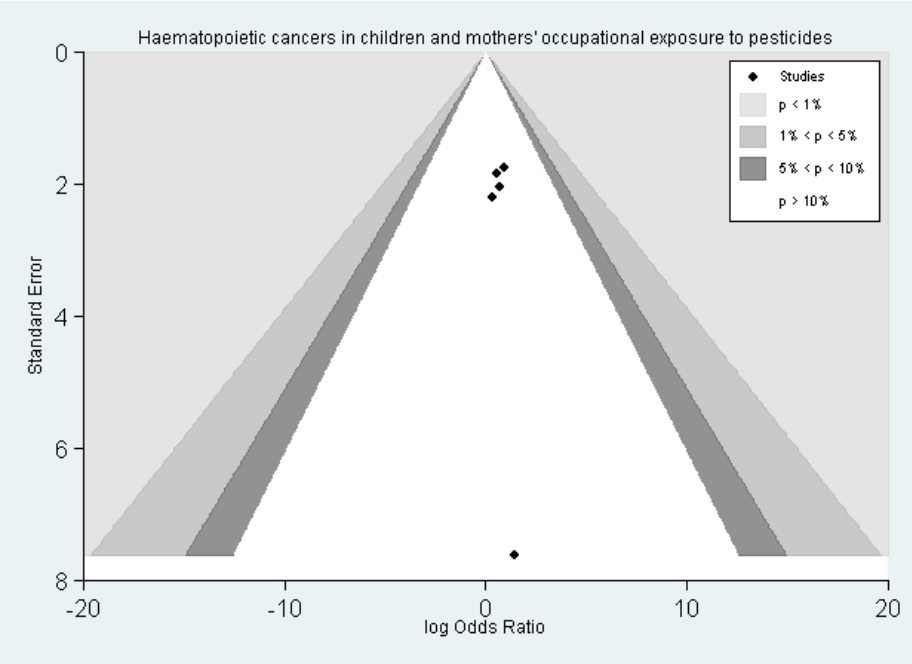
Figure 3. Haematopoietic cancers in children and mothers' occupational exposure to pesticides



20. Figure 3 shows that the greatest weight contributed to the results was again from the Meinert (2000) leukaemia results (46.7%). The pooled OR is 2.27, but the 95% Confidence Interval ranges from 0.94 to 5.47. This might support a positive association between mothers' occupational exposure to pesticides and the occurrence of haematopoietic cancers in children exposed

via para-occupational routes when considered in conjunction with the results of a recent publication by Van Maele-Fabry (2010) of occupational exposure to pesticides[26] (paragraphs 32 - 34 below and Annexes 3 - 4). Tests for heterogeneity indicated that there was no significant heterogeneity between the studies. A funnel plot was produced for the results for haematopoietic cancers in children and mothers' occupational exposure to pesticides to investigate potential publication bias (Figure 4).

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



21. The position of the data points on the funnel plot again might suggest possible publication bias, since all 5 studies appear on the right-hand side of the plot. However, the sample size is small. The contours on the plot suggested that all 5 study results appear in the area where p>10%, an area of non-significance with regard to possible publication bias. Egger's test was also performed on the data and indicated that there were no small-study (publication bias) effects in this data (P=0.702).

Child's Exposure to Professional Pest Control Agents

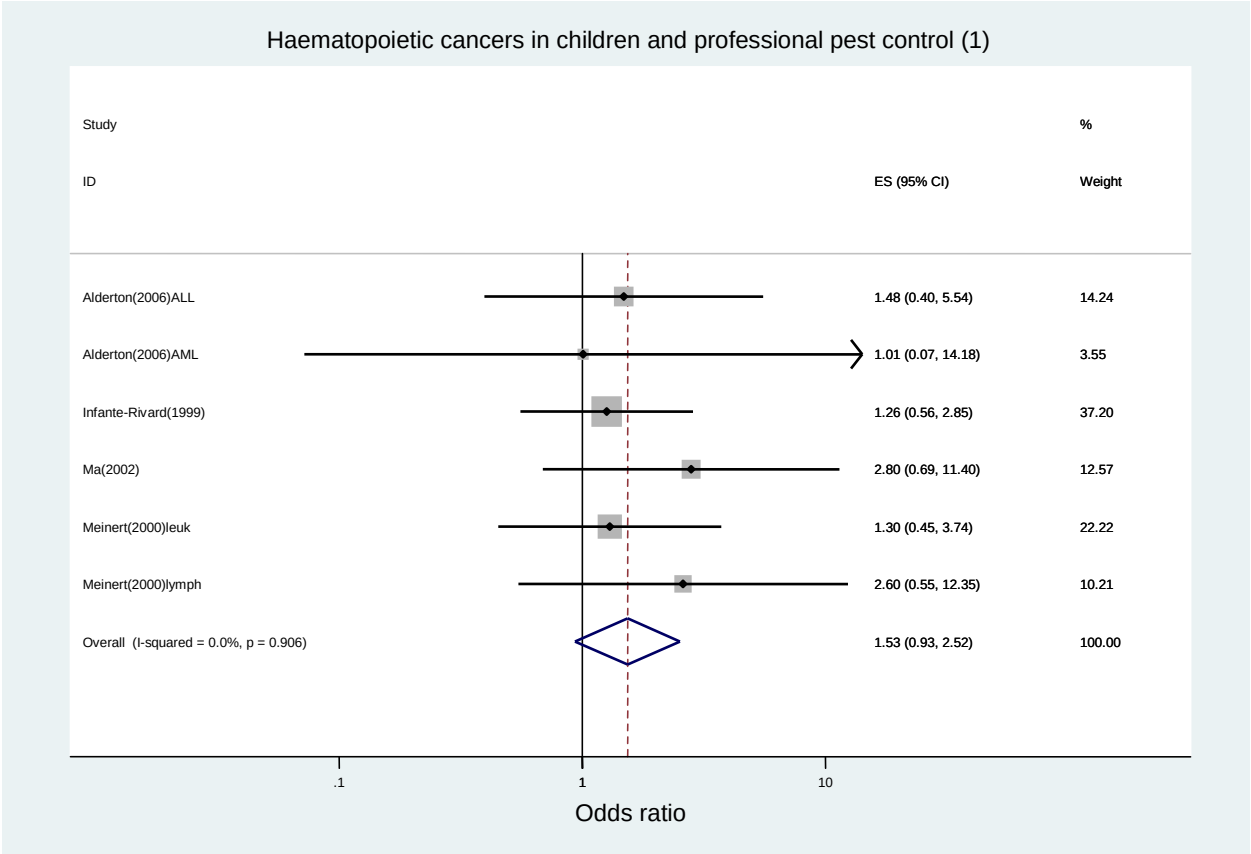
22. Table 4B (Annex 2) shows 7 studies reporting on the child's exposure to professional pest control agents.[7,8,11,12,14,16,19] Five of these concerned leukaemia, lymphoma or specific types of leukaemia or lymphoma, and again could be grouped as 'haematopoietic cancers'. The Cooney (2007) and Daniels (2001) studies reported on Wilms' tumour and neuroblastoma, and so could not be compared with the other studies. There were 7 ORs extracted from the studies relating to haematopoietic cancers which related to any exposure of the child to professional pest control agents (Table 8).

Table 8. Haematopoietic cancers in children and professional pest control

Study	Disease	Exposure	Effect measure	Lower limit	Upper limit
Alderton (2006)	ALL	any exposure to professional pest control	OR 1.48	0.77	2.88
Alderton (2006)	AML	any exposure to professional pest control	OR 1.01	0.27	3.79
Infante –Rivard (1999)	ALL	1-5 treatments of home	OR 1.26	0.84	1.9
Infante –Rivard (1999)	ALL	>5 treatments of home	OR 2.35	0.89	6.17
Ma (2002)	leukaemia	3 months before pregnancy to age 3 of child	OR 2.8	1.4	5.7
Meinert (2000)	leukaemia	professional pest control	OR 1.3	0.8	2.3
Meinert (2000)	lymphoma	professional pest control	OR 2.6	1.2	5.7

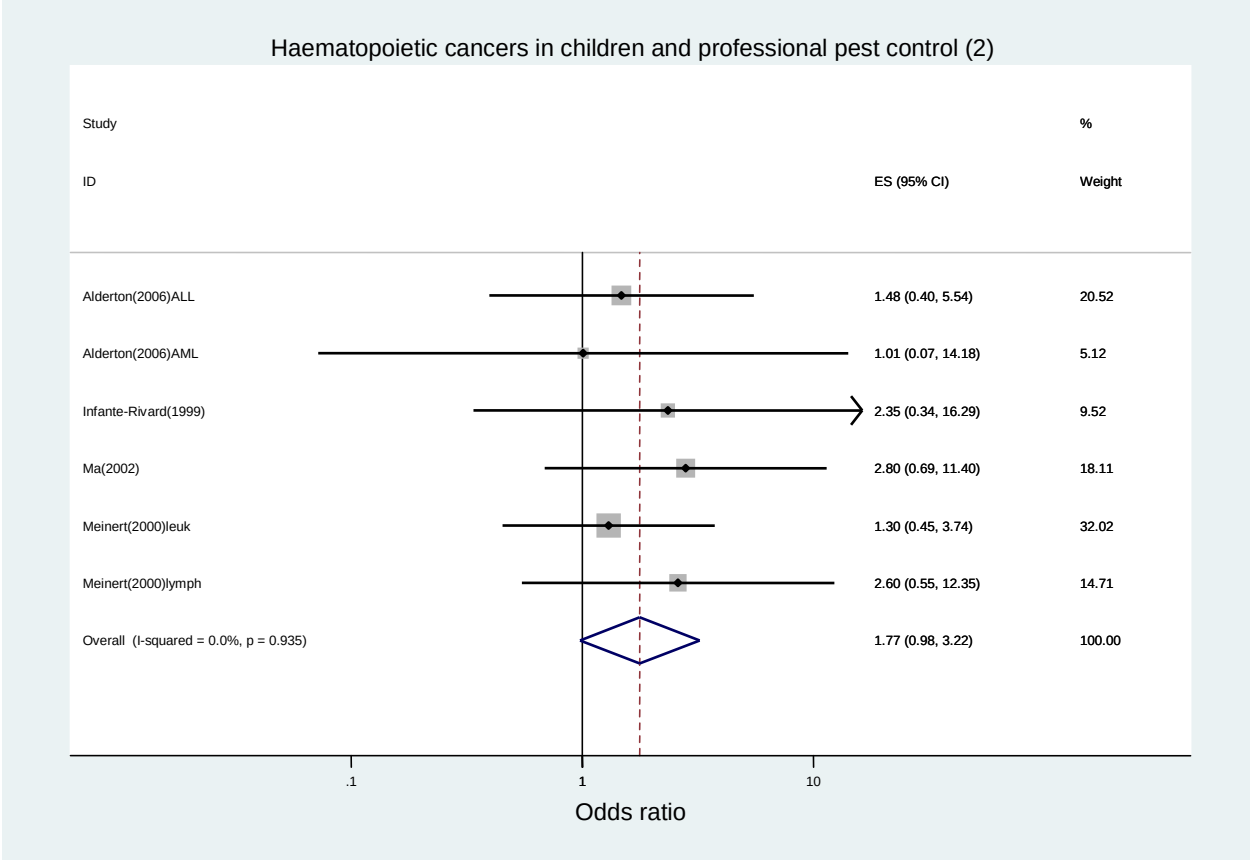
23. The Infante-Rivard (1999) paper had two exposure measures, the second, >5 home treatments, presumed to be of higher exposure than the first. A sensitivity analysis of these results was performed for exposure to professional pest control in two meta-analyses using ORs from the Alderton (2006), Ma (2002) and Meinert (2000) studies (5 effect measures in total) combined with either the measure for 1-5 treatments (Analysis 1) or >5 treatments (Analysis 2) of home from the Infante-Rivard study. Figures 5 and 6 show the forest plots for the analyses 1 and 2 respectively.

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



24. In Figure 5, the pooled OR was 1.53, but the 95% Confidence Interval, 0.93-2.52, suggested no significance. There was no evidence of significant heterogeneity in the results. The Infante-Rivard result for 1-5 treatments of the home contributed the largest weight in the results (37.2%).

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



26. In Figure 6, the pooled OR for professional pest control was 1.77, with a 95% Confidence Interval of 0.98-3.23. In this case, the Infante-Rivard data contributed only 9.52% weight to the result. Although the overall OR was higher than in the analysis for professional pest control shown in Figure 5, the Confidence Interval was not ≥1.0. There was no evidence of significant heterogeneity between the studies. The funnel plots for the two analyses, Figures 7 and 8 below, showed no evidence of publication bias.

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

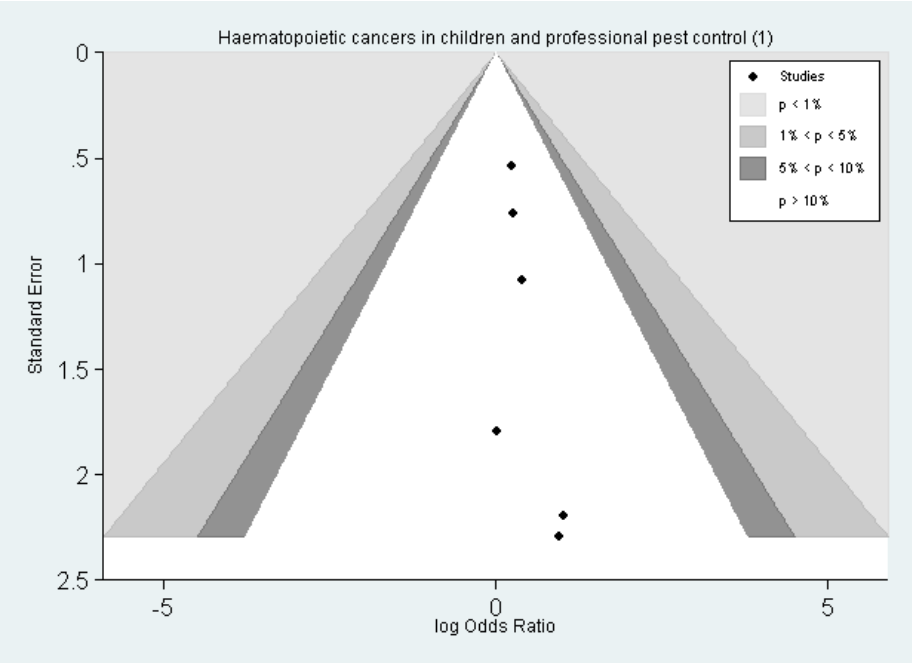
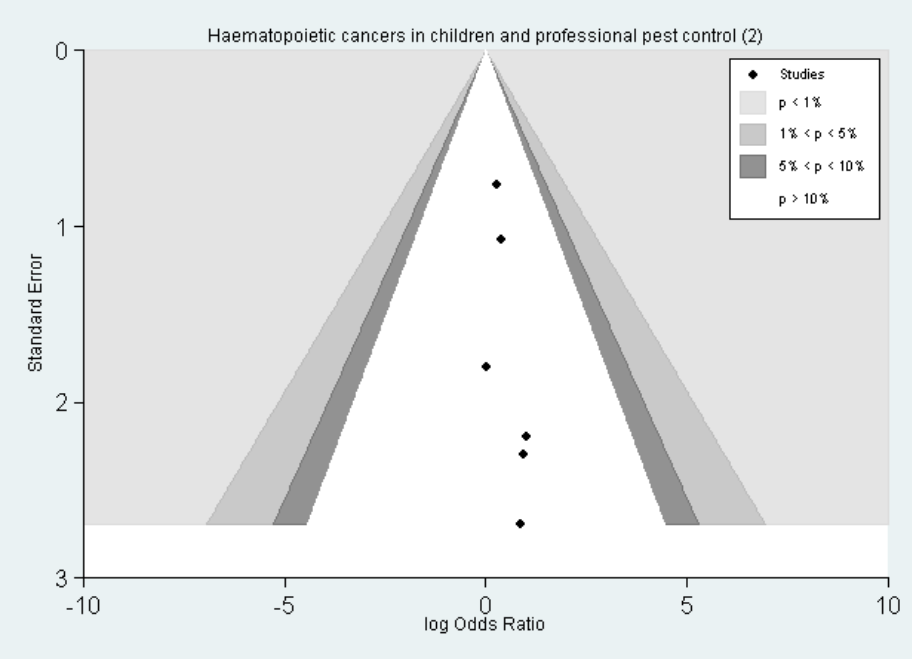


Figure 8. Haematopoietic cancers in children and professional pest control (Analysis 2)



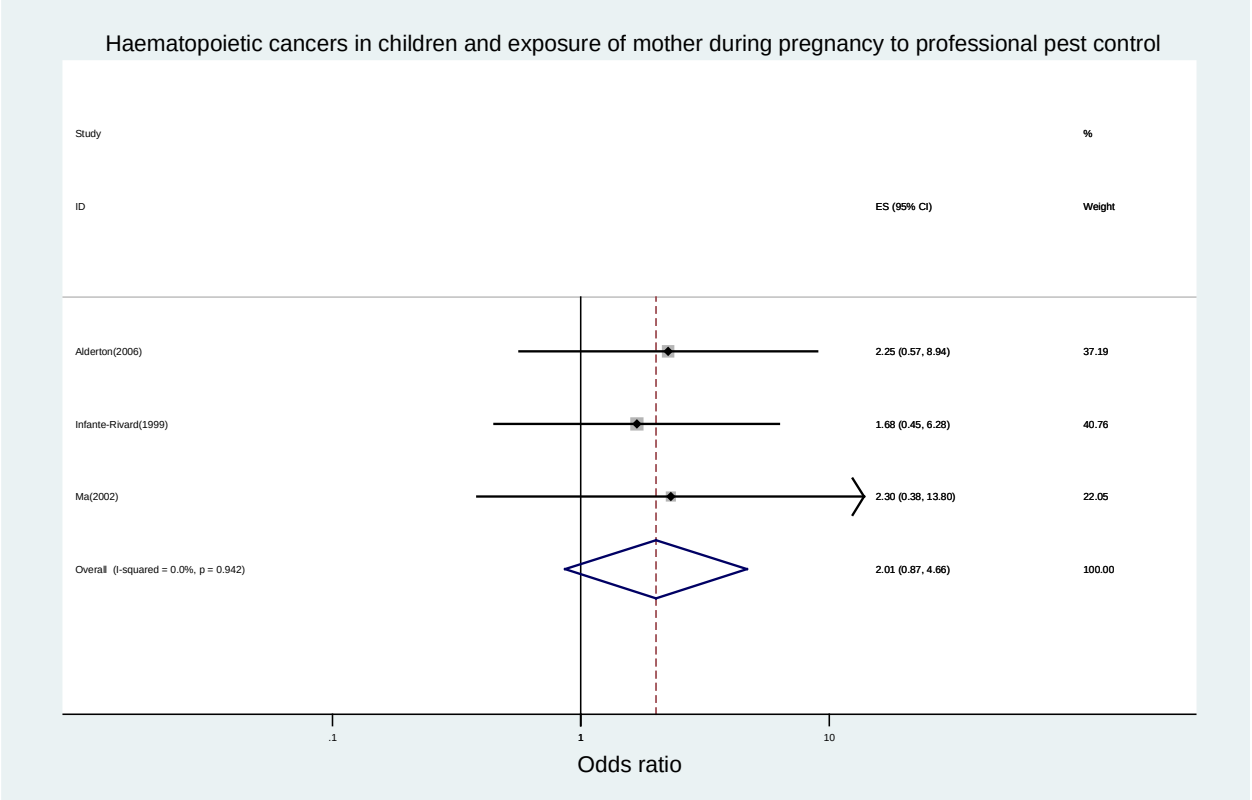
27. In both funnel plots, the points appeared only on the right-hand side of the plot in an area of insignificance for possible publication bias (p>10%). Egger's test for professional pest control (Analysis 1) showed no small-study effects in the results (P=0.148), and similarly for professional pest control (Analysis 2) (P=0.136).

28. Table 4C (Annex 2) shows that 4 of the 7 studies reporting on a child's exposure to professional pest control agents also provided effect measures for the risk of cancer in the child after mother's exposure during pregnancy.[7,8,14,16] All 4 studies referred to haematopoietic cancers. With omission of the Buckley study on NHL, the 3 remaining studies reported specifically on ALL as the disease outcome for the same exposure scenario. The effect measures used in the meta-analysis, forest and funnel plots are shown in Table 9 and Figures 9 - 10 respectively.

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

Study	Disease	Exposure	Effect measure	Lower limit	Upper limit
Alderton (2006)	ALL	any exposure to professional pest control	OR 2.25	1.13	4.49
Infante-Rivard (1999)	ALL	professional pest control	OR 1.68	0.87	3.25
Ma (2002)	ALL	professional pest control	OR 2.3	0.9	5.4

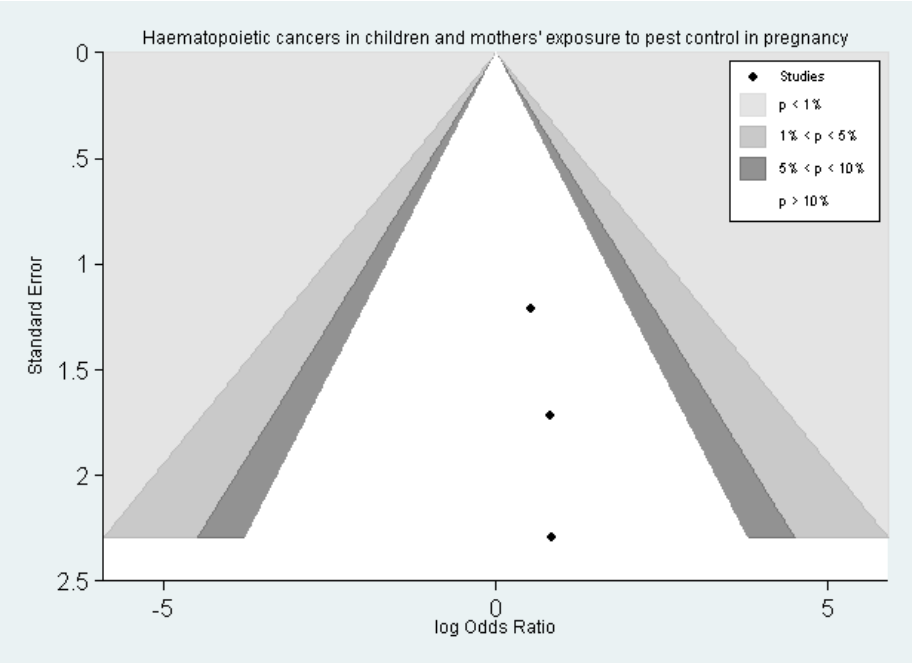
Figure 9. Haematopoietic cancers in children and exposure of mother during pregnancy to professional pest control



29. The pooled OR was 2.01, but the 95% Confidence Interval 0.87-4.66 suggested no significant association between mothers' exposure during pregnancy to professional pest control agents and ALL in children. However,

only 3 studies were available for analysis. Neither the funnel plot, Figure 10, (p>10%) nor the Egger's test (P=0.278) suggested publication bias.

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



Adult Exposure and Disease Outcomes

30. Table 4D (Annex 2) shows that there are 8 case-control studies which report on disease outcomes in adults and various para-occupational exposures.[9,10,13,15,17,21-23] The two Ruder studies, 2004 and 2006, related to the same group of subjects, with the 2006 study reporting on a greater number of individuals, so they could not be treated as separate studies.

31. At first glance it appeared that there were 4 studies with NHL as the disease outcome which could be compared. However, the exposures were different in each study and so the situations could not be compared. The Ruder and Carreon studies reported on glioma and on some similar exposure scenarios, but two studies (considering Ruder 2006 instead of 2004) were insufficient to make a meaningful comparison. The results from the Teitelbaum paper on breast cancer could not be compared to the other disease outcomes. Thus, the papers relating to adult exposure and health outcomes were too dissimilar in terms of exposure scenario and disease outcome to allow comparison.

RECENT PUBLICATIONS

32. A systematic review and meta-analysis of published studies on the association between childhood leukaemia and parental occupational exposure has recently been published (Annex 3).[26] The review concluded that there was no statistically significant association between childhood leukaemia and

parental occupation as farmers/agricultural workers. A positive association was reported for maternal exposure to pesticides for all studies combined (meta-rate ratio estimate (mRR): 1.62; 95% CI: 1.22-2.16) and for acute non-lymphocytic leukaemia. No association was seen with paternal exposure when combining all studies (mRR: 1.14; 95% CI: 0.76-1.69) but significant increased risks were seen for paternal exposure in some exposure windows. No statistically significant increased risk was seen among the cohort studies, although there were limitations in the studies analysed.

33. The Van Maele-Fabry review used a broader range of exposures and different selection criteria to the COC review. There were 3 major differences. Firstly, the COC review focused on para-occupational exposure of the child from birth, to either or both parents being exposed occupationally to pesticide use. The Van Maele-Fabry review considered 5 exposure windows including exposure before pregnancy/conception which was classified in the COC review as para-occupational exposure of the mother or father. In the COC review, i*n utero* exposure of the child was included in the scenario of exposure to professional pest control, where the mother was para-occupationally exposed and not a direct user of pesticides. Secondly, the COC review only included papers from 1996 onwards and, lastly, did not consider organochlorines within its scope.

34. Consequently, only 5 of the 25 papers analysed by Van Maele-Fabry (2010) overlapped the COC review: Buckley (2000), Meinert (1996), Meinert (2000), Monge (2007) and Flower (2004) (Annex 4). Only 5 of the meta-analyses by Van Maele-Fabry (2010) (A.4, A.13, A.15, B.9 and B.11) compared directly with the analyses performed in this COC review.

35. Wigle and colleagues have published a similar meta-analysis of occupational exposure to pesticides compared to Van Maele-Fabry (2010).[27] The same publications were analysed. Wigle (2009) reported evidence for an association between childhood leukaemia and prenatal maternal occupational exposure (OR: 2.09; 95 % CI: 1.56-3.62).

CONCLUSIONS ON QUALITY SCORING AND META-ANALYSES

36. Overall, a qualitative assessment of the cancer papers gave inconclusive results. 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.

37. It was not possible to perform a meaningful meta-analysis on the cohort studies. Only 2 cohorts of individuals were involved in the studies and there were no readily comparable exposure conditions where a risk of disease was also reported.

38. 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. The majority of papers related to cancer in children, and it was possible to group together small numbers of studies which report on

haematopoietic cancers and have a similar exposure scenario. However, the broad grouping of 'haematopoietic cancers' meant that the same disease was not being compared in the analyses. Although the pooled OR are >1 in all of the meta-analyses performed, the Confidence Intervals suggested no significant association between the exposure and the occurrence of cancer. The possible exception is childhood leukaemia following maternal para-occupational exposure to pesticides where two recent meta-analyses of maternal prenatal occupational exposure also support an association between pesticides and childhood leukaemia. There was no evidence of significant heterogeneity among the papers, or of publication bias. The papers reporting on adult exposure were too diverse, in terms of the disease type and exposure, to be readily compared.

DISCUSSION

39. Members are asked to consider this further analysis of the studies and answer the following questions.

QUESTIONS FOR THE COMMITTEE

1. Given the variety of limitations in the studies analysed, can any conclusions be drawn on the studies of para-occupational exposure to pesticides and cancer?
2. Can it be established that there is an association between para-occupational exposure, cancer and any exposure to specific pesticides?
3. Can conclusions from para-occupational exposure studies be extended to bystanders and residents?
4. Are there any specific chemicals or populations identified in this review that would warrant further investigation by ACP?

Secretariat

July 2010

ANNEXES

Annex 1 Quality of papers with cancer as health outcome and scoring criteria

Annex 2 Cancer cohort and case-control study comparisons

Annex 3 Review article – Childhood leukaemia and parental occupational exposure to pesticides: a systematic review and meta-analysis. Van Maele-Fabry et al. Cancer Causes Control. 10 Jun;21(6):787-809

Annex 4 Brief summaries of studies used as part of the Van Maele-Fabry review

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2. Committee on Carcinogenicity of Chemicals in Food Consumer Products and the Environment. Draft Minutes of meeting held 19 November 2009. CC/MIN/2009/3. November 2009. http://www.iacoc.org.uk/meetings/documents/091119draft.pdf

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Notes: CORPORATE NAME: Brain Cancer Collaborative Study Group

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