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

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

INTRODUCTION

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

2. In this context, bystanders are persons located within or directly adjacent to an area where a plant protection product is being or has recently been applied, and whose presence is incidental and unrelated to work involving pesticides, but whose position may put them at risk of exposure. Residents are persons who live, work or attend school or any other institution adjacent to an area that is being or has been treated with a plant protection product, and whose presence is incidental and unrelated to work involving pesticides but whose position may put them at risk of exposure.

3. In paragraph 6.21 of their 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 the Department for Environment Food and Rural Affairs (Defra) and the Advisory Committee on Pesticides (ACP) to comment on the RCEP report. In 2006, the COT and COC published a joint statement.[2] In this statement, the COT noted that RCEP did not come to any conclusion as to whether pesticide exposure was causing ill-health, and it was suggested that one possible way forward would be to consider studies of para-occupational exposure – for example, in spouses and children of farmers, who might have exposures above those of bystanders and residents. A review of the available published scientific literature on para-occupational exposure to pesticides and health outcomes might provide useful information on priorities for epidemiological or biomonitoring studies of bystander and resident exposures to pesticides. As part of their response to the above-mentioned RCEP recommendation, the COT therefore agreed that an epidemiological review of para-occupational exposure to pesticides should be undertaken.[2]

5. In framing its response to the RCEP report, the Government considered the evidence set out in the report and advice published by the ACP, COT and COC on scientific issues raised by the report.[3] 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. Following on from their earlier advice, the COT and COC have now carried out a review of the epidemiological literature on para-occupational exposure to pesticides and health. A separate COC statement concerning risks of cancer has already been published.[4] This statement sets out the findings of COT on health outcomes other than cancer.

Approach to review

7. Para-occupational exposure for the purposes of this COT statement is regarded as exposure of household members who live with an occupationally exposed worker, but who are not themselves occupationally exposed. This is a strict definition of para-occupational exposure, and unlike COC, we did not also consider *pesticide exposures at school or home related to pesticide application by professional exterminators*[4] These are bystander or residential exposures and would not normally be classed as para-occupational.

8. The COT review was informed by a detailed assessment of relevant papers that was undertaken jointly by the HPA Toxicology Unit, Imperial College London and the HPA COT secretariat. An earlier COT discussion paper (TOX/2009/27[5]) describes the initial approach taken in the review, including search terms, references included and exclusions. In brief, 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, and covering 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, but a small number were in French. The papers written in French were evaluated from their published abstracts in English.

9. All the retrieved papers were screened individually against specified inclusion/exclusion criteria applied first to title, then abstract. Any duplicate papers were omitted.[5]

10. In total, 419 potentially relevant papers were identified, of which 187 addressed possible health effects and 232 provided information only about exposure. A list of the latter papers was supplied to the Health and Safety Executive Chemicals Regulatory Directorate (HSE CRD) for assessment, and a summary of key findings, comparing occupational and para-occupational exposures to various agricultural pesticides in the U.S.A., is presented in Annex 1. These findings are discussed further in paragraph 14.

11. Full papers relating to health effects were obtained and evaluated. Of the original 187 papers, 53 were considered relevant to para-occupational exposure.[6-10,12-59] (two papers[11,22] that had been identified earlier as potentially relevant was excluded from consideration as exposures were not clearly para-occupational). The 53 papers were summarised and then grouped into the following categories of health outcome (in line with those considered in the RCEP report): cancer, neurological and mental health, reproductive health, respiratory health, acute health effects, ocular effects, and other health outcomes. References listed in these papers were checked for further papers not identified through the initial searches, but none was found to present information on health effects in relation to para-occupational exposure. One further paper was subsequently identified as relevant by a COT member and was added to those already retrieved. [60]

12. Toxicological data on specific pesticides considered in the papers reviewed were extracted from the EU regulatory Draft Assessment Reports by HSE CRD, and were provided for COT Members' information.

13. Papers reporting findings on para-occupational exposure to pesticides and cancer were notified to the COC, and COT consideration was limited to those concerning health outcomes other than cancer.

Levels of Para-Occupational Exposure to Pesticides

14. A summary of published biomonitoring studies, which provide comparative information on occupational and para-occupational exposures (measurements in farmers or applicators and parallel measurements in their spouses and children) is provided in Annex 1. The data presented suggest that para-occupational exposure to pesticides, when expressed as a percentage of the exposure of pesticide applicators, can vary substantially. It is evident, however, that doses of pesticides in relation to body weight tended to be higher in children than in spouses. Moreover, the highest para-occupational exposures were all lower than the highest occupational exposures recorded in the same studies. It is uncertain how far these data, which are all from US studies, can be extrapolated to the UK. This is because of differences in the training of applicators (in the UK operators must be trained or work under supervision of someone who is trained) and in the extent to which children might be in close proximity when pesticides were being mixed and applied.

Overview of Literature Reviewed

15. Studies were identified that addressed all but two of the categories of health outcome considered in the RCEP report (there were none on acute health effects or other health outcomes). However, they were too heterogeneous and information on exposures was insufficient to permit any meta-analysis of quantitative relationships between exposures and health outcomes. Therefore, a narrative review was conducted.

MAIN HEALTH OUTCOMES

NEUROLOGICAL AND MENTAL HEALTH EFFECTS

16. The literature search identified one study that investigated a possible association of para-occupational exposure to pesticides with the occurrence of Parkinson's Disease (PD)[30], and a number of studies concerning abnormalities of neurobehavioural development and cognitive functioning in children[25,31,32,39,46,48]. In addition, a case-series report was retrieved on possible neurophysiological and neuropsychological effects in adults with para-occupational exposure to pesticides.[36]

Parkinson's Disease (PD)

Case-Control Study

17. A US case-control study (319 cases, 296 controls of whom 252 were relatives of cases) found a significant association between PD and direct pesticide application (OR 1.61, 95% CI 1.13-2.29 for those who reported ever using pesticides).[30] However, no significant association was seen with para-occupational exposure inferred indirectly from residence on a farm (OR 1.25, 95% CI 0.80-1.96 for residence on a farm >26 years compared with never). Case ascertainment was good (all individuals were assessed for PD using the full Unified PD Rating Scale), but some bias may have been introduced as cases were identified via self-referral as well as through clinics. The farm residence analyses did not separate out individuals who were not themselves farmers, so some of the farm residents may also have been occupationally exposed. However, if pesticides caused PD, the effect of this would be to bias risk estimates for para-occupational exposure upwards, and not to obscure a hazard.

Conclusions on Parkinson's Disease

18. The COT agreed that no useful conclusions could be reached from the limited information that was available on PD in relation to para-occupational exposure to pesticides. In general, studies of occupational exposure were likely to be more informative in the identification or exclusion of a hazard of PD, since such exposure would tend to be higher, making any elevation of risk more readily detectable. The COT noted that the ACP had previously commented[61] on a 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*.'

Neurobehavioural Development and Cognitive Functioning in Children

19. One cohort[25] and five cross-sectional studies were retrieved concerning para-occupational exposure to pesticides and neurobehavioural development and cognitive functioning in children.[31,32,39,46,48]

Cohort Study

20. In the USA, Eskenazi et al, 2007[25] undertook a study of approximately 400 children born to pregnant women receiving prenatal care between October 1999 and 2000 at community clinics in California, which predominantly served farmworker families. Neurodevelopmental and behavioural outcomes were assessed using two validated instruments: the Bayley Scales of Infant Development, Mental Development and Psychomotor Development Indices; and three Child Behavior Checklist (CBCL) scales – the Attention Problems scale, Attention Deficit/Hyperactivity Disorder (ADHS) scale and the Pervasive Development Disorder scale. Exposure estimation incorporated urinary biomarker measurements for exposure to organophosphate pesticides (six non-specific dialkyl phosphate (DAP) metabolites of organophosphates and two specific metabolites of malathion and chlorpyrifos) during pregnancy and at ages 6, 12 and 24 months in children. A rise in DAP levels with age was noted in the children.

21. A negative association was seen between DAP metabolite levels during pregnancy and Mental Development Index (MDI) at 24 months of age: for every 10-fold increase in metabolite levels a 3.5 (95%CI 0.5 to 6.6) point reduction in the MDI was observed. However, contrary to expectation, a statistically significant *positive* association was seen between the same metabolites measured in the child and MDI (2.37 (95%CI 0.5 to 4.2) point increase per 10-fold increase in metabolites), for which the authors had no explanation. With regard to the Child Behaviour Checklist, 14.4% children had clinically significant scores in the Pervasive Developmental Disorder scale (which includes items consistent with Aspergers' and autistic disorder), as compared to ≤3% in a national reference sample (binomial test $p<0.0001$). Children with higher prenatal and postnatal total DAP metabolites were at higher risk of Pervasive Developmental Disorder, with an approximately 2-fold increase in risk for each 10-fold increase in metabolites: OR 2.3, 95% CI 1.0-5.2 ($p=0.05$) for prenatal DAP metabolites; OR 1.7, 95% CI 1.0-2.9 ($p=0.04$) for 24-month dialkyl phosphate metabolite levels. No associations were seen with metabolites specific to malathion or chlorpyrifos.

22. The Committee noted that in about half of the mothers exposed during pregnancy the exposure was occupational rather than para-occupational (43% worked in agriculture), but that this would not invalidate positive indications of hazard. Also, the spot urine samples which were analysed for dialkyl phosphate metabolites reflected exposures during the previous 48hr, which may not have been representative of long-term average exposures. This could have reduced the study's ability to detect adverse effects of exposure.

Cross Sectional Studies

23. Two cross-sectional studies in a flower-growing region in Ecuador investigated neurobehavioral development in children, one at ages 24-61 months[31] and the other at ages 3-61 months.[32] Neurobehavioural development was assessed using the Ages and Stages Questionnaire (ASQ). Exposure was assessed from the mother's report of her own and her spouse's exposure, and from the distance of the child's residence from the flower plantation. Three subgroups were distinguished: two high exposure communities and a third with low exposure. Neither of the studies ascertained exposures to specific pesticides.

24. 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 motor skills, fine motor skills, problem-solving and personal social skills).[31] This study additionally assessed visual motor integration (VMI) in a subset of children aged 48-61 months, using a standardised test (the Beery-Buktenica VMI developmental test). For the subgroup of children tested, mothers' current employment in the flower industry was associated, but not statistically significantly, with poorer visual motor skills (% difference -2.2, 95% CI -11.4 to 4.4). Children who played with irrigation water scored lower on fine motor skills (% difference -8.2, 95% CI -9.3 to -0.5) and on problem solving skills (% difference -7.3, 95% CI -8.4 to -0.4) in the ASQ. Associations with other domains of the ASQ and with VMI were negative but not statistically significant.

25. In the study of children aged 3-61 months, after adjustment for their health status and other characteristics of the home environment, children aged 3-23 months from the high-exposure communities scored significantly lower on gross motor skills, on average by 8.8 points, p=0.002.[32] Furthermore, they scored 5.0 points lower on fine motor skills, (p=0.06), and 5.8 points lower in socio-individual skills (p=0.02). Children aged 24-61 months in the high-exposure communities scored 3.8 points lower on gross motor skills than children of the same age living in the low-exposure community (p=0.06).

26. Interpretation of these two studies is difficult. The ASQ has been validated in the U.S.A., but may be less culturally appropriate for a rural Andean population. Furthermore, a high prevalence of anaemia and stunting among the children included in these studies may have affected assessments of development, although analyses did attempt to control for their potential confounding effects.

27. A cross-sectional study of neurobehavioural performance was undertaken in 78 Latino children from agricultural regions of Oregon and North Carolina.[46] Neurobehavioral performance was assessed using five tests from the Behavioural Assessment and Research System (BARS) and three non-computerised tests (Object Memory, Purdue Pegboard and Visual Motor Integration). Exposure was defined as residence in an agricultural community (with at least one parent working in agriculture), while children who lived in a non-agricultural community (with neither parent working in agriculture in the previous year) were chosen as non-exposed controls. Eleven out of thirteen measures showed no deficit in agricultural (AG) children compared to non-AG children. However, in subsets of children defined by sex and location (Oregon or North Carolina), associations were observed with

measures of response speed (Finger Tapping) and latency (Match-to-Sample): 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); and 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). In contrast, the results were suggestive of better performance in object memory and Purdue Pegboard for children from AG communities but this was not formally assessed statistically (in statistical analyses, a one-tailed t-test was used, which assumed that children from AG communities would perform worse than non-AG children and did not allow statistical assessment of whether they performed better).

28. Lizardi et al[39] used measurements of urinary biomarkers for exposure to organophosphate pesticides (six non-specific dialkylphosphate metabolites and specific metabolites of malathion and chlorpyrifos) in a study of cognitive function in children of school age exposed para-occupationally to organophosphate pesticides. Forty-eight children (aged 10 years and younger – median 7 years) were assessed by the Wechsler Intelligence Scale (WISC-IIISF), the Children's Memory Scale (CMS), the Wisconsin Card Sorting Test (WCST) and the trail Making Test A&B (TMTA&B). All urine samples contained measurable levels of organophosphate metabolites and the results suggested detrimental effects on the WCST, which involves sorting cards of differing shapes and colours under changing rules to provide measures of cognitive skills – specifically 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 following WCST measures: the number of errors ($r=0.31$, $p=0.03$), number of preservative responses ($r=0.34$, $p=0.01$), number of preservative errors ($r=0.35$, $p=0.01$), conceptual level of responses ($r=0.38$, $p=0.01$) and "failure to maintain set" ($r=0.38$, $p=0.02$). There were no significant positive correlations between urinary levels of organophosphate metabolites and findings on the four other tests used (WISC-IIISF, CMS, and TMTA&B). These data suggest that short-term OP exposure had deleterious effects on children's speed of attention, sequencing, mental flexibility, visual search, concept formation and conceptual flexibility. However, when two outlying urine samples with particularly high biomarker concentrations were excluded from the analysis, no significant correlations were seen. Thus, the findings should not be considered more than suggestive.

29. The children included in the above study by Lizardi et al[39] were selected from those participating in a previous survey[63] In measurements conducted 2-4 years earlier, 25 of the children included in the study above had a detectable level of an OP pesticide metabolite in the urine ('exposed' group) and 23 did not. After exclusion of the two outliers with very high current concentrations, there was a significant association with performance on the 'Trail Making Test B' – children classified as exposed 2-4 years earlier took more time to complete the test (283s vs. 204s, $p=0.01$). However, there were no associations with any other measures.

Conclusions on Neurobehavioural Development and Cognitive Functioning in Children

30. The COT agreed that the available information did not allow any strong conclusions concerning the association of para-occupational exposure to pesticides in general, or to specific pesticide active ingredients, with neurobehavioural development and cognitive functioning in children. Reported positive associations with adverse effects tended to be with only one or two of multiple outcome measures that were examined in a study, and in the absence of a strong *a priori* expectation of effects on these outcomes specifically, may have arisen by chance.

REPRODUCTION

31. The literature search identified one case-control[29] and one cross-sectional[19] analysis of para-occupational exposure to pesticides that had addressed fertility (in the latter study[19] assessed by time to pregnancy), and four cross-sectional analyses[9,10 28 45] (two using data from the time to pregnancy study[9,10]) of para-occupational exposure to pesticides and spontaneous abortion (i.e. miscarriage) or pregnancy loss. One cohort study had explored effects on conception[19]. Additionally, one study [28] considered the sex ratio of children born to pesticide applicators (a deviation from the normal sex ratio might indicate selective fetal loss)..

Female Fertility

Cross-sectional analysis

32. Curtis et al 1999 investigated time to pregnancy (the number of months required for a couple to conceive) in 1048 farm couples from the Ontario Farm Family Health Study.[19] Exposure to pesticides was assessed by self-report, using questionnaires sent to farm operators and farm couples. Information from farm operators, husbands and wives was combined to construct a history of monthly pesticide usage for each farm, including chemical names and date of use. For analysis, pesticides were divided into four classes (herbicides, insecticides, fungicides, and miscellaneous) and nine specific active ingredients were documented. In the para-occupational exposure category (pesticide used on the farm, but neither husband or wife engaged in pesticide activities), no statistically significant associations were found for twenty pesticide types in 17 categories, except for a statistically significant *increase* in fecundability with use of triazines (adjusted conditional fecundity ratio (CFR) of 1.50, 95% CI 1.13-2.00), which may have been a chance finding given the absence of prior expectation for such an effect.

Case-Control Study

33. Greenlee et al 2003[29] undertook an exploratory case-control study of 322 women attending for treatment at a medical clinic in Wisconsin, between June 1997 and February 2001, with difficulty in having a child (defined as '12 months of unprotected intercourse without conceiving a pregnancy ending in live birth'), whose male partner was fertile. The controls were pregnant women of similar age (18-35

years) seeking prenatal care during their first trimester, who had conceived after less than 12 months of trying. Information on para-occupational exposure to pesticides overall and to classes of pesticide (e.g. herbicides) and location of residence prior to trying to conceive (e.g. 'ever lived on farm aged >19yr') was obtained by telephone interview, and medical histories were abstracted from records. There was no evidence of an association between para-occupational exposure and reduced female fertility in this study, but the methods for assessment of exposure, were very limited.

Conclusions on fertility

34. The COT agreed that the studies reviewed did not indicate any adverse effects on fertility from para-occupational exposure to pesticides in general or to specific pesticides. However, the available evidence was extremely limited.

Spontaneous Abortion (miscarriage)

35. Arbuckle et al[9] investigated phenoxy herbicide exposure and spontaneous abortion in spouses of farm operators in the Ontario Farm Family Health Study (n=2,110 women, 3,936 pregnancies for analysis, 395 spontaneous abortions at <20 weeks' gestation), using a self-administered questionnaire for approximately two thirds of respondents, and telephone interview for the remainder. Exposure to any phenoxy herbicide and to three specific active ingredients: 2,4-D, 4-(2,4-dichloro-phenoxy) butyric acid, and (4-chloro-2-methylphenoxy) acetic acid (MCPA) was assessed by questionnaire. A distinction was made according to timing of exposure (up to three months pre-conception and up to the end of the first trimester post-conception), but not between occupational and para-occupational exposure. However, it was stated that 85% of men and 20% of women reported handling pesticides on the farm.

36. Associations with any spontaneous abortion at <20 weeks were non-significant (adjusted OR for all phenoxy herbicides 1.1, 95% CI 0.6-1.9). However, statistically significant associations were found for early abortions (<12 weeks): in particular, pre-conception exposure to any phenoxy herbicide gave an adjusted OR 2.5, 95% CI 1.0-6.4. Analysis restricted to reported exposures of >1 month gave a similar risk estimate for all phenoxy herbicides (OR 2.7, 95% CI 1.0-7.6), and a previously positive but non-significant association with MCPA exposure (OR 2.3) increased and became statistically significant (OR 5.4, 95% CI 1.7-17.3). Raised but non-statistically significant ORs for spontaneous abortion at <12 weeks were reported in each pesticide category when the male pesticide applicator did not use protective equipment in either the preconception or post-conception periods. Post-conception exposure to herbicides was not associated with spontaneous abortion. .

37. Arbuckle et al[10] undertook a further analysis of early (<12 weeks) and late (12-19 weeks) spontaneous abortions using the same Ontario Farm Family Health data, but looking at a wider selection of pesticide categories, defined according to chemical family (e.g. phenoxy acetic acids, organosphosphates), class of use (herbicides, insecticides, fungicides, miscellaneous) and specific active ingredient (nine compounds). A statistically significant association between preconception exposure to pesticides and early spontaneous abortion was reported for phenoxy acetic acid herbicides (OR 1.5, 95% CI 1.1–2.1), triazines (OR 1.4, 95% CI 1.0–2.0),

and any herbicide (OR 1.4 95% CI 1.1–1.9). An increased risk of late spontaneous abortion was reported for preconception exposure to glyphosate (OR 1.7, 95% CI 1.0–2.9), thiocarbamates (OR 1.8, 95% CI 1.1–3.0) and a miscellaneous class of pesticides (OR 1.5, 95% CI 1.0–2.4). Further, a statistically significant association was noted for preconception fungicide exposure with early and late abortions combined (OR 1.4, 95% CI 1.1–1.8) – associations were positive but not significant for early and late abortions separately.

38. The study also used a Classification and Regression Tree (CART) analysis to assess interaction among risk factors for all spontaneous abortions combined and for early and late abortions separately. This found that associations with preconception exposure to pesticides were seen only in pregnant women aged 35 years and older. Effects in this group of women were observed with all of the pesticides mentioned in the previous paragraph except two (glyphosphate and miscellaneous), and ORs were generally higher than in analyses for all ages where ORs were all <2. In pregnant women aged 35 years or older, the OR for preconception exposure was 2.7 (95% CI 1.1-6.9) for triazines, 2.3 (95% CI 0.6-8.6) for phenoxy acetic acid herbicides, and 7.5 (95% CI 1.1-51.5) for thiocarbamates. Additionally, interaction effects were seen with two further pesticides: combined carbaryl and 2,4-D preconception exposures in women aged 35 years or older carried a 27-fold increase in risk, albeit with wide confidence intervals (OR 27.0, 95% CI 2.0 – 368.3).

39. Arbuckle et al[10] also investigated post-conception exposures in the same study. Elevated risks were observed for late spontaneous abortions (12-19 weeks) in relation 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), but none of these associations was statistically significant. A similar CART analysis to that for pre-conception exposures again found that maternal age of 35 years or older was a strong predictor of spontaneous abortion. In these older women, ORs were higher than ORs for all ages combined – OR 3.2 (95% CI 0.8-23.0) for post-conception exposure to glyphosate and OR 2.4 (95% CI 0.5-10.5) for post-conception exposure to thiocarbamates – but again did not reach statistical significance.

40. The COT agreed that the studies based on the Ontario Farm Family Health Study, which had found evidence for associations of spontaneous abortion with para-occupational exposure to a number of pesticide active ingredients, had been well conducted. However, 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. Recall bias may have spuriously inflated risk estimates, although the authors did attempt to minimise this by pooling information from both husband and wife as well as from the person responsible for day-to-day operations of the farm (if different – approximately 50% of the husbands and 6% of the wives indicated that they were the farm operator).[60] The numbers of individuals with spontaneous abortion and preconception exposure were small when subdivided by exposure group. Furthermore, the studies entailed multiple comparisons with no strong prior suspicions regarding the subset that emerged as positive. Thus, the positive findings could well have occurred by chance, and can only be regarded as hypothesis-generating.

41. Petrelli et al 2003[45] investigated para-occupational exposure to 10 specified pesticides (selected because of experimental evidence that they were endocrine-disrupting or otherwise affected male or female reproductive health) during the first pregnancy of 184 spouses of greenhouse workers in southern Italy. Among these women, 48 were classed as exposed to one or more of the listed pesticides, and 136 as non-exposed. In the 48 exposed spouses, there were 7 spontaneous abortions (14.6%) as compared with 6 (4.4%) in the non-exposed, a statistically significant difference (p=0.02, using a X^2 test). Those exposed had an unadjusted OR for spontaneous abortion at first pregnancy of 3.7 (95% CI 1.2-11.7) and this increased to 11.8 (95% CI 2.3-59.6) after adjustment for the age, smoking habits and education of each partner, the woman's type of work, and time between the pregnancy outcome and the interview. Interpretation of this study is limited by its small size and the potential for bias in recall of both exposures and spontaneous abortions.

42. Garry et al 2002[28] investigated reproductive outcomes in a survey of families of applicators licensed to apply pesticides in the Red River Valley area of Minnesota in the period 1991-1996. A telephone interview about general health and pesticide use, and a self-administered questionnaire about pesticide use and reproductive health were completed by both applicators and their spouses. Self-reported exposure of applicators and spouses to four pesticide classes (herbicides, insecticides, fungicides, fumigants) and to five specific fungicides and six specific herbicides was ascertained.

43. In analyses of pregnancies fathered by 522 applicators[28], the spouses of applicators who used all of herbicides, insecticides and fungicides at the time of a pregnancy had more pregnancy losses than any other pesticide application group: OR in comparison with a referent group of herbicides only 1.64 (95% CI 1.00-2.67). Further analyses were conducted for exposure to specific fungicides. The spouses of applicators who used ethylene bisdithiocarbamate (EBDC)-containing fungicides such as maneb or mancozeb were found to be at increased risk for pregnancy loss compared to a referent group who did not use fungicides (OR 1.77, 95% CI 1.11-2.83). Those using organotin fungicides were also reported to be at higher risk of pregnancy loss (OR 1.55, 95% CI 1.01-2.37).

44. Garry et al 2002[28] also investigated maternal use of, and exposure to, pesticides from the responses of 379 female spouses who had been pregnant or had children. Among these 379 women, 269 reported aerial application on their own or a neighbouring farm, 126 had carried food to pesticide-treated fields within 48 hours of application, and 315 had washed "pesticide-treated" clothing. It was reported that these exposures, some of which were para-occupational, were not significantly associated with frequency of fetal loss. Only 36 of the 379 women themselves used pesticides (mixing, loading or applying pesticides), and this,was a significant risk factor for fetal loss (OR for fetal loss per pregnancy 1.81; 95%CI 1.04–3.12).

45. Further analyses of the responses from female spouses[28] showed that the frequency of all first-trimester miscarriages regardless of pesticide use was significantly elevated in the spring as compared with all other seasons, p=0.034. However, the highest frequency of first-trimester miscarriages occurring in the spring was observed among spouses of applicators who had applied herbicides but had not applied fungicides. Further analyses suggested that the risk of miscarriage in spring

was significantly higher among spouses of applicators who used herbicide products containing sulfonylureas (OR 2.11, 95% CI 1.09-4.09), imidizolinone (OR 2.56, 95% CI 1.11 – 5.87) or mixture 9100 (a mixture of chorophenoxy herbicides and bromophenol; OR 2.94, 95% CI 1.40 – 6.16), compared to use of all other pesticides. These findings were supported by comparative analyses using information from applicators about their wives' pregnancies, although in this case, the associations did not achieve statistical significance.

46. Finally, Garry et al[28] investigated sex ratio in relation to exposure to pesticide classes (herbicides, insecticides, fungicides, fumigants). They found that the sex ratio of children born to applicators applying all of fungicides, insecticides and herbicides was altered (p=0.02) in comparison with a referent group who used herbicides only, and that 21% fewer boys were born in this group (282 girls vs. 226 boys).

47. Overall, the authors suggested that use of fungicides, and of some specific compounds, by applicators may increase the risk of miscarriage in their spouses.

Conclusions on Spontaneous Abortion / Pregnancy Loss

48. The COT agreed that the overall evidence for associations of spontaneous abortion with para-occupational exposure to specific pesticides and classes of pesticides was weak. This was mainly because the positive associations which had been reported had been observed in a context of multiple statistical testing without strong prior hypotheses regarding the particular pesticides concerned. Thus, in the absence of consistent independent replication, it was quite likely that they had occurred simply by chance. Also there was a possibility that in some cases, risk estimates had been inflated by recall bias.

49. The greatest suspicion of a hazard of spontaneous abortion was for fungicides and phenoxy herbicides, and future studies might usefully focus on specific compounds within these classes of pesticide. However, as a means of detecting or excluding hazard, it would be more efficient to study women who were exposed occupationally rather than para-occupationally, since occupational exposures are likely to be higher. Studies of this sort are more likely to be feasible in countries other than the UK, since in the UK professional application of pesticides by women is relatively uncommon.

RESPIRATORY EFFECTS

50. Seven studies were identified that provided information on para-occupational exposure to pesticides and aspects of respiratory disease and function. [23,51,52,53, 54, 55,60] A cohort study gave information on lung function in adults in rural Canada in relation to seasonal para-occupational exposure to pesticides.[55] Two cross-sectional analyses examined respiratory symptoms and asthma in children in Canada and in the Lebanon.[53,60] Three studies provided information specifically on asthma,[23,51,52] of which one was a cohort study of predominantly Hispanic children in California evaluating cytokine profiles that are associated with allergic asthma[23] and two were case-control studies of asthma[51,52] (one in children in California and one in adults in

the Lebanon). The sixth study was a case-control investigation of chronic bronchitis in the Lebanon.[54]

Lung Function

Cohort Study

51. Senthilselvan et al 2000[55] investigated 200 adult patients (106 men and 94 women) aged >17 years and resident in six administrative regions (three rural municipalities and three towns) in south-western Saskatchewan, where grain production was the main farming operation. Subjects were assessed twice (using spirometry and a self-administered questionnaire about respiratory conditions). The first assessment was undertaken in February and March 1996 for the winter season, and the second in June and July 1996 for the summer season. There was little farming activity in the area in the winter season, but activities in the summer season included spraying of herbicides and insecticides. For the analysis, subjects were divided into four study groups: i) town non-farmers, ii) town farmers, iii) farm-resident non-farmers (considered to be para-occupationally exposed to insecticides and herbicides, and within which, 32 individuals had both summer and winter assessments); and iv) farm-resident farmers. Greater declines in Maximal Midexpiratory Flow Rate (MMFR) and FEV_1:FVC (the ratio of forced expiratory volume in 1 second to forced vital capacity, which is lowered in obstructive lung diseases such as asthma) between winter and summer were seen among farm- than town-residents. For 'farm-resident non-farmers', the difference for FEV_1:FVC was statistically significant (-2.12%, p=0.04), while for MMFR it was not (-5.49%, p=0.20). Limitations of this study included the low participation rate (21.9% of eligible households), the small number of individuals examined, and the lack of any direct measure of exposure. The observed associations were not due to confounding by asthma (the study reported that a variable for asthma was not statistically significant in the analyses). However, the authors noted there were many other possible causes of reduced lung function in farm residents in summer as compared with winter, including grain dust, grain dust mites, pollen, fungal spores, animal products, fertilizers, fumigants, and plant-derived gases.

Childhood Respiratory Symptoms and Asthma

Cohort Study of Asthma in Children

52. Duramad et al 2006[23] analysed Th1/Th2 cytokine profiles in relation to para-occupational pesticide exposures in a cohort of children aged 24 months. The children's mothers had been identified during pregnancy through the Centre for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) project in California. This is a longitudinal birth cohort study of the effects of pesticides and other environmental exposures on the health of pregnant women and their children. Para-occupational exposure of children was assessed from mother's report of her own agricultural work and that of the father and other household members. Clinician's diagnosis of respiratory complaints was taken from medical records from birth to 24 months of age. For statistical analyses, asthma was defined as at least three separate diagnoses of reactive airway disease, all separated by at least one month in time. In addition, maternal report of asthma symptoms, such as wheezing

when the child did not have a cold, was gathered at interview at 6, 12 and 24 months. A blood sample analysis was undertaken for specific types of lymphocyte white blood cells ($CD4^+$ T helper cells), which have been extensively studied in asthma: T-helper 1 (Th1) and T-helper 2 (Th2). The rationale was that asthma is characterised by chronic inflammation and predominance of Th2 cells in the airways, and these Th2 cells may be involved in immunogenesis of asthma, while Th1 cells are thought to protect against development of asthma by regulating Th2 cytokine production. A clinical diagnosis of asthma was made for 32 children (23 with blood analysis for Th1/Th2).

53. Children who were diagnosed with asthma had a higher percentage of Th2 $CD4^+$ lymphocytes at 24 months (1% of all $CD4^+$ lymphocytes, 95% CI 0.7-1.2%) than children without asthma (0.7%, 95% CI 0.6-0.7%), $p<0.05$; and children with maternal report of wheezing without a cold at 24 months had higher Th2 levels (1.2%, 95% CI 0.8-1.8%) than children without the condition (0.7%, 95% CI 0.6-0.8%), $p<0.05$. Further bivariate analyses showed that children who lived with agricultural workers had higher levels of Th2 (0.8%, 95% CI 0.7-0.9%) than children who did not (0.6%, 95% CI 0.5-0.7%), $p=0.02$; and that children of women who worked in the fields had higher Th2 levels (0.9%, 95% CI 0.7-1.0%) than children of mothers who did not work in agriculture (0.6%, 95% CI 0.6-0.7%), $p=0.001$. In a final multivariate regression model for Th2, 'mother working in the fields' was significantly associated with a 25.9% increase in children's Th2 levels, 95% CI 0.8-57.3%, $p=0.04$, and a positive but non-significant association was seen with 'agricultural workers living in the home' (17.5% increase in Th2 $CD4^+$ lymphocytes, 95% CI -4.2 to 44.3). These results were independent of the level of $CD4^+$ cells. Th1 percentages were not significantly associated with 'mother worked in fields' or 'agricultural workers living in the home' in a final multivariate regression model. The immunologic biomarkers used were mechanistically relevant to development of asthma and the number of children with available data on Th2 levels was relatively large (n=239). However, the authors could not exclude the possibility that other exposures besides pesticides, such as dust, coarse particulate matter, endotoxin, or bacteria, were responsible for the increased Th2 levels reported in this study.[23]

Case-Control Study of Childhood Asthma

54. Salam et al 2004[51] 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. There were 279 asthma cases included who were aged between 8 and 18 years when they enrolled in the CHS, and who had been diagnosed with asthma before 5 years of age. The 412 controls were asthma-free and matched by school grade (age), sex, community and maternal smoking in pregnancy. A structured telephone interview with the mother was used to obtain information on farm-related exposures (crops or dusts, farm animals, herbicides, and other pesticides). The interview also collected information on demographics, family history of asthma, feeding practices in infancy, day care attendance, tobacco smoke exposures and household environment (pets, cockroaches, and wood smoke, oil or exhaust fumes). Mothers were also asked whether a doctor had ever diagnosed the child as having asthma, and if so, the age of onset. This information was used to distinguish early (<3 years) and late (>3 years) onset asthma.

55. Statistically significant associations were observed[51] for exposure to herbicides in 'first year of life and later' with risk of developing any asthma (early or late or early transient wheezing) (OR 4.58, 95% CI 1.36-15.43, 11 exposed cases) and with the risk of early persistent asthma (OR 10.08, 95% CI 2.46-41.33, 10 exposed cases). Statistically significant increases in risk were also seen for exposure to other pesticides in 'first year of life and later' with risk of developing any asthma OR 2.39, 95% CI 1.17-4.89 (n=23 exposed cases) and with risk of early persistent asthma OR 3.58, 95% CI 1.59-8.06 (n=17 exposed cases). For exposure to farm crops or dust 'in first year of life and later', the risk of early persistent asthma was OR 2.06, 95% CI 1.02-4.15 (n=22 exposed cases). No significant associations were found between exposure to pesticides, farm crops or dust exposure after the first year of life but not earlier, and risk of developing early transient wheezing, later-onset asthma, or early persistent asthma.

56. This case-control study was nested in a large population-based cohort of children (4,244 children aged 8-18 years at the time of enrolment) and had a good participation rate: 82.5% in cases (279) and 72.3% in controls (412). However, relatively small numbers were exposed, multiple analyses were conducted without strong prior hypotheses, there was no direct measure of exposure, and exposures were not well characterised – in particular, the retrospective recall of exposure by mothers of cases may have been more complete than for mothers of controls, which would have tended to inflate risk estimates.[51]

Cross-sectional studies of childhood respiratory symptoms and asthma

57. A cross-sectional analysis by Weselaka et al used data from the Ontario Farm Family Health Study on parental use of pesticides during the pregnancy period (the month of conception until month of delivery) in relation to chronic bronchitis or cough, asthma and hayfever or allergies in offspring.[60] This Study was considered in detail with respect to reproductive outcomes discussed in paragraphs 32 and 40 above[19,60]. Seventeen pesticide exposure variables were used in analyses as described in paragraphs 37-39[10]. Comparisons were made with pregnancies for which there was no reported pesticide use during the pregnancy period. Information on respiratory outcomes was taken from the questionnaire completed by the wife, which included a complete reproductive history of her first five pregnancies as well as self-report of whether "a doctor had ever told the parents "that their child had the following health problems: chronic bronchitis or cough, asthma, and hayfever or allergies".

58. Any parental pesticide use during pregnancy was significantly associated with the development of allergies or hay fever in offspring for all three major pesticide classes, with odds ratios of 1.69 (95% CI 1.15 to 2.47) for fungicides,1.56 (95% CI 1.15 to 2.11) for herbicides, and 1.48 (95% CI 1.07 to 2.03) for insecticides. Furthermore, exposure to the pesticide families, phenoxy herbicides (OR 1.43, 95% CI 1.03–1.99) and organophosphates (OR 1.55, 95% CI 1.02–2.36), and to the active ingredient 2,4-D (OR 1.66, 95% CI 1.11–2.49) also showed significant associations with allergies or hay fever. Stratification by sex suggested that these associations were limited to males (highest OR 2.12, 95% CI 1.20–3.76 for fungicides in males), and stratification by three year age band suggested increasing risks with increasing age, the highest risks being in children aged 12 years and older

at the time the questionnaire was completed. However, no significant relationships were seen between parental use of pesticides and asthma, or for 'persistent cough or bronchitis'. It was noted that 45% of children with asthma had allergies or hay fever.

59. This was a carefully conducted study and the most important limitations were all acknowledged in the paper – child's age at diagnosis was not provided; there was potential for exposure assessment bias (the recall period of pesticide use exceeded 10 years for approximately 30% of pregnancies); more than 10% of the exposures were imputed for some pesticide groupings; there was an inability to account for postnatal exposures; and some positive results may have arisen by chance in a context of multiple testing. The authors also investigated relationships with farm characteristics to see if an expected[64] protective relationship was seen for children growing up on farms with livestock. Children from farms with poultry (OR=0.72, 95% CI: 0.49, 1.06) and pigs (OR: 0.66, 95% CI: 0.46, 0.95) were less likely to have allergies, whereas high crop acreage of grains, hay and fodder crops, oilseeds and other field crops, or parental field or livestock work during the pregnancy interval did not show an association with childhood allergies or hay fever. The reported associations of pesticides with allergies or hay fever appear not to have been adjusted for the presence of livestock on the farm.

60. Salameh et al 2003[53] studied 3,291 children aged 5-16 years (71% response rate) from 18 schools randomly chosen from a list of all Lebanese schools. A self-administered questionnaire completed by their parents provided information on exposure and on the child's health. Para-occupational exposure was defined as reported occupational use of pesticides by a household member, or a parent in one of the following professions: pesticide applicator, agricultural worker, farmer, wood preservative painter. A translation of a validated American Thoracic Society questionnaire was used to identify cases of chronic respiratory disease, and within this group, clinical confirmation of asthma was undertaken. There were 407 children with a chronic respiratory disease diagnosis. In a multivariate logistic regression analysis, associations were observed between the following symptoms/diseases and para-occupational exposure to pesticides: 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, $p<0.05$[*]; and ever wheezing, OR 1.73, 95% CI 1.09-2.74, $p<0.05$. In contrast, chronic cough was not associated with para-occupational exposure to pesticides (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. The authors noted that use of a cross-sectional design could introduce bias, since it was not possible to be sure that exposures preceded the onset of disease, and there may have been errors in the recall of exposures. [53]

[*] A two-sided p-value of <0.05 was reported in the paper although the 95%CI included 1. This suggests an error.

Asthma in Children and Adults

Case-Control Study

61. Salameh et al 2006[52] identified 245 cases of newly diagnosed asthma in outpatients from 10 Lebanese hospital centres, and 262 controls who were either individuals accompanying cases (parents, friends), or outpatients at the same hospital being treated in a different department, and without respiratory problems or symptoms. Participants were aged 12-99 years (mean 36.2 years in cases, 37.6 years in controls). Both cases and controls answered a questionnaire that included items on occupational and para-occupational exposure to pesticides. Para-occupational exposure was defined as having "a family member occupationally exposed to pesticides' – individual pesticides were not specified. Diagnosis of asthma was made by a pulmonologist and confirmed using the self-reported symptoms from the questionnaire, which included an Arabic translation of a standardised American Thoracic Society questionnaire. Cases with chronic bronchitis or unclassified respiratory problems were not included in the analyses. In multivariate logistic regression analyses the association of asthma with para-occupational exposure to pesticides was not statistically significant (OR 1.45, 95% CI 0.60-3.51, p= 0.40). However, only 12 cases and 9 controls were exposed para-occupationally.

Chronic Bronchitis

Case-Control Study

62. Salameh et al[54] identified 110 outpatients with newly diagnosed chronic bronchitis, who were recruited from 10 Lebanese hospital centres as part of the study described above[52]. These included individuals with or without obstruction (on lung function testing). The diagnosis of chronic bronchitis was confirmed by a pulmonologist and according to questionnaire-reported symptoms of cough and phlegm. Patients with additional diagnoses (asthma, tuberculosis, cancer etc.) were excluded. These cases were compared with 262 controls who were either individuals accompanying cases (parents, friends), or outpatients at the same hospital being treated in a different department and without respiratory problems. Participants were again stated to be aged 12-99 years (mean 50.7 years in cases, and 37.6 years in controls). Para-occupational exposure was ascertained as previously, through questionnaire reports from participants of occupational use of pesticides by a family member. Five cases and nine controls were para-occupationally exposed and the association with exposure was not statistically significant (OR 1.35, 95% CI 0.44- 4.13).[54]

63. In both of the studies by Salameh et al published in 2006[52 54], although para-occupational exposure was clearly defined, only small numbers of participants were exposed in this way, and no quantitative estimates of exposure were reported . Further, the controls (family members and friends and outpatients from other hospital departments) may not have been representative of the population at risk of being included in the study as cases. In particular, the para-occupational exposures of family members may have been too similar to those of the cases, which in an unmatched analysis could lead to under-estimation of risk.

Conclusions on Respiratory Effects

64. The COT agreed that while there was some evidence suggesting an association of para-occupational exposure to pesticides with asthma and allergic disease, the findings were limited and not entirely consistent. The Committee noted that very few pesticide products have been found to cause asthma through occupational exposure, and therefore the finding in some studies that para-occupational exposure to a wide variety of pesticides was associated with asthma raises the possibility of unrecognised bias. While observations were at odds with findings that asthma is generally less common in people who have been brought up on farms[64], the observed protective effect of farms may be related specifically to livestock exposure [65]. One research team looked for and found this protective association with farm livestock in their data, despite positive associations of pesticides with allergic disease or hayfever[60] In light of the findings reviewed, there is a case for further research on atopic disease in children of farmers who use pesticides, but only if reliable information can be obtained on use of specific compounds.

ACUTE EFFECTS

65. A number of studies were identified which looked at acute health effects from bystander exposure to pesticides, but none that related to para-occupational exposures.

OCULAR EFFECTS

66. There was only one study of ocular effects in relation to para-occupational exposure to pesticides.[37] This was a questionnaire survey of retinal detachment in wives of farmer pesticide applicators in the Agricultural Health Study in North Carolina and Iowa, during 1993-1997. An increased risk of self-reported doctor-diagnosed retinal detachment was found with husband's ever use of fungicides (adjusted OR 1.9, 95% CI 1.2-3.1) but not in analyses for specific fungicides. COT agreed that this single cross-sectional study could only be regarded as exploratory and hypothesis-generating.

OTHER HEALTH EFFECTS

67. No studies were identified which looked at other health effects from para-occupational exposure to pesticides.

DISCUSSION

68. Epidemiological studies of para-occupational exposure to pesticides allow investigation of health outcomes that cannot readily be addressed in relation to occupational exposure – for example, possible effects on cognitive development and allergic disease in children. It is for such health outcomes that study of para-occupational exposures is likely to be most rewarding. Furthermore, because para-

occupational exposures can be higher than those that occur in residents, adverse effects, if they occur, should be more readily detectable (since risks will tend to be higher when exposures are higher).

69. At the same time, there are challenges in investigating the effects of para-occupational exposures, especially in the valid and meaningful characterisation of exposures. Perhaps for this reason, the epidemiological literature on such exposures is rather sparse.

70. The Committee identified a number of generic limitations which applied 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 from each other substantially in their toxicology, and which therefore would be expected to have different health effects. Combining such compounds in a single exposure category will tend to dilute and obscure any adverse effects that they produce. At the same time, in studies where exposures to specific compounds were investigated, the numbers of individuals exposed to any one chemical were small, again limiting the power to detect adverse effects.

71. Few studies of associations with health entailed direct measurement of para-occupational exposure through biomarkers or environmental sampling. In most of the studies, exposure was self-reported, and in some cases this may have led to bias from errors of recall.

72. In some studies, subjects with para-occupational exposure to pesticides were also exposed residentially or occupationally. This would not obscure the effects of a hazard, but if a hazard were present, it could cause the risks from para-occupational exposures to be over-estimated.

73. No studies of para-occupational exposure to pesticides in relation to health were identified from the UK. Again, this is not a concern with regard to the identification of hazards, but risk estimates reported for para-occupational exposures cannot necessarily be extrapolated to the UK, since levels of exposure may be different.

74. Selective publication of studies, or of positive findings within studies, may have distorted the overall balance of evidence in the literature. Furthermore, where positive findings have been reported, they have often emerged in a context of multiple testing with no strong a priori reason to expect the specific associations observed. This may be an indication for further confirmatory research, but in the absence of replication, the associations can be given little weight.

75. Among the positive findings identified in the review, a possibly increased risk of spontaneous abortion in association with para-occupational exposure to certain fungicides and phenoxy herbicides would be worthy of further investigation if suitable opportunities arose. In particular, an association is plausible for a number of fungicides that are aneugens or interfere with reproductive hormones. However, as a means of detecting or excluding hazard, it would be more efficient to study women who were exposed occupationally rather than para-occupationally, since

occupational exposures are likely to be higher. Studies of this sort are more likely to be feasible in countries other than the UK, since in the UK professional application of pesticides by women is relatively uncommon.

76. There is also a case for further research on atopic disease in children of farmers who use pesticides, but only if reliable information can be obtained on use of specific compounds.

77. The review does not point to any pesticides that should be a particular priority for biomonitoring studies in bystanders or residents.

CONCLUSIONS

78. The COT concluded:

i) Epidemiological studies of para-occupational exposure to pesticides allow investigation of health outcomes that cannot readily be addressed in relation to occupational exposure – for example, possible effects on cognitive development and allergic disease in children. Moreover, para-occupational exposures may be higher than those that occur in bystanders and residents, making it easier to detect adverse effects where they occur (because risks will tend to be higher).

ii) Despite these theoretical advantages, currently available studies of para-occupational exposure to pesticides are limited in number, scope and design, and do not provide strong pointers to any health hazard, either from broad classes of pesticide or from specific compounds.

iii) Most worthy of further investigation are a possible association of spontaneous abortion with para-occupational exposure to fungicides and phenoxy herbicides, and further research on atopic disease in children of farmers who use pesticides. However, studies of pesticides and spontaneous abortion would be better conducted among women with occupational rather than para-occupational exposure, and are more likely to be feasible in countries other than the UK.

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October 2011

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Annex 1

Table 1. Comparison of systemic exposure based on urinary metabolites biomonitoring for farm families

Study	Occupational exposure of farmers (mg/kg bw/d)	Para occupational Exposure group	n	Systemic exposure (mg/kg bw/d)	Comments
Acquavella J.F et al.(2004) [66] Glyphosate	Farm Family Exposure Study 0.004 maximum	Spouses	48	0.00004 maximum	Five consecutive 24h samples from day before to 3 days post application. Absorbed glyphosate excreted unchanged in urine. Systemic doses not reported in detail
		Children	79	0.0008 maximum	
Alexander B.H., et al (2006) [67] Chlorpyrifos	Farm Family Exposure Study 0.0021 geometric mean	Spouses	34	0.0007 geometric mean 0.0041 maximum	Five consecutive 24h samples from day before to 3 days post application Systemic doses estimated on total 3,5,6-trichlorochlorpyrifos (TCP) excretion over 3 day post application period.
		Children	50	0.001 geometric mean 0.0063 maximum	
Alexander B.H., et al (2007) [68] 2,4-D	Farm Family Exposure Study 0.00246 geometric mean 0.00928 75th percentile 0.02399 90th percentile 0.05848 maximum	Spouses	34	0.00008 geometric mean 0.00016 75th percentile 0.00025 90th percentile 0.00114 maximum	Five consecutive 24h samples from day before to 3 days post application. 2,4-D excreted unchanged in urine (93% clearance).
		Children	53	0.00022 geometric mean 0.00046 75th percentile 0.000107 90th percentile 0.03107 maximum	
Bernard C.E., et al (2001) [69] Chlorpyrifos	Occupational exposure not reported (Pesticide applied by custom applicator at low pressure)	Female (Jazzercise activity)	5 (whole body covered)	0.0011 mean	Exposure started 3h post application. Urine collected for 5 days after 20 minute exposure period. Daily 3,5,6-trichlorochlorpyrifos (TCP) clearance estimated
			6 (1 piece dance suit)	0.0015 mean	
			11 (2 piece dance suit)	0.0014 mean	

Fenske R.A. et al (2000) [70] Azinphos-methyl/phosmet	Study undertaken in agricultural region surrounding Wenatchee, Washington, U.S.A. Occupational exposure not reported	Children (of operators)	49	0.0054 ± 0.0062 mean ± SD 0.0078 75th percentile 0.0153[a] max*	Single voids taken from children on two occasions. The second sample was taken 3-7 days after the first and all within the 6-8 week spraying season. Dialkylphosphate metabolites analysed and data converted to OP concentrations and daily doses. Median dose of children of operators was 4-9x reference children. Estimates for all agricultural children 3-6x higher than reference children.
		Children (of workers)	13	0.0038 ± 0.0044 mean ± SD 0.0045 75th percentile 0.0153 maximum	
		Children (control)	14	0.0035 ± 0.0050 mean ± SD 0.0073 75th percentile 0.015 maximum	
Krieger R.I.and Dinoff T.M. (2000) [71]` Malathion	Date gardens in the Coachella Valley, California, U.S.A. Applicators 1-3	Girl aged 9	1	0.0006	Spot measurements of two children and spouse who lived within the date garden. Urine analysed for dimethylphosphates. No equivalent use of malathion in U.K.
		Boy aged 4	1	0.005	
		Spouse	1	0.004	

* spray season estimates calculated by volume adjusted presented here as these were highest

[a] there appears to be an error in the paper and this value should be 0.029 mg/kg bw/d. In addition, higher maximum values were observed in siblings of the study focus children up to 0.036 mg/kg bw/d, and up to 0.072 mg/kg bw/d for single day samples.