

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

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

BACKGROUND

1. In 2005, the Royal Commission for 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, and whose presence is incidental and unrelated to work involving pesticides, but whose position may put them at risk of potential exposure. Residents are 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.
3. In paragraph 6.21 of the report, the RCEP recommended '*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 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 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 regarding

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the value of a comprehensive systematic review and favoured smaller and more directed reviews.³

7. In discussions about the RCEP report, COT considered '*... that the review of epidemiological studies had been limited and that a more substantive review of the literature should be undertaken. Members noted that the RCEP did not come to any conclusion as to whether pesticide exposure was causing ill-health. It was suggested that one possible way forward would be to consider para-occupational exposure, e.g. spouses and children of farmers who might have exposures above that of bystanders. It was noted that the American Farm Survey of Occupation might be one useful source, but a literature review should identify other relevant research projects. It was noted that such data did not necessarily establish cause and effect.*'⁴

INTRODUCTION

Definition of Para-Occupational Exposure to Pesticides

8. Para-occupational exposure, for the purposes of this statement is regarded as exposure of close family members who live with an occupationally exposed worker, but who are not themselves occupationally exposed. This exposure scenario would apply in agricultural settings, where it may be considered intermediate between occupational exposure, that is, exposure of applicators and farmers or workers who mix/apply pesticides themselves and exposure of bystanders and residents.

9. 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 COT discussion paper provides a summary of the approach taken to undertake the review including search terms, references included and those excluded from the review.⁵ An overview of the review process is given below.

10. 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.

11. All the retrieved papers were screened individually against inclusion/exclusion criteria (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

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criteria were applied to the abstracts for the majority of the retrieved papers. Any duplicate papers were omitted.

12. 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 9 above.

13. 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.⁶⁻⁵⁹ 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. One further paper by Costello (2009) published after the cut-off date was considered by the COT although the information within this paper related predominantly to bystander exposure to pesticides.⁶⁰

14. 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 COT Members' information.

Overview of Literature Reviewed

15. The COT agreed there were several limitations to the studies reviewed. Thus, no UK epidemiology studies were identified and therefore there is a problem in equating the reported para-occupational exposures to UK circumstances. The COT agreed that exposure assessment and misclassification were important areas to consider when assessing epidemiological studies of para-occupational exposure to pesticides. In most studies reviewed, the data were not adequate to assess exposure to specific pesticides. The reported exposures were predominantly qualitative rather than quantitative, and it was unknown whether individuals were exposed to the named active ingredient only. It is uncertain how the assessments could be extrapolated to UK bystander/resident exposures. The COT noted that overall objective of the review was to identify good epidemiological evidence of para-occupational exposure and health outcomes that could be extrapolated to bystanders/residents. The COT agreed that funnel plots should be undertaken to assess publication bias for all health outcomes reviewed. The COT agreed that recall bias was likely to have been a factor in many of the case-control and cross-sectional studies reviewed that

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ascertained exposures through questionnaires, although in some instances the use of additional information from family and friends could help corroborate exposure data.

16. The COT considered advice from HSE CRD on the studies reviewed. The most useful epidemiological data were generated in the US where spraying practices are not as tightly controlled as in the UK. In particular, there are generally no formal training or certification requirements equivalent to those in the UK. In addition, it is believed that in the US there is an equivalent overarching requirement for employers or the self-employed to assess risks and control risks of all human exposures as there is under the Control of Substances Hazardous to Health Regulations (COSHH). There is the possibility, therefore, that para-occupational exposures might be higher in the US, although CRD do not have evidence for this. There is also probably a greater para-occupational involvement of children/spouses in the US, but again CRD are not aware of direct evidence, but this should be limited in the UK due to the requirements for certification, the former Poisonous Substances in Agriculture Regulations, which prohibited children working with certain pesticides, and COSHH. CRD also reported that some of the US states have considerably higher residential use (often professionally applied) in homes than in UK.

MAIN HEALTH OUTCOMES

CANCER

17. The information from 22 studies relating to para-occupational exposure to pesticides and cancer were forwarded to the COC for their consideration.

18. Twenty-two papers with information relevant to para-occupational exposure to pesticides and cancer were identified in the systematic literature review.^{7,8,14-17,21,24,27,33-35,38,40-44,49,50,56,57} Of these 22 papers, 4 related to cohort studies,^{7,24,27,38} 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.

19. 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 2). The score was awarded if two or more criteria in a score category applied to the paper. The lower the score, the more robust the paper.

20. Using the quality criteria, a score of one 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 Hartge (2005) and Infante-Rivard (1999).^{33,34} Both

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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.

21. 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.^{27,43} Alderton (2006), Ma (2002) and Meinert (2000) suggested possible positive associations between exposure to professional pest control and ALL, leukaemia or lymphoma in children.^{8,40,43} 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 three.

22. Meta-analyses were undertaken using a random effects model, potential publication bias was assessed using funnel plots, and by performing Egger's test.⁶¹ A meta-analysis of cohort studies was not undertaken, as data were only available for two cohorts of individuals.

Fathers' Occupational Exposure to Pesticides and Haematopoietic Cancers in Children

Case-Control Studies

23. The results of meta-analysis gave an Odds Ratio (OR) 1.41, 95% CI 0.88-2.25 for combined haematopoietic cancers. The study by Meinert (2000)⁴³ on childhood leukaemia contributed the greatest weight to the analysis (40.09%) (OR 1.60, 95% CI 0.77-3.35). There was no evidence for publication bias based on Egger's test.

Mothers' Occupational Exposure to Pesticides and Haematopoietic Cancers in Children

Case-Control Studies

24. 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. The study by Meinert (2000)⁴³ on childhood leukaemia contributed the greatest weight to the analysis (46.70%) (OR 2.50, 95% CI 0.69-9.04). There was no evidence for publication bias based on Egger's test.

Child's Exposure to Professional Pest Control Agents

Case-Control Studies

25. Analysis included a range of haematopoietic cancers (pooled OR 1.53, 95% CI 0.93-2.52 for 1-5 treatments, pooled OR 1.77, 95% CI 0.98-3.22 for >5 treatments). The study by Infante-Rivard (1999)³⁴ 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 (2000)⁴³ on childhood leukaemia contributed the greatest weight to the analysis (32.02%) for >5 treatments (OR 1.30, 95% CI 0.45-3.74). There was no evidence for publication bias based on Egger's test.

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

Case-Control Studies

26. All studies considered ALL (pooled OR 2.01, 95% CI 0.87-4.66). The study by Infante-Rivard (1999)³⁴ on ALL contributed the greatest weight to the analysis (40.76%) (OR 1.68, 95% CI 0.45-6.28). There was no evidence for publication bias based on Egger's test.

Adult Exposure and Disease Outcome

27. There were 8 case-control studies which reported on cancer outcomes in adults and various para-occupational exposures.^{15,16,33,35,41,49,50,56} However, the studies were too dissimilar in terms of exposure scenario and disease outcome to allow comparison.

Conclusion for Cancer

28. There is limited evidence for an association between the broad grouping of childhood 'haematopoietic cancers' and mothers' para-occupational exposure to pesticides.

NEUROLOGICAL AND MENTAL HEALTH EFFECTS

29. Studies investigating the potential association of para-occupational exposure to pesticides on the occurrence of Parkinson's Disease (PD)^{11,30} and effects on neurobehavioural development and cognitive functioning in children^{25,31,32,39,46,48} were identified by the literature search strategy. A case-series report on neurophysiological and neuropsychological effects in adults with para-occupational exposure to pesticides was retrieved.³⁶

Parkinson's Disease

30. One cohort¹¹ and one case-control study³⁰ of para-occupational exposure to pesticides were retrieved for review.

Cohort Study

31. Ascherio et al, 2006¹¹ published a US cohort study, reported a positive association between para-occupational exposure to unspecified pesticides and the risk of developing PD (Rate Ratio (RR) 1.7, 95% CI 1.2-2.5 for the characteristic 'occupation: not a farmer, exposed to pesticide'). This prospective study was conducted over a long period of time (1992-2001) and included a large number of individuals (143,325 who returned a follow-up survey in 2001), although the number of people with PD who were exposed to pesticides non-occupationally was small (n=30 in the above group). Information on pesticide exposure (self-reported) was only collected in 1992.

Case-Control Study

32. A family-based case-control study found a significant association between direct pesticide application and PD (for those who reported ever using non-specified pesticides, OR 1.61, 95% CI 1.13-2.29), but not with para-occupational exposure assessed indirectly through residence on a farm (for residence on a farm >26 years, OR 1.25, 95% CI 0.80-1.96).³⁰

Conclusion for Parkinson's Disease

33. The COT agreed that no definite conclusions could be reached from the available information on para-occupational exposure to pesticides in general or specific pesticide active ingredients and PD. The COT was aware that the ACP commented on the review of pesticides and PD by the Institute for Environment and Health (IEH) (2004).⁶² The ACP considered that '*...further epidemiology could be useful where exposure to specific pesticides could be ascertained with reasonable confidence (e.g. cohort studies of pesticide production workers or long-term prospective studies of pesticides users). The review indicated a correlation between recalled pesticide exposure and Parkinson's disease, but did not point to a particular toxic mechanism or a hazard from a specific compound or group of compounds.*' The COT considered that the paper published by Costello et al 2009⁶⁰ on PD following residential exposure reported some novel findings. Members were aware that maneb and paraquat induced CNS pathology in laboratory animals only when excessively high doses were injected. The COT agreed that further consideration of this paper should be requested from the ACP Medical and Toxicology Panel.

Neurobehavioural Development and Cognitive Functioning in Children

34. One cohort²⁵ and five cross-sectional studies of para-occupational exposure to pesticides were retrieved.^{31,32,39,46,48}

Cohort Study

35. Eskenazi et al, 2007²⁵ undertook a US based study of children born to pregnant women between October 1999 and 2000 using Bayley Scales of Infant Development, Mental Development and Psychomotor Development Indices. Exposure estimation incorporated urinary biomarker measurements for exposure to organophosphate pesticides (dialkyl phosphates which measure exposure 24-48h prior to assessment of cognitive performance) during pregnancy and at 6, 12, 24 months in children. An association was seen between metabolite levels during pregnancy and Mental Development Index (MDI) at 24 months of age: for every 10-fold increase in pregnancy of dialkyl phosphate metabolites, a 3.5 point decrease was seen in the 24-month olds' MDI, 95% CI -6.6 to -0.5, $p=0.02$. With regard to the Child Behaviour Checklist, 14.4% children scored in the pervasive developmental disorder scale, as compared to $\leq 3\%$ in the national reference sample (binomial test $p<0.0001$). Children with higher prenatal and postnatal total dialkyl phosphate metabolites were at higher risk of pervasive developmental disorder, with approximately 2-fold increase in risk for each 10-fold increase in metabolites: prenatal dialkyl phosphate metabolites, OR 2.3, 95% CI 1.0-5.2, $p=0.05$; 24-month dialkyl phosphate metabolite levels, OR 1.7, 95% CI 1.0-2.9, $p=0.04$. No associations were seen with metabolites specific to malathion or chlorpyrifos. The Committee noted that about half of the mothers exposed during pregnancy were occupationally rather than para-occupationally exposed (43% worked in agriculture themselves) and that spot urine samples which were taken for dialkyl phosphate metabolite analyses reflected exposure during the previous 48hr and may not represent exposure over time. The authors also stated that many analyses were conducted and that some statistical results may have been chance findings due to the multiple comparisons made.

Cross Sectional Studies

36. Two cross sectional studies published in 2007 of neurobehavioural development in children from a flower-growing region in Ecuador which investigated neurobehavioral development in children aged 24-61 months³¹ and children aged 3-61 months.³²

37. Neurobehavioural development was assessed in children using the Ages and Stages Questionnaire (ASQ). The ASQ has been validated in the U.S. and may be less culturally appropriate for a rural Andean population. Exposure was assessed using mother's report of self and spouse's exposure, and residence distance from the flower plantation. Three subgroups were identified: two high exposure communities (A and B) and a low exposure community (C). Conditions of pesticide use in Ecuador may be different to the UK, so the relevance of any findings is difficult to assess. There was evidence for a high prevalence of anaemia and stunting in the study groups which was included in the regression analysis. In the study of children aged 24-61 months, mothers' current employment in the flower industry was associated with better scores for all five ASQ domains (communication, gross

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motor skills, fine motor skills, problem-solving and personal social skills). Mothers' current employment in the flower industry for a sub-group of children tested was associated with lower visual motor skills (% decrease -2.2, 95% CI -11.4 to 4.4), but the effect size, Cohen's d , was not reported. The exposure considered was to unspecified pesticides.³²

38. In the cross-sectional study of children aged 3-61 months from Ecuador, children aged 3-23 months from the high-exposure communities scored significantly lower on gross motor skills, on average 8.8 points lower, $p=0.002$, Cohen's $d=0.4$ ($d=2$ is small effect size, $d=5$ is medium). Furthermore, they scored 5.0 points lower on fine motor skills, but $p=0.06$ and $d=0.2$, and 5.8 points lower in socio-individual skills, with $p=0.02$, and $d=0.3$. Children aged 3-23 months residing in the high-exposure communities and also suffering from chronic malnutrition (stunting) scored 17 points lower on gross motor skills than children from the same community not presenting with stunting, and lower than all children residing in the low-exposure community C ($p<0.001$). Children aged 24-61 months residing in the high-exposure communities A and B scored 3.8 points lower on gross motor skills compared with children of the same age living in community C, but $p=0.06$ and $d=0.2$. The exposure considered was to unspecified pesticides.³³

39. A cross sectional study of neurobehavioural performance was undertaken in 78 Latino children from agricultural regions of Oregon and North Carolina.⁴⁶ The Behavioural Assessment and Research System (BARS) was used to assess neurobehavioural performance. Exposure was based on residence in agricultural community (with at least one parent working in agriculture) for exposed or residence in non-agricultural community (with neither parent working in agriculture for previous year) for non-exposed. Eleven out of thirteen measures showed no deficit in agricultural (AG) children compared to non-AG children. AG children performed poorer on measures of response speed (Finger Tapping) and latency (Match-to-Sample), when controlling for gender and location. Male AG children from Oregon performed significantly worse than male non-AG children on right hand Finger Tapping ($t(60)=-2.08$, one-sided p -value 0.02). Male AG children from North Carolina had significantly longer latencies on the Match-to-Sample test than male non-AG children ($t(51)=2.47$, one-sided p -value 0.01). The small sample size limited the power of the study to detect effects in the majority of tests applied in this study including those where statistically significant changes were reported. The results suggested modest deficits in performance.

40. The remaining two cross-sectional studies retrieved reported investigations of cognitive function in children (school age) exposed para-occupationally to organophosphate pesticides³⁹ and investigations of neurobehavioural performance in children (aged <6 years) with exposure to methyl parathion (MP).⁴⁸

41. Lizardi et al³⁹ incorporated urinary biomarker measurements for exposure to organophosphate pesticides (dialkyl phosphates which measure exposure 24-48h prior to assessment of cognitive performance). Forty-eight children participated (age range not provided) using the Wechsler Intelligence

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Scale, the Children's memory Scale and the Wisconsin Card Sorting Test (WCST). All samples contained measurable levels of organophosphate metabolites and the results suggested detrimental effects only on the WCST cognitive skills measures of speed of attention, sequencing, mental flexibility, visual search, motor functioning, concept formation and conceptual flexibility. A significant positive correlation was found between urinary organophosphate metabolite concentration and the number of errors made on the test ($r=0.31$, $p=0.03$), and on four other measures. However, there were no significant positive correlations between urinary levels of organophosphate metabolites and four other tests used. Furthermore, when 2 samples with particularly high concentrations were removed from the analysis, no significant correlations were seen. Biomarker levels also varied between different analyses, specifically between the screening stage of the study and the study itself. The specific cognitive measures in this study have been used predominantly with adults, and may not be the most appropriate to detect differences in cognitive functioning of children, with primary language Spanish.

42. Ruckert et al 2004⁴⁸ identified children whose homes had been sprayed with MP. Urine samples from 'exposed' children where homes had been sprayed with MP by applicators and from 'un-exposed' controls were tested for creatinine-adjusted p-nitrophenol (a metabolite of MP), and environmental wipe samples for MP were taken from these residences. A total of 132 'exposed' children were tested for neurobehavioural functioning in year 1 of the study (summer 1999), and 107 of those children were retested in year 2 (summer 2000) 147 'unexposed' children from the same communities were tested for neurobehavioural functioning in year 1 of the study (summer 1999), and 119 of those children were retested in year 2 (summer 2000). The Paediatric Environmental Neurobehavioural Test Battery (PENTB) was used to assess neurobehavioural functioning of the children.

43. In year 1, a similar number of exposed and unexposed children were classified as 'below expected' in the PENTB and more exposed children than unexposed were classified as 'expected' in the PENTB. In year 2, each child's overall outcome group was compared with their overall outcome group in year 1, and it was found that 33% of the exposed children who were classified as below expected in year 1 did not improve their classification score from year 1 to year 2, compared with 60% of unexposed children. Additionally, 61% of exposed children who were classified as equivocal in year 1 did not improve their classification from year 1 to year 2, compared with 75% of unexposed children. These results suggest that exposure to MP was not associated with persistent deficits in year 2 among children who performed lower than expected in year 1. For performance-based tests, no effects were seen for exposed children in tests measuring general intelligence, integration of visual and motor skills, and multistep processing. For performance-based tests where exposed children performed worse than unexposed children in year 1, only the Verbal Cancellation test, Non-ordered form, for Mississippi, gave a statistically significant result: OR 10.29, 90% CI 2.23-47.41; for the 5 other performance-based tests where exposed children performed worse, the confidence intervals of the ORs all include 1.0. For informant-based tests (responses given by parent/guardian) relating to the

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child's behaviour/mood where exposed children performed worse than unexposed, all 90% confidence intervals of the ORs included 1.0.⁴⁸

Conclusion for Neurobehavioural Development and Cognitive Functioning in Children

44. The COT agreed that no definite conclusions could be reached from the available information on para-occupational exposure to pesticides in general or specific pesticide active ingredients and neurobehavioural development and cognitive functioning in children.

Neurophysiological and Neuropsychological Effects in Adults

Case Series

45. A case series analysis of data from 22 patients (19 with confirmed para-occupational exposure to pesticides following spraying of residences or offices) from 8 US states out of 384 patients who had undergone evaluation for possible neurobehavioural effects (using a neurophysiological and neuropsychological test battery) of chemicals in a neurotoxicology clinic at the University of Southern California School of Medicine from 1991-1997.³⁶ The authors reported control data for 364 individuals. There was a significant difference in simple and choice reaction times between exposed and unexposed subjects, $p=0.0001$. In the exposed group, there was an impairment in body balance ($p=0.0001$ for sway-balance measurements), grip strength and colour discrimination ($p=0.0001$ for scores in both domains). Also, there was an impairment in cognitive function (digit symbol test, $p=0.0001$) and memory (immediate story recall, $p=0.0002$ for difference in scores; long-term memory picture completion, $p=0.011$ for difference in scores) in exposed compared to unexposed subjects. There was a significant difference in the Profile of Mood States (POMS) scores: the mean POMS score was elevated in exposed subjects, $p=0.0001$, and the depression mean score was also elevated, $p=0.0002$. Abnormally high frequencies of 33 individual symptoms were observed in the exposed group of subjects. Examples of these symptoms are chest tightness, palpitations, burning in chest, shortness of breath ($p=0.0001$ for symptom frequency of all 4 symptoms in exposed compared to unexposed); also extreme fatigue, insomnia, loss of concentration, mood swings ($p=0.0001$ for symptom frequency of all 4 symptoms in exposed compared to unexposed). The COT was aware that there were long intervals (ca 9-108 months) between exposure and neurophysiological and/or neuropsychological investigation of patients in this study and that details of potential exposure could only be identified for six of the cases investigated.³⁶

Conclusion for Neurophysiological and/or Neuropsychological Effects in Adults.

46. The COT agreed that no definite conclusions could be reached from the available information on para-occupational exposure to pesticides in

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general or specific pesticide active ingredients and neurophysiological and/or neuropsychological in adults.

REPRODUCTION

47. The literature search process identified one case-control study of para-occupational exposure to pesticides had reported results of investigations on female fertility,²⁹ and three studies (two cohort^{9,10} and one cross sectional⁴⁵) of para-occupational exposure to pesticides reporting investigations of spontaneous abortion. One cohort study had reported results of investigations of effects on conception¹⁹ and one cross sectional study reported results regarding para-occupational exposure to pesticides and pregnancy loss.²⁸

Female Fertility

Cross Sectional Study

48. Greenlee et al 2003²⁹ undertook an exploratory cross sectional study of 322 women coming for treatment at a medical clinic in Wisconsin, recruited between June 1997-February 2001, with infertility defined as '12 months of unprotected intercourse without conceiving a pregnancy ending in live birth'. A similar number females (aged 18-35 years of age) seeking prenatal care during their first trimester, attending the same clinic, and who conceived in less than 12 months of trying were used as a control group. Information on para-occupational exposure to pesticides and classes of pesticide (e.g. herbicides) and location of residence prior to trying to conceive (e.g. 'ever lived on farm aged >19yr') were obtained via telephone interview and medical history was obtained from records. There was no evidence for an association between para-occupational exposure and reduced female fertility in this study but the methods, particularly for estimation of exposure, were very limited.

Conclusion for Female Fertility

49. The COT concluded that no definite conclusions could be reached from the available information on para-occupational exposure to pesticides in general or specific pesticide active ingredients and effects on female fertility.

Conception

50. Curtis et al 1999 investigated time to pregnancy (the number of months required for a couple to conceive) in a cohort study of 1048 farm couples from the Ontario Farm Family Health Study.¹⁹ Self-reported exposure by farm operator, husband and wife to pesticides divided into 4 pesticide classes (herbicides, insecticides, fungicides, and miscellaneous) and 9 active ingredients was documented. In the para-occupational exposure (of the woman) category 'pesticide used on the farm, but only the man engaged in

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pesticide activities', 4 pesticide types were associated with a 12-15% decrease in fecundability: 2,4- dichlorophenoxybutyric acid (2,4-DB), conditional fecundability ratio, CFR= 0.85, 95% CI 0.63-1.13; cyanazine, CFR=0.86, 95% CI 0.58-1.26; fungicides, CFR=0.88, 95% CI 0.72-1.09, and captan, CFR=0.87, 95% CI 0.65-1.10. However, 3 other pesticide categories, herbicides, dicamba and glyphosate, were associated with a 17-30% increase in fecundability. In the para-occupational exposure category, 'pesticide used on the farm, but neither the man nor the woman participated in pesticide activities', pesticide categories were associated with at least a 10% decrease in fecundability: dicamba, CFR 0.82, 95% CI 0.47-1.40; 2,4-D, CFR 0.75, 95% CI 0.49-1.14, and thiocarbamate, CFR 0.76, 95% CI 0.42-1.40. Again, some pesticide categories showed an increase in fecundability (8 of the 18 categories). Although the overall cohort size was large (1,048 farm couples), there is no apparent biological plausibility for the pattern of increased and decreased fecundity reported in this study and no evidence of direct exposure to support the findings.

Conclusion for Conception

51. The COT agreed that no definite conclusions could be reached from the available information on para-occupational exposure to pesticides in general or specific pesticide active ingredients and effects on conception fertility.

Spontaneous Abortion

Cohort Studies

52. Arbuckle et al 1999⁹ investigated pesticide exposure and spontaneous abortion using in spouses of farm operators in the Ontario Farm Family Health Study (n=2,110 women, 3,936 pregnancies for analysis, 395 spontaneous abortions, <20 weeks' gestation using a self-administered questionnaire for approximately two thirds of respondents, the remainder by telephone). Exposure to any phenoxy herbicide and to 3 specific active ingredients: 2,4-D, 4-(2,4-dichloro-phenoxy) butyric acid, and (4-chloro-2-methylphenoxy) acetic acid (MCPA) was estimated. For spontaneous abortion at less than 20 weeks gestation associated with preconception exposure to any phenoxy herbicide crude OR 1.3, 95% CI 0.7-2.3; for earlier abortions <12 weeks, adjusted OR=2.5, 95% CI 1.0-6.4. For preconception exposure when the male pesticide applicator did not use protective equipment or clothing for exposure to phenoxy herbicides, spontaneous abortion for all gestational ages <20 weeks, crude OR 1.5, 95% CI 0.6-3.7; for spontaneous abortions <12 weeks, crude OR 5.0, 95% CI 0.7-36.2; 3). For post-conception exposure when male pesticide applicator did not use protective equipment, exposure to any phenoxy herbicides, spontaneous abortion <12 weeks, crude OR 2.8, 95% CI 0.4-21.0. For exposure to the active ingredient 4-chloro-2-methylphenoxy acetic acid (MCPA), for exposure of >1 month in the preconception window, OR 5.4 for spontaneous abortion <12 weeks, 95% CI 1.7-17.3. These data suggest an effect of occupational exposure of the husband, rather than para-

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occupational exposure of the wife. The study also suffered from the problem of multiple comparisons, with a number of risk factors being analysed at the same time. Furthermore, 20% of wives reported handling pesticides on the farm, and were not treated separately in the analysis, so the exposure was not purely para-occupational.

53. Arbuckle et al 2001¹⁰ undertook a further analysis of early (<12 weeks) and late (12-19 weeks) spontaneous abortions in the same Ontario Farm Family Health cohort. Assessment of exposure to pesticides classes (e.g. herbicides, insecticides etc) and exposure to nine pesticide active ingredients was reported. An increased risk for all spontaneous abortions <20 weeks is reported for preconception exposure to glyphosate, OR 1.4, 95% CI 1.0-2.1; triazines, OR 1.3, 95% CI 1.0-1.8; thiocarbamates, OR 1.5, 95% CI 1.0-2.1; herbicides, OR 1.3, 95% CI 1.0-1.6; fungicides, OR 1.4, 95% CI 1.1-1.8, and miscellaneous pesticides, OR 1.5, 95% CI 1.1-2.0. For phenoxy acetic acid, there was an increased risk of early abortions <12 weeks, OR 1.5, 95% CI 1.1-2.1. For pre-conception exposure to active ingredients, glyphosate, atrazine, carbaryl and 2,4-dichlorophenoxyacetic acid (2,4-D) were associated with a 20%-40% relative increase in risk. For post-conception exposure, higher ORs were observed only in late abortions. For exposure to: 2,4-D, OR 1.6, 95% CI 0.9-2.7; dicamba, OR 1.6, 95% CI 0.8-3.2; glyphosate, OR 1.4, 95% CI 0.8-2.5, and phenoxy acetic acid herbicides, OR 1.3, 95% CI 0.8-2.0. For the Classification and Regression Tree (CART) analysis of interaction among risk factors, interaction effects were found between maternal age (pregnant women age 35 or older) and preconception exposure to triazines, OR 2.7, 95% CI 1.1-6.9, phenoxy acetic acid herbicides, OR 2.3, but 95% CI does not suggest significance, 0.6-8.6, and thiocarbamates, OR 7.5, 95% CI 1.1-51.5. For post-conception exposure to glyphosate and to thiocarbamates, the CIs include 1.0:- glyphosate, OR 3.2, 95% CI 0.8-23.0, thiocarbamates, OR 2.4, 95% CI 0.5-10.5. However, maternal age >35 years was a big risk factor for spontaneous abortion: OR 2.6, 95% CI 1.7-3.9 reported an association between the use of herbicides (OR 1.3, 95% CI 1.0-1.6) and fungicides (OR 1.4, 95% CI 1.1-1.8) and spontaneous abortions <20 weeks, although the confidence intervals suggested only marginal significance of the results.⁹

Cross Sectional Study

54. Petrelli et al 2003⁴⁵ investigated para-occupational exposure of spouses of greenhouse workers (to a list of ten chemicals which included the pesticides benomyl, carbendazim, carbaryl, atrazine and DDT). Spontaneous abortion in first pregnancy of spouses of 184 greenhouse workers in southern Italy aged 20-55 years of whom 48 were considered exposed to pesticides via a para-occupational route. Out of 48 workers considered exposed to pesticides at first pregnancy of their spouses, there were 7 spontaneous abortions in spouses (14.6%); among the spouses of 136 workers considered non-exposed, there were 6 spontaneous abortions (4.4%); the higher percentage of abortions among the exposed group was found to be statistically significant using the X^2 test, $p=0.02$. An OR was reported for spontaneous abortion among the first pregnancies of the greenhouse workers'

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spouses: unadjusted OR 3.7, 95% CI 1.2-11.7, adjusted OR 11.8, 95% CI 2.3-59.6 (adjusted for age, smoking habit, education of both partners, spouse's type of work, and time between the pregnancy outcome and the interview). Among a group of 30 workers reporting exposure to benomyl and 6 to carbendazim, there were 5 spontaneous abortions (13.9%); among 31 workers exposed to carbaryl, there were 4 spontaneous abortions (12.9%); only carbendazim is approved in UK. Odds ratios were not reported for exposure to single products, nor was there any detailed analysis of the timing of exposure, such as exposure during pre- and post-conception windows; the authors stated that the size of the study (sample size=48) did not allow more detailed analysis.

Conclusion for Spontaneous Abortion

55. The COT agreed that the reports based on the Ontario Farm Family Health Study which documented evidence for an association between para-occupational exposure to a number of pesticide active ingredients and spontaneous abortion had been well conducted. However, the numbers of individuals with spontaneous abortion and preconception exposure was small. Members considered that the potential impact of recall bias limited the value of these studies.

56. The COT concluded that no definite conclusions could be reached from the available information on para-occupational exposure to pesticides in general or specific pesticide active ingredients and effects on spontaneous abortion.

Pregnancy Loss

57. Garry et al 2002²⁸ investigated reproductive outcomes in the women (pregnancy losses among spouses of pesticide applicators) of the Red River Valley of the north Iowa, U.S. Pregnancies fathered by 522 applicators licensed to apply pesticides in the Red River Valley area of Minnesota in the period 1991-1996; maternal use and exposure to pesticides examined in a reproductive health survey of 379 spouses who had been pregnant or had children. Self-reported exposure by applicators and spouses to 4 pesticide classes (herbicide, insecticide, fungicide, fumigant) and to 5 specific fungicides and 6 specific herbicides was obtained. A phone interview for general health and pesticide use, and a written pesticide use and reproductive health assessment questionnaire were given to both applicators and spouses.

58. Of 522 applicator families studied for pregnancy loss, spouses of applicators who used herbicides / insecticides / fungicides had more pregnancy losses than any other pesticide application group (herbicide only; herbicide/insecticide; herbicide/ insecticide/fumigant): OR 1.64, 95% CI 1.01-2.67. For maternal exposure to pesticides, 126 out of 379 women carried food to pesticide-treated fields within 48 hours of application, and 315 women washed pesticide-treated clothing. It was reported that these para-occupational exposures did not significantly affect frequency of fetal loss (data

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not shown). Only 36 out of these 379 women applied or mixed pesticides themselves, so most of the exposure was para-occupational. Number of fetal losses per pregnancy is significantly elevated only in those who did mix or apply pesticides (15% vs. 8.9%, but data not shown). The frequency of all spring first-trimester miscarriages regardless of pesticide use was significantly elevated in spring, compared to all other seasons, $p=0.034$, Fisher's exact test. The highest frequency of first-trimester miscarriages occurring in the spring was observed among spouses of applicators who apply herbicides but not fungicides, $p=0.007$, Fisher's exact test. The risk of spring miscarriage was significantly higher among spouses of applicators who used herbicide products containing sulfonyleureas, OR 2.11, 95% CI 1.09-4.09, compared to all other pesticides used.

59. The spouses of applicators who used ethylene bisdithiocarbamate (EBDC)-containing fungicides such as maneb or macozeb were found to be at increased risk for miscarriage compared to referent group of no use of fungicides, OR 1.77, 95% CI 1.11-2.83. Reproductive life span among women living on farms or rurally was 36.5yrs, shorter than for women currently living in an urban setting, 38.9 yrs, $p=0.02$.²⁸

60. Overall, the authors suggested that use of fungicides, and some specific compounds, by the applicator may increase the risk of miscarriage in spouses. However, this conclusion is limited, particularly since it is not possible to separate occupational and para-occupational exposure to pesticides.

Conclusion for Pregnancy Loss

61. The COT agreed that no definite conclusions could be reached from the available information on para-occupational exposure to pesticides in general or specific pesticide active ingredients and effects on pregnancy loss.

RESPIRATORY EFFECTS

62. The literature search identified two studies reporting information on para-occupational exposure to pesticides and aspects of respiratory disease and function.^{53,55} Seasonal changes in respiratory health in a rural population of children were investigated in one cohort study.⁵⁵ A cross sectional study was undertaken to investigate chronic respiratory disease in children following para-occupational exposure to pesticides.⁵³ Three studies published information specifically on asthma and para-occupational exposure to pesticides.^{23,51,52} One cohort investigation included an evaluation of allergic asthma in children²³ and two case-control studies of asthma^{51,52} (one in children and one in adults) were available. One case-control study of chronic bronchitis was retrieved.⁵⁴

Respiratory Disease / Function

Cohort Study

63. Senthilselvan et al 2000⁵⁵ investigated 200 adult patients (106 men and 94 women) aged >17 years resident in 6 administrative regions (3 rural municipalities and 3 towns) in south-western Saskatchewan, where grain production is the main farming operation; subjects were divided into 4 study groups: i) town non-farmers, ii) town farmers, iii) farm resident non-farmers, n=32; iv) farm resident farmers. Subjects were assessed twice (spirometer; self-administered questionnaire for information on respiratory conditions). The first assessment was undertaken in February and March 1996 for the winter season, and in June and July 1996 for the summer season. There is little farming activity in the area in the winter season, and then a number of activities, including spraying of herbicides and insecticides, in the summer season. In the summer season for 'farm resident non-farmers' (i.e. para-occupationally exposed), there was a non-significant decline in Maximal Midexpiratory Flow Rate (MMFR) from the winter to the summer season: Beta -5.49, Standard error 4.31, $p=0.20$. For the lung function measurement, FEV₁:FVC, the ratio of forced expiratory volume in 1 second to forced vital capacity, in farm resident non-farmers, there was a significant decline from the winter to the summer season: Beta -2.12, Standard error 1.00, $p=0.04$. The participation rate was low in this study, the number of individuals examined was low, and there was no direct measure of exposure.

Cross Sectional Study

64. Salameh et al 2003⁵³ selected 18 schools randomly from a list of Lebanese schools, and 3,291 children aged 5-16 years participated in the study; there were 407 children with a chronic respiratory disease diagnosis (2,016 children served as controls). A self-administered questionnaire was used by parents to provide information on exposure and on their child's health. Clinical confirmation of asthma diagnosis was undertaken. multivariate analysis, associations were observed between the following symptoms/diseases and para-occupational exposure: respiratory disease, OR 1.85, 95% CI=1.13-3.02, $p<0.01$; asthma, OR 4.61, 95% CI 2.06-10.29, $p<0.001$; chronic phlegm, OR 2.56, 95% CI 1.56-4.21, $p<0.001$; recurrent wheezing, OR 1.57, 95% CI 0.92-2.72, $p<0.05$; ever wheezing, OR 1.73, 95% CI 1.09-2.74, $p<0.05$; chronic cough was not seen to be associated with para-occupational exposure to pesticides: chronic cough, OR 0.95, 95% CI 0.62-1.45. Although a large number of subjects participated in the study (3,291 completed questionnaires), from a random selection of schools in the country and para-occupational exposure was identified as a separate category of exposure, there was no direct measure of exposure. In addition there were few medically confirmed diagnoses of respiratory disease e.g. for asthma, 84 children had a medically confirmed diagnosis, which constitutes only 2.6% of the total number of responses.⁵³

Childhood Asthma

Cohort Study on Allergic Asthma in Children

65. Duramad et al 2006²³ recruited a cohort of 239 children aged 24 months, whose mothers had been identified during pregnancy through the Centre for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) project. This project is a component of the Centre for Children's Environmental Health Research at the University of California Berkeley, a longitudinal birth cohort study of the effects of pesticides and other environmental exposures on the health of pregnant women and their children. Clinician's diagnosis of asthma, eczema, bronchitis, bronchiolitis or pneumonia taken from medical records from birth to 24 months of age. Maternal report of asthma symptoms, such as wheezing when the child did not have a cold, was gathered at interview. A blood sample analysis for T-helper 1 (Th1) and T-helper 2 (Th2) cells was undertaken. Exposure details were gathered from interviews with mothers of children included in the cohort.

66. Children who were diagnosed with asthma had higher Th2 levels (1% increase, 95% CI 0.7-1.2%), than children without asthma (0.7% increase, 95% CI 0.6-0.7%), $p < 0.05$. Children with maternal report of wheezing without a cold at 24 months had higher Th2 levels (1.2% increase, 95% CI 0.8-1.8%) than children without the condition (0.7% increase, 95% CI 0.6-0.8%), $p < 0.05$. Children who lived with agricultural workers had higher levels of Th2 (0.8% increase, 95% CI 0.7-0.9%) than children who did not (0.6% increase, 95% CI 0.5-0.7%), $p = 0.02$. Children of women who worked in the fields had higher Th2 levels (0.9% increase, 95% CI 0.7-1.0%) than children of mothers who did not work in agriculture (0.6% increase in levels, 95% CI 0.6-0.7%), $p = 0.001$. In the final regression model for Th2, mother working in the fields was associated with a 25.9% increase in children's Th2 levels, 95% CI 0.8-57.3%, $p = 0.04$. Significant increases of Th2 were also associated with having a gas stove at home: 46.8% increase in the multiple linear regression model, 95% CI 11.9-92.5%, $p < 0.01$, and with signs of rodents in the home in bivariate analyses, $p = 0.04$. The immunologic biomarkers used are mechanistically relevant to asthma development and the number of children with available data on Th2 levels is relatively large ($n = 239$). However, other exposures in the agricultural environment besides pesticides, such as exposures to dust, coarse particulate matter, endotoxin, or bacteria, could be responsible for the increased Th2 levels.²³

Case-Control Study of Childhood Asthma

67. Salam et al 2004⁵¹ identified subjects for this case-control study from the Children's Health Study (CHS), a population-based study of respiratory health in 12 southern California communities. Seventy-nine cases were children aged between 8 and 18 when they enrolled in the CHS, and who had been diagnosed with asthma before 5 years of age. The investigators used reports by mother in telephone interview; mothers were asked if a doctor had ever diagnosed the child as having asthma. The 412 controls were asthma-free children, matched to cases on age, sex, and community of residence,

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and counter-matched on whether they were exposed or unexposed to maternal smoking while *in utero*. Statistically significant associations were observed for exposure to herbicides in the first year of life and later, risk of developing any asthma, OR 4.58, 95% CI 1.36-15.43 (n=11, controls=5). The risk of early persistent asthma, OR 10.08, 95% CI 2.46-41.33 (n=10). For exposure to pesticides in the first year of life and later, risk of developing any asthma, OR 2.39, 95% CI 1.17-4.89 (n=23, controls=23). The risk of early persistent asthma, OR 3.58, 95% CI 1.59-8.06 (n=17). For exposure to farm crops or dust in the first year of life and later, risk of early persistent asthma, OR 2.33, 95% CI 1.19-4.54 (n=22, controls= 39). The authors noted that associations between the above three types of exposure and risk of developing early transient wheezing, later-onset asthma, or early persistent asthma for exposures after the first year of life, were not considered to be statistically significant (CIs include 1.0).

68. This study was a large population-based cohort of children (4,244 children aged 8-18 years at time of enrolment in the Children's Health Study) with a good participation rate: 82.5% cases (279) and 72.3% controls (412). However, the numbers of cases and controls in each exposure category were small, there was no direct measure of exposure, and exposures were not well characterised as the retrospective recall of exposure may be inaccurate. The asthma status of children was based on parental report of physician diagnosis.⁵¹

Asthma in Children and Adults

Case-Control Study

69. Salameh et al 2006⁵² identified 245 cases of newly diagnosed asthma outpatients from 10 Lebanese hospital centres; participants aged 12 -99 years. The 262 controls were either individuals accompanying cases (parents, friends), or outpatients at the same hospital being treated in a different outpatient department. Para-occupational exposure, report by participants of occupational use of pesticides by a family member. Diagnosis of asthma was made by a pulmonologist using self-reported symptoms in a questionnaire. The OR for asthma from para-occupational exposure to unspecified pesticides (family member occupationally exposed) was OR 1.45, 95% CI 0.60-3.51, $p=0.40$. For 'house exposure', that is house treated by unspecified pesticides by someone else (applicator), the OR 1.75, 95% CI 1.21-2.54, $p=0.003$. For 'house exposure' in the multivariate analysis, the OR increased to OR 2.59, 95% CI 1.58-4.26, $p<10^{-4}$, and in the multiple exposure model OR 2.17, 95% CI 1.37-3.50, with $p=10^{-3}$. Although para-occupational exposure was clearly defined, there was no quantitative estimate of exposure and the controls used (outpatients from other hospital departments) may not be comparable to the general population.

Chronic Bronchitis

Case-Control Study

70. Salameh et al 2006⁵⁴ identified 110 newly diagnosed chronic bronchitis outpatients recruited from 10 Lebanese hospital centres; participants aged 12-99 years. The 262 controls were either individuals accompanying cases (parents, friends), or outpatients at the same hospital being treated in a different department. Para-occupational exposure, report by participants of occupational use of pesticides by a family member. Diagnosis of asthma was made by a pulmonologist using self-reported symptoms in a questionnaire. The OR for exposure to unspecified pesticides through house treatment by professional applicator and risk of developing chronic bronchitis was OR 1.54, 95% CI 0.96-2.47, and for para-occupational exposure where a family member is occupationally exposed to pesticides, OR 1.35, 95% CI 0.44- 4.13. Overall, the Confidence Intervals do not suggest statistical significance for these findings. However, some analyses reported provided contradictory results: in a multivariate analysis by variable, 'house exposure', that is, house treatment by others, has OR 4.92, 95% CI 2.26-10.75, but in a multiple exposure model OR 1.62, 95% CI 0.54-4.90. In a subgroup analysis by smokers and non-smokers, 'house exposure' for smokers has OR 4.10, 95% CI 1.26-13.33, while for non-smokers the OR appears to be higher: OR 6.99, 95% CI 2.14-22.73. For mean cumulative exposure to pesticides through 'house exposure', OR 0.55 for 12-31 applications, OR 1.21 for 32-47 applications, and OR 3.65 for >47 applications, trend test $p=5 \times 10^{-4}$.

71. The study identified 'house exposure' (treatment of house by others) and 'para-occupational exposure' as separate exposure categories although there was no direct measure of exposure. There was no random selection of controls, and as the study was hospital-based, controls were outpatients attending for different conditions, and some controls were family members or friends of the cases. Overall, no conclusions could be reached in view of the contradictory nature of the results from this study (e.g. subgroup analysis by smokers and non-smokers contradicts the main findings of this study).⁵⁴

Conclusion for Respiratory Effects

72. The COT agreed that no definite conclusions could be reached from the available information on para-occupational exposure to pesticides in general or specific pesticide active ingredients and respiratory effects.

ACUTE EFFECTS

73. There were seven studies identified for the review which reported acute effects but the COT concluded that these studies identified bystander exposure to pesticides (i.e. 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 the work involving pesticides, but whose position may put them at risk of potential exposure).^{6,13,14,18,26,45,58}

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The COT noted that usage conditions in the countries where these studies had been undertaken might differ significantly from UK patterns of pesticide use. In addition, there was no biological plausibility for the acute health effects reported.

OCULAR EFFECTS

74. The COT concluded that no conclusions could be reached from the one available cross-sectional study of ocular effects in relation to para-occupational exposure to pesticides.³⁷

OTHER HEALTH EFFECTS

75. The COT concluded that no conclusions could be reached from the one available study on other health effects which had been retrieved (a case-control study of rheumatoid arthritis) in relation to para-occupational exposure to pesticides.²²

DISCUSSION

76. The Committees agreed that there were limitations in the data that apply to most of the studies summarised in this statement. Most studies investigated exposure to 'pesticides', or to classes of pesticides, such as insecticides, fungicides or herbicides. These broad terms cover a wide variety of chemical compounds which differ significantly from each other and which might be expected to have different effects. In studies where exposure to specific compounds had been investigated, the numbers of individuals exposed to any one chemical were small. Few studies contained direct measures of para-occupational exposure, in the form of biomarker data or environmental samples taken from buildings, and linked exposure to a health outcome. In most of the studies, exposure was self-reported and other possible routes of intake or exposure, such as diet, were not taken into account.

77. A number of the associations reported with specific compounds may not be relevant to the UK because the compounds are either not used or unapproved in the UK, or the conditions of use vary significantly from the UK.

CONCLUSIONS

78. The COC concluded:
- i. There was limited evidence for an association between the broad grouping of childhood 'haematopoietic cancers' and mothers' para-occupational exposure to pesticides;

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- ii. If there was an association between para-occupational exposure, cancer and specific pesticide active ingredients it would be small and difficult to investigate further;
 - iii. There is insufficient evidence to extend conclusions from para-occupational studies to bystanders and residents.
79. The COT concluded:
- i) No firm conclusions could be drawn from the limited information that was available on the relation between health outcomes reviewed and para-occupational exposure to pesticides in general;
 - ii) There was no clear evidence of an association between para-occupational exposure to any specific pesticide active ingredient and health outcomes reviewed;
 - iii) The studies on para-occupational exposure reviewed did not suggest specific hypothesis regarding health outcomes that should be further studied in bystanders or residents.
80. Neither Committee identified any specific pesticide active ingredient(s) from this review that would warrant further investigation by ACP with regards to bystander or resident exposure.

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

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

**INCLUSION / EXCLUSION CRITERIA APPLIED TO ALL RETRIEVED
REFERENCES**

Inclusion criteria:

- para-occupational exposure – i.e. exposure of close family members who live with the occupationally exposed worker, but who are not occupationally exposed themselves;
- residential (domestic) exposure where the exposed persons did not apply pesticide themselves, that is, professional applicators applied pesticides;
- exposure of children to pesticides applied at school or nursery;
- proximity to crop spraying as a “bystander”. This term includes those who live, work or are at school or hospital in the vicinity of sprayed fields. It also includes those using roads or paths close to sprayed fields, or visitors or trespassers on sprayed land or land subject to spray drift;
- proximity to amenity spraying as a “bystander”. This term includes those who live or work in the vicinity of sprayed recreation grounds, or use paths close to sprayed verges and open wayside areas.

Exclusion criteria:

- articles dealing only with exposure of occupational workers;
- analysis of birth defects in babies; however, para-occupational exposure of the mother during pregnancy is included;
- children exposed by domestic household use of pesticides by parents;
- genotoxic effects of pesticides;
- effects of organochlorines;
- effects of hazardous waste sites;
- dietary exposure;
- contaminated drinking water/groundwater;
- cases of poisoning;
- articles dealing only with methodology;
- review articles.

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QUALITY SCORING CRITERIA FOR CANCER OUTCOME PAPERS

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

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