

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

**SYSTEMATIC REVIEW OF EPIDEMIOLOGICAL LITERATURE ON PARA-
OCCUPATIONAL EXPOSURE TO PESTICIDES AND CANCER**

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. 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*'.
3. The Committees on Carcinogenicity (COC) and Toxicity (COT) 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 COC and COT 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.
4. In framing its response, the Government considered the evidence given in the RCEP report and advice published by the COC and COT on scientific issues raised by the report.³
5. 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 the value of a comprehensive systematic review and favoured smaller and more directed reviews.³
6. In discussions about the RCEP report, the 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*

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*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 TO REVIEW

7. This discussion paper details a systematic review of epidemiological literature of para-occupational exposure to pesticides and cancer undertaken by the DH Toxicology Unit, Imperial College. Para-occupational exposure, for the purposes of this review, was defined in terms of 3 exposure scenarios:

- i. Scenario 1. Exposure of close family members who live with an occupationally exposed worker, but who are not themselves occupationally exposed. This exposure scenario would apply in agricultural settings, where it may be considered to be intermediate between occupational exposure, that is, exposure of applicators and farmers or workers who mix/apply pesticides themselves, and exposure of bystanders or residents. Bystanders are defined by the Health and Safety Executive's Chemicals Regulation Directorate (CRD)¹ as persons located within or directly adjacent to an area where a plant protection application or treatment is in process, and whose presence is incidental and unrelated to work involving pesticides, but whose position may put them at risk of potential exposure. Residents are described by CRD as persons who live, work or attend school or any other institution adjacent to an area that has been treated with a plant protection product, and whose presence is incidental and unrelated to work involving pesticides but whose position may put them at risk of potential exposure.
- ii. Scenario 2. Indirect domestic exposure in the home where the exposed persons did not apply pesticides themselves, but where professional exterminators applied the pesticides.
- iii. Scenario 3. Exposure of children at school or nursery to pesticides applied by exterminators.

8. It should be noted that only exposure scenario 1 is considered as the strict definition of para-occupational exposure, and there may be overlap between the CRD definitions of bystanders and residents in the scenarios 2 and 3 above.

9. The indirect exposure scenarios 2 and 3 were included as a comparison to scenario 1. The professional application of pesticides in scenarios 2 and 3 should involve recording the details of the substance used, its concentration and amount applied, and the dates of application.

¹ The Chemicals Regulation Directorate is responsible for the regulation of pesticides within the UK. It incorporates the former Pesticide Safety Directorate.

SYSTEMATIC REVIEW OF EPIDEMIOLOGICAL LITERATURE

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 with the respective search terms listed in Tables 1–5 (Annex 1) 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 and inclusion / exclusion criteria were applied (Table 6 (Annex 1)). Selection criteria were applied first to the titles of retrieved papers and, if the references were clearly unrelated or irrelevant, the reference was excluded at that stage. In practice, the selection criteria were applied to the abstracts for the majority of the retrieved papers. Any duplicate papers were omitted. The flow chart in Figure 1 (Annex 1) summarises the data acquisition process and details the number of references identified at each stage and the cumulative totals.

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, Table 8) (Annex 3) were separated from those reporting exposure information only (232 papers, Table 10) (Annex 5). A list of the exposure references was supplied to CRD and equated with references held by them. An overview of key exposure references was supplied as Annex 8.

13. A decision was made to focus on health effects in the instance of this review and all papers relating to this subject were obtained. The full papers were evaluated and those found to be irrelevant were excluded (Table 9 (Annex 4)). A total of 54 papers were considered to be relevant to para-occupational exposure.⁵⁻⁵⁸ 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 (Table 11 (Annex 6)). However, none of these additional identified references were considered relevant to para-occupational exposure and worthy of review.

14. Out of the 54 summarised papers, 22 studies related para-occupational exposure to pesticides with cancer (Table 7 (Annex 2)). Of these, 12 reported positive outcomes for cancer and are considered in detail below.

15. The studies reporting cancer are referred to COC for evaluation. Studies reporting other health outcomes were considered by COT at its September 2009 meeting.

16. Toxicological data on specific chemicals identified through the review was extracted from the EU regulatory draft assessment reports (DARs) by

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CRD and has been provided for Members' information (Annex 7). The toxicological data is summarised at appropriate sections in the discussion paper.

EVALUATION OF SYSTEMATIC REVIEW

17. The papers in the cancer category were sub-divided as cohort, cross-sectional, case-control, case series or case reports and the details, major findings, strengths and weaknesses, and conclusions of each study were summarised in Table 7 (Annex 2).

18. Table 7 was subdivided into sections A, B and C. Section A gives the reference details, the health outcome studied in the paper and the type of study. Section B contains the study design details:

- a. paper identification by first author and date of publication;
- b. the country in which the study was conducted;
- c. description of the study subjects, including numbers of subjects, ages (where provided) and areas of residence (where provided);
- d. description of any reference population or of controls;
- e. description of the health assessment method used, which was frequently a response to a self-administered questionnaire or an interview; diagnosis by medical experts was included where available;
- f. an indication of the health outcome investigated;
- g. description of the exposure assessment available, which was frequently self-reported exposure; occasionally exposure indicators, such as "orchards or greenhouses on holding", were used; in a few studies, levels of selected herbicides/insecticides were measured in carpet dust samples, and a few studies contained biomarker measurements of pesticide metabolites in urine samples of children, or family members of a farmer who applied pesticides, or residents in houses sprayed with insecticides;
- h. description of the statistical analysis, which is most often logistic regression with the calculation of odds ratios;
- i. description of other risk factors.

19. Section C presents the major findings, strengths and weaknesses, and conclusions for the summarised studies. The major findings of each study that are relevant to para-occupational exposure are presented, quoting odds ratios (ORs) and results of any statistical analysis. P values are quoted where given. For the purposes of this discussion paper, when a 95% confidence interval (CI) includes the value of ≤ 1.0 , the results are considered to be statistically non-significant; this is equivalent to a P value >0.05 .

20. Several limitations to the data have been identified. No UK epidemiology studies have been identified and therefore there is a problem in equating the reported para-occupational exposures to UK circumstances. The reported exposures are qualitative and not quantitative, and it is 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 initial objective was to identify good epidemiological evidence of para-occupational exposure and health outcomes

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that could be extrapolated to bystanders/residents. A weight of evidence approach was used.

CANCER AS A HEALTH OUTCOME

21. Twenty-two studies related para-occupational exposure to pesticides with cancer (Tables 7A, B and C) (Annex 2). The number and type of studies reporting cancer are given below:

RESULTS FOR CANCER AS HEALTH OUTCOME	
Number of studies summarised	22 (4 cohort studies, 18 case-control)
Number of studies reporting positive outcomes	12 (3 cohort studies, 9 case-control)
Studies reporting positive outcomes with effects associated with para-occupational exposure to pesticides in general or categories of pesticides	Alavanja (2005), Flower (2004), Alderton (2006), Buckley (2000), Kato (2004), Ma (2002), Meinert (1996), Meinert (2000), Ruder (2006), Teitelbaum (2007)
Studies reporting positive outcomes with effects associated with specific pesticides	Engel (2005), Monge (2007)

Cancer Cohort Studies

22. Three cohort studies (Alavanja (2005), Engel (2005), Flower (2004)) gave standardised incidence ratios (SIRs) for several types of cancer, and reported positive outcomes. All three of these studies were part of the US Agricultural Health Study, an ongoing project which started in 1994 and gathers information about the health of farmers, pesticide applicators and their families.

23. The Alavanja (2005) study reported effects associated with unspecified pesticides. It reported a significantly lower than expected overall cancer incidence among spouses of farmers or private applicators (SIR 0.84, 95% CI 0.80-0.90), and a lower than expected incidence of several types of cancer (cancer of the digestive system, SIR 0.85, 95% CI 0.72-0.99; ovarian cancer, SIR 0.55, 95% CI 0.38-0.78), but an unexpected result of a significant excess of melanoma cases in spouses (SIR 1.64, 95% CI 1.27-2.09), which was not observed among applicators. However, this population-level study did not focus on exposure details, and the unexpected finding may be a statistical chance effect.

24. The Engel (2005) study reported effects associated with specific pesticides, and is discussed in paragraph 32 below. Flower (2004) examined childhood cancer among children para-occupationally exposed to pesticides because one or both of their parents apply pesticides. The study related to cancer rates in Iowa in children up to 19 years of age. The exposure considered was self-reported mixing and/or application of unspecified pesticides by applicators and spouses. In addition, information was obtained on exposure to classes of pesticides and to 50 specific pesticides. However, these were reported only where the number of exposed cases was 5 or more. Consequently, results were given for 16 specific pesticides and 3 pesticide classes, but the only significant result was for the organochlorine, aldrin.

25. The study suggested that there is a small increase in risk for all childhood cancers combined (SIR 1.36, 95% CI 1.03-1.79), and for lymphoma (SIR 2.18, 95% CI 1.13-4.19) and Hodgkin's lymphoma (SIR 2.56, 95% CI 1.06-6.14) in particular. However, the confidence intervals for the SIRs were only just above 1.0, and the overall number of cases was small (n=50). Furthermore, the information on ever use of 50 specific pesticides and pesticide classes was limited because the number of exposed cases was small for each individual pesticide or pesticide class, often between 5 and 10 cases. A modest increase in risk was observed in the study for children whose fathers apply pesticides without using chemically resistant gloves (OR 1.98, 95% CI 1.05-3.76), but these results were based on only 13 cases.

Cancer Case-Control Studies

26. Five of the case-control studies (Alderton (2006), Buckley (2000), Ma (2002), Meinert (1996) and (2000)) reported positive outcomes from exposure to professional pest control and concerned children.

27. Alderton (2006) presented evidence for an association between para-occupational exposure of the mother during pregnancy to unspecified pesticides through professional pest control applications and acute lymphocytic leukaemia in children with Down's syndrome (OR 2.25, 95% CI 1.13-4.49). This was an exploratory study based on telephone interviews. Exposure of the child, instead of the mother during pregnancy, to professional pest control applications was not found to be significant (OR 1.48, 95% CI 0.77-2.88). Buckley (2000), a US study based on telephone interviews, suggested an association between para-occupational exposure of the mother during pregnancy to applications of unspecified insecticides by professional pest control and non-Hodgkin's lymphoma in the child (OR 2.98, 95% CI 1.44-6.16, P=0.002). Numbers of exposed cases were small: 31 cases and 12 controls. Ma (2002), a US study based in Northern California, suggested an association between para-occupational exposure of the mother during pregnancy through applications of unspecified insecticides by professional pest control, and leukaemia in the child (OR 2.2, 95% CI 1.0-4.8, based on 22 cases and 14 controls exposed). Exposure of the child to insecticides through professional pest control in the first 3 years of life was also associated with an increased risk of leukaemia, with the highest odds ratio for year 2 of the child's life: OR 3.6, 95% CI 1.6-8.3, based on 31 cases and 15 controls exposed. Overall, for exposure of the mother 3 months before pregnancy to year 3 of the child's life, OR 2.8 and 95% CI 1.4-5.7, based on 39 cases and 25 controls exposed. However, the numbers of cases and controls in the various time windows were small.

28. Meinert (1996) was a German study that suggested an association between childhood leukaemia and exposure of the child to applications of unspecified pesticides by a pest control operator (OR 1.03 for leukaemia cases versus "local" control group, OR 1.20 for leukaemia cases versus "state" control group, OR 2.00 for solid tumours versus all controls). However, the numbers of cases and controls were very small (3 leukaemia cases, 5

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solid tumour cases, and 7 controls in total), and the study did not report confidence intervals or P values for the calculated odds ratios. Meinert (2000) was a larger German study with reported confidence intervals, and is discussed in more detail below.

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

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

31. Three of the case-control studies (Buckley (2000), Meinert (1996) and (2000)) also provided evidence for an association between parental occupational exposure to pesticides and cancer in children. Buckley (2000) suggested an association with Burkitt lymphoma (OR 9.6, $0.01 < P < 0.05$) and unspecified pesticides. The authors cautioned that their measurement of exposure was likely to be subject to substantial misclassification. Meinert (1996) found an association between parents' direct occupational exposure to insecticides, herbicides or fungicides and leukaemia (OR 1.53 with direct occupational exposure of either father or mother, no confidence intervals given). Meinert (2000) is discussed in paragraph 32 below. Another study, Ruder (2006), presented evidence which suggested that moving to a farm as an adolescent aged 11 to 20, as opposed to as an adult, was associated with a greater risk of glioma (OR 1.96, 95% CI 1.13-3.39 for respondents including proxies). However, there were no significant positive results for residence on a farm or for moving to a farm as a child aged 1 to 10 or as an infant under 1 year, so this association may be a statistical chance effect.

Key Study

Meinert 2000

32. The Meinert et al. (2000) study has been summarised below:
- a. study undertaken in West Germany, covered 1993-1997; agricultural users probably similar to users on smaller UK farms
 - b. two populations sampled, a nationwide group, and those located geographically near to nuclear installations
 - c. total of 2,358 cases sampled for the study
 - d. good response rate (84% cases, 71% controls)
 - e. occupational exposure of father to herbicides, insecticides and fungicides was reported to be associated with leukaemia in children (OR 1.6, 95% CI 1.1-2.3)
 - f. occupational exposure of mother to herbicides, insecticides and fungicides was reported to be associated with leukaemia (OR 2.5, 95% CI 1.3-4.7) and with lymphoma (OR 4.1, 95% CI 1.1-16) in children
 - g. weak association reported with unspecified pesticide use on farms and occurrence of childhood leukaemia (OR 1.5, 95% CI 1.0-2.2)
 - h. significant incidence of lymphoma in children was associated with residential treatment of insects by pest control operators (OR 2.6, 95% CI 1.2-5.7)
 - i. misclassification of exposure was possible because data were obtained solely through questionnaire and telephone interviews; e.g. 50% of fathers allegedly exposed to pesticides listed occupations for which an exposure did not seem plausible, suggesting, as the authors noted, that parents were sometimes unaware whether a specific substance was a pesticide. This observation would place some uncertainty on the study conclusions with regard to parental occupational exposure and an association with childhood cancer.

Studies reporting cancer associated with use of specific pesticides

Engel et al. (2005)

33. The Engel (2005) study has been summarised below:
- a. large cohort study of over 30,000 wives of private pesticide applicators enrolled in the Agricultural Health Study (AHS); 152 cases of breast cancer identified
 - b. AHS subjects were from the US, specifically North Carolina and Iowa; crop application practices, as described in Dosemeci (2002), were probably not dissimilar to the UK. However, the UK has broader requirements for operator training and certification than the US, which might give rise to differences in occupational hygiene practice – e.g. the use of rubber gloves and coveralls in North Carolina and Iowa (Dosemeci (2002)). It is therefore possible that both individual applicator and “take-home” exposures were higher in the AHS than they might be in the UK.
 - c. little evidence of association between measures of potential direct and indirect cumulative exposure and breast cancer risk: growing up on a

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- farm was not related to breast cancer risk among wives who never used pesticides (rate ratio (RR) 0.9, 95% CI 0.7-1.3), and there was no significant association with frequency of washing work clothes worn during pesticide application among wives who never used pesticides (RR 1.4, 95% CI 0.8-2.7 for >20 days/year of washing work clothes worn during pesticide application)
- d study considered self-reported use of 50 specific pesticides by farmers and spouses
 - e out of the significant findings for individual compounds, those relating to captan and chlorpyrifos are possibly relevant to the UK. There was an increased risk of breast cancer in relation to the husbands' use among wives who never used pesticides for the fungicide captan (RR 2.7, 95% CI 1.7-4.3), but not for chlorpyrifos, (RR 1.3, 95% CI 0.9-1.8)
 - f in general, findings in the study were inconsistent and appeared difficult to interpret: e.g., increased risk was found for husband's use among wives who never used pesticides for the fungicide captan (RR 2.7, 95% CI 1.7-4.3), but no elevation of risk was seen for women who applied this pesticide themselves (RR 0.5, 95% CI 0.2-1.2)
 - g patterns of risk were generally inconsistent between Iowa and North Carolina
 - h findings stratified by menopausal status are difficult to interpret. Significantly increased risks related to the women's own pesticide use occurred among premenopausal women (for chlorpyrifos, RR 2.2, 95% CI 1.0-4.9), while lower risks associated with women's own use and increased risks associated with the husbands' use were found among postmenopausal women (for chlorpyrifos, women's own use RR 1.0, 95% CI 0.5-2.2, and husband's use RR 1.6, 95% CI 1.1-2.4). For captan, data are not available for women's own use, but for husband's use among postmenopausal women RR 3.6, 95% CI 2.1-6.1
 - i authors acknowledged that findings needed to be confirmed in Iowa/North Carolina and in other populations

Overview of carcinogenicity data on Captan

34. In a 2-year toxicity and carcinogenicity study in the rat, there was no statistically or toxicologically significant increase in any tumour type, total tumours, total benign tumours or total malignant tumours (Annex 7). Further, in a life-span toxicity study in the rat, there was no significant difference between treatment groups and controls in the incidence of any tumour types and no relationship between dose and tumour incidence. No association between the occurrence of tumours and the presence of hyperplastic or pre-neoplastic changes was apparent.

35. In an oncogenicity study in the mouse, there was a positive correlation between the administration of captan and the incidence of duodenal adenomas and adenocarcinomas in males and females and a negative correlation with the incidence of lung and liver tumours. In another life-span oncogenicity study in the mouse, there was an increased incidence of non-neoplastic and neoplastic lesions in the small intestine. The incidence of duodenal hyperplasia, and the number of animals with benign and malignant

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duodenal neoplasms increased in the high dose (6000 parts per million) group. The distribution and incidence of benign and malignant neoplasms that developed in various other organs and tissues were similar to the control, bearing no obvious relation to treatment. There was no treatment-related effect on the incidence of non-neoplastic lesions.

36. Captan is considered a non-genotoxic rodent carcinogen and is classified in the EU as a Category 3 carcinogen (R40: Limited evidence of a carcinogenic effect)

Monge et al. (2007)

37. The Monge (2007) study has been summarised below:
- a. Costa Rican study including over 330 cases of childhood leukaemia
 - b. good response rate (90% cases, 90.5% controls)
 - c. reported results for specific pesticides
 - d. increased risk of acute lymphocytic leukaemia in the child for father's exposure during the child's first year of life to the herbicide picloram (OR 12.4, 95% CI 1.6-98.3, based on 10 cases), and the fungicide benomyl (OR 6.6, 95% CI 1.2-35.4, based on 12 cases) if a semi-quantitative measure of low versus high exposure was considered; benomyl is no longer approved in the UK
 - e. marginally significant increase in risk (OR 2.5, 95% CI 1.0-6.5, based on 9 cases) of acute lymphocytic leukaemia in the child for mother's exposure during the child's first year of life to paraquat, chlorothalonil and glyphosate: paraquat is no longer approved in the UK
 - f. little is known about pesticide application in Costa Rica. Monge (2005) reports that chlorothalonil and glyphosate are used on such plantation crops as coffee and banana, and it is possible that these crops are treated by hand-held sprayers and give rise to higher exposures than would be expected in the UK. Training and certification of spray operators and use of personal protective equipment may also be different in Costa Rica from the UK.

Overview of carcinogenicity of Picloram

38. CRD provided information from two chronic toxicity/carcinogenicity studies in the rat and one mouse study considered for the EU review and two National Toxicology Program studies in the rat and mouse (Annex 7). In the rat, one study provided limited evidence for hepatocellular adenoma, and another of thyroid follicular hyperplasia, C-cell hyperplasia and C-cell adenoma. Reference values in the EU review were based on fetal toxicity at a maternally toxic dose in the rabbit teratology study, supported by reduced weight gain and food consumption in the dog. The EU review of picloram currently recommends that it is unclassified in terms of carcinogenicity, mutagenicity and reproductive hazard.

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Overview of carcinogenicity of Chlorothalonil

39. CRD provided information from six chronic toxicity/carcinogenicity studies considered for the EU review (Annex 7). Chlorothalonil induced tumours of the forestomach in rats and mice. Chlorothalonil is classified in the EU as a Category 3 carcinogen (R40).

Overview of carcinogenicity of Glyphosate

40. CRD provided information from five chronic toxicity/carcinogenicity studies in the rat and four in the mouse considered for the EU review (Annex 7). No evidence for carcinogenicity was reported.

CHEMICALS USE AND PARA-OCCUPATIONAL EXPOSURE IN THE UK

41. CRD provided information on exposure patterns (chemicals, their use, exposure patterns) in the UK for Members information (paragraphs 42 and 43 below; Annex 8).

42. The following points might be relevant when considering the studies reviewed above. The most useful 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 does not have evidence for this. There is also probably a greater para-occupational involvement of children/spouses in the US but, again, CRD is not aware of direct evidence. In the UK, the requirements for certification, the former Poisonous Substances in Agriculture Regulations, which prohibited children working with certain pesticides and the Control of Substances Hazardous to Health legislation (COSHH) should limit children's exposure. It is also worth noting that some of the States have considerably higher residential use of pesticides (often professionally applied) than in UK.

43. It is largely a matter of conjecture, but in the US it appears that spraying is considered a dirty/unskilled task and is often given to migrant workers who are poorly supported, lacking appropriate work hygiene facilities and take dirty gear back to substandard housing, often on farms. Because of the UK certification requirements, spraying in UK is seen as skilled task. Prior to the introduction of certification in the UK, the situation was similar to the US. Therefore, the US might be a worst case compared to the current UK situation. However, although there is no UK research evidence, the "take home" pathway must exist in the UK.

CONCLUSIONS

Study Limitations

44. There were limitations in the data that apply to most of the studies summarised in this paper. 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 was 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.

45. 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.

Main Conclusions from the Review of Para-Occupational Literature and Cancer

46. Out of the 12 studies reporting positive outcomes, 10 reported on unspecified pesticides or classes of pesticides, and 2 reported on effects associated with specific compounds.

47. A US study (Engel et al, 2005) reporting an increase in breast cancer risk associated with the fungicide captan may be relevant to the UK, although the study findings are generally inconsistent and difficult to interpret.

48. Another study (Monge et al, 2007) presented some evidence for an increased risk of childhood leukaemia from exposure in early life to picloram, chlorothalonil and glyphosate. However, the study was undertaken in Costa Rica and conditions of use may differ from the UK.

49. Three US studies (Alderton (2006), Buckley (2000), Ma (2002)) suggested an association between exposure of the mother during pregnancy to indoor application of insecticides by a pest control operator and leukaemia or lymphoma in the child.

50. Two German studies (Meinert (1996), (2000)) suggested an association between exposure of children to the application of unspecified pesticides or insecticides by a pest control operator and childhood leukaemia or lymphoma.

51. One German (Meinert 2000)) and one US study (Flower (2004)) suggested an association between para-occupational exposure of children on farms, or whose parents apply pesticides, to unspecified pesticides and

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childhood leukaemia or lymphoma. However, there was evidence that the German study was likely subject to some misclassification of exposure, and the US study involved small numbers of cases.

DISCUSSION

52. It was thought that individuals who are para-occupationally exposed might have exposures above that of bystanders and residents. Members are asked to consider the studies analysed and discuss whether there are clear associations between para-occupational exposure to pesticides and cancer that can be extrapolated to the UK. Further, Members are asked whether it is possible to postulate a link between (possibly) lesser exposure of bystanders and residents and adverse health effects.

QUESTIONS FOR THE COMMITTEE

1. Given the variety of limitations in the studies analysed, can any conclusions be drawn about 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 exposure to any 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 the ACP?

Secretariat

October 2009

ANNEXES

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|---------|---|
| Annex 1 | Details of literature searches undertaken using either 'pesticides', 'fungicides', 'herbicides' or 'insecticides' as a search term in PUBMED, EMBASE, Toxline, CAB Abstracts and Web of Science |
| | Inclusion/exclusion criteria applied to retrieved references |
| | Document acquisition flow chart |
| Annex 2 | References relevant to para-occupational exposure and cancer |
| Annex 3 | References reporting para-occupational health effects |
| Annex 4 | Excluded papers reporting health effects |

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- Annex 5 References reporting para-occupational exposure information alone
- Annex 6 References identified through cross-referencing the summarised health effects papers
- Annex 7 Toxicological data on specific chemicals identified through the review extracted from the EU regulatory draft assessment reports (DARs) by CRD
- Annex 8 Chemicals use and para-occupational exposure in the UK. Information provided by CRD

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