I·I·A·C·

INDUSTRIAL INJURIES ADVISORY COUNCIL

POSITION PAPER 19

PESTICIDES and PARKINSON'S DISEASE

www.iiac.org.uk

INDUSTRIAL INJURIES ADVISORY COUNCIL

Professor A J NEWMAN TAYLOR, CBE, FRCP, FFOM, FMedSci (Chairman)

Dr J ASHERSON, BSc, D Phil, MBA, MIOSH

Professor M AYLWARD, CB, MD, FRCP, FFPM, FFOM, DDAM

Professor M G BRITTON, MD, MSc, FRCP, Dip(Ind. Health)

Dr A COCKCROFT, MD, FRCP, FFOM, MB BS

Mrs D KLOSS, LLB, LLM

Dr I J LAWSON, MB BS, DRCOG, CMIOSH, FFOM, FACOEM

Mr S LEVENE, MA

Dr K PALMER, MA, MSc, DM, FFOM, FRCP, MRCGP

Mr H ROBERTSON

Dr A SPURGEON, BSc, PhD, C. Psychol

Ms C SULLIVAN, MA, GradDipPhys, MCSP

Mr A TURNER, TechSP

Mr F M WHITTY, BA

Dr L WRIGHT, BMedSci, BMBS, FFOM

Previous Council Members

MR J PRESTON-HOOD, MBA, DipHS, CMIOSH

Parkinson's Disease and Pesticide Exposure

Position Paper 19

Summary

- There is a growing body of literature which suggests that exposure to pesticides may have a role in the causation of Parkinson's disease (PD). A Council member drew the Council's attention to this literature and to recent reports in the media on the subject. This paper considers the case for prescription of PD associated with occupational exposure to pesticides.

- The Council noted that a comprehensive review of the literature had been commissioned by the Department for Environment, Food and Rural Affairs (DEFRA) Advisory Group on Pesticides and completed by the Medical Research Council's (MRC) Institute for Environment and Health in 2003. The conclusion of this review was that the weight of evidence favoured an association between pesticide exposure in general and PD, but was insufficient to indicate a causal relationship. The Council considered the evidence and the conclusions of the MRC review, and also evaluated evidence published subsequently between 2003 and 2007.

- A total of 54 relevant epidemiological studies published between 1983 and 2007 were identified, including five cohort studies, 41 case-control studies and eight further descriptive studies.

- The results of the cohort studies indicate that employment in certain occupations involving pesticide exposure may increase the risk of PD. However, they do not consistently indicate a sufficiently elevated level of risk to support the case for prescription. Similarly, while a number of case-control studies suggest an association between pesticide exposure and PD, few indicate a risk which is more than doubled. In addition, few studies have examined the level or duration of exposure which might be associated with an effect, thus there is only limited information on this aspect.

- A number of methodological difficulties were noted which might account for the observed inconsistency in findings, notably variation in diagnostic criteria for PD, limitations in exposure assessment and variable adjustment for other potential risk factors. In particular, there is evidence for an association between PD and rural living and between PD and well water consumption. The role of these factors in the causation of PD and the nature of their relationship with pesticide exposure is currently unclear.

- In most studies exposure was assessed without reference to specific pesticides or groups of pesticides. The authors of the MRC review drew attention to the wide range of compounds subsumed under the term 'pesticide' and noted the biological implausibility of a common toxicological action occurring across all

pesticides. However, it is not possible from current evidence to identify the specific pesticides, if any, which may be involved in the causation of PD.

- On balance the Council has concluded that current evidence, while suggestive of a role for some pesticides in the causation of PD, is insufficient to recommend prescription. However, this is an active field of research and the Council will continue to monitor the emerging literature on the subject.

Introduction

The Industrial Injuries Disablement Benefit Scheme

1. The Industrial Injuries Advisory Council (IIAC) is an independent statutory body set up in 1946 to advise the Secretary of State for Social Security on matters relating to the Industrial Injuries Scheme. The major part of the Council's time is spent considering whether the list of prescribed diseases for which benefit may be paid should be enlarged or amended.

2. The Industrial Injuries Disablement Benefit (IIDB) Scheme provides a benefit that can be paid to an employed earner because of an industrial accident or Prescribed Disease.

The legal requirements for prescription

3. The Social Security Contributions and Benefits Act 1992 states that the Secretary of State may prescribe a disease where s/he is satisfied that the disease:
    a. ought to be treated, having regard to its causes and incidence and any other relevant considerations, as a risk of the occupation and not as a risk common to all persons; and
    b. is such that, in the absence of special circumstances, the attribution of particular cases to the nature of the employment can be established or presumed with reasonable certainty.
4. In other words, a disease may only be prescribed if there is a recognised risk to workers in an occupation, and the link between disease and occupation can be established or reasonably presumed in individual cases.
5. In seeking to address the question of prescription for any particular condition, the Council first looks for a workable definition of the disease. Then it searches for a practical way to demonstrate in the individual case that the disease can be attributed to occupational exposure with reasonable confidence. For this purpose, reasonable confidence is interpreted as being based on the

balance of probabilities according to available scientific evidence. If the condition might result from occupational exposure in the absence of an identifiable accident, the Council must consider whether it should be included in the list of diseases that are prescribed for benefit purposes. In these circumstances, it may be possible to ascribe a disease to a particular occupational exposure in two ways – from specific clinical features of the disease or from epidemiological evidence that the risk of disease is at least doubled by the relevant occupational exposure.

Clinical features

6. For some diseases attribution to occupation may be possible from specific clinical features of the individual case. For example, the proof that an individual's dermatitis is caused by his/her occupation may lie in its improvement when s/he is on holiday, and regression when s/he returns to work, and in the demonstration that s/he is allergic to a specific substance with which s/he comes into contact only at work. It can be that the disease *only* occurs as a result of an occupational hazard (e.g. coal workers' pneumoconiosis).

Doubling of risk

7. Other diseases are not uniquely occupational, and when caused by occupation, are indistinguishable from the same disease occurring in someone who has not been exposed to a hazard at work. In these circumstances, attribution to occupation on the balance of probabilities depends on epidemiological evidence that work in the prescribed job, or with the prescribed occupational exposure, increases the risk of developing the disease by a factor of two or more. The requirement for, at least, a doubling of risk is not arbitrary. It follows from the fact that if a hazardous exposure doubles risk, for every 50 cases that would normally occur in an unexposed population, an additional 50 would be expected if the population were exposed to the hazard. Thus, out of every 100 cases that occurred in an exposed population, 50 would do so only as a consequence of their exposure while the other 50 would have been expected to develop the disease, even in the absence of the exposure. Therefore, for any individual case occurring in the exposed population, there would be a 50% chance that the disease resulted from exposure to the hazard, and a 50% chance that it would have occurred even without the exposure. Below the threshold of a doubling of risk only a minority of cases in an exposed population would be caused by the hazard and individual cases therefore could not be attributed to exposure on the balance of probabilities. The epidemiological evidence required should ideally be drawn from several independent studies, and be sufficiently robust that further research at a later date would be unlikely to overturn it.

Background to the review

8. Concerns about a possible relationship between pesticides and Parkinson's Disease (PD) was highlighted by a Council member following reports in the media of an excess of cases of PD associated with pesticide exposure.

9. The subject was discussed at a meeting of IIAC's Research Working Group (RWG) in January 2007. It was noted that the Medical and Toxicology Panel of the Advisory Committee on Pesticides (ACP)[1] regularly monitors the scientific literature relating to the human health effects of pesticides, in order to assess any potential implications for pesticide regulation. Where appropriate ACP initiates detailed scientific reviews and one such review, on the possible association between pesticide exposure and PD, was commissioned in February 2003 and was undertaken by the Medical Research Council (MRC) Institute for Environment and Health. This detailed critical review considered the epidemiological and toxicological literature relating to this subject published between 1983 and 2003.[2]

10. The review identified fairly consistent evidence of an excess risk of PD associated with exposure to pesticides, although in many reports this risk was not more than doubled. An association was also found with rural living, a potential confounder of the relation between PD and work with pesticides. The RWG noted that the most recent national Decennial Supplement did not show an excess mortality from PD in farmers relative to social class peers.

11. The authors of the MRC review also noted that the association with PD was not restricted to any particular pesticide or class of pesticide. They expressed doubts as to how different types of pesticides, which act in different ways, could produce a shared causal mechanism leading to the development of PD.

12. The MRC review concluded that the weight of evidence indicated a general association between pesticide exposure and PD, but was insufficient to confirm a causal relationship. It was also insufficient to indicate a causal relationship between PD and a particular pesticide compound or combined pesticide or other toxin exposure.

13. These conclusions suggested that the existing evidence was unlikely to provide a sufficient basis for prescription of PD following pesticide exposure. However, this remains a complex subject and is an active area of research. IIAC therefore decided to carry out a further investigation of the evidence, including both a review of the MRC findings and an evaluation of new research published since 2003.

---

[1] An advisory committee of the Pesticides Safety Directorate, an Executive Agency of DEFRA.

[2] Full report posted October 2005 at, http://www.le.ac.uk. Abridged version published as: Brown TP, Rumsby PC, Capleton AC, Rushton L, Levy LS. 'Pesticides and Parkinson's Disease – Is there a link?' Environmental Health Perspectives 2006;114(2):156-64.

Parkinson's Disease

14. Parkinson's Disease is a disease of the nervous system with no established cause. It has an estimated prevalence of 1.8% in persons over the age of 65 years and an incidence of approximately 16-19 cases per 100,000 per year. Diagnosis depends on the presence and progression of clinical signs and symptoms, notably tremor, bradykinesia (slow movements), rigidity and postural instability. Diagnosis in life is not always straightforward and misdiagnosis has been shown to be common, particularly in the early stages of the disease (Litvan *et al* 1996). Diagnosis can, however, be confirmed at autopsy since a major pathological feature of PD is the loss of neurones related to the chemical neurotransmitter, dopamine, situated in a part of the brain which controls voluntary movement. It has been shown that clinical signs tend to emerge once approximately 70-80% of these neurones have been lost.

15. The cause of PD is uncertain but is thought to be multifactorial. There is some evidence that genetic factors may influence the risk of the disease, particularly in the case of young onset PD (before the age of 50 years), which is relatively rare. Twin studies have shown 100% concordance in the occurrence of young onset PD in identical twins and 16% concordance in non-identical twins. Genetic factors appear to play a lesser but contributory role in older onset disease. For example, concordance rates for any-age onset PD have been shown to be more similar in identical twins (16%) and non-identical twins (11%). If genetic factors were of major importance, one would expect a much higher concordance rate in identical twins, whereas similar rates may arise through shared environmental exposures.

16. Several factors have been shown to induce a form of parkinsonism which is clinically and pathologically similar to those cases where the cause is unknown. These factors include head trauma, strokes and occupational exposure to manganese. Central nervous system toxicity characterised by Parkinsonism as a result of exposure to manganese is currently prescribed under conditions due to chemical agents (Prescribed Disease C2).

17. It has also been noted that caffeine consumption and smoking appear to offer a degree of protection from the development of PD. A recent meta-analysis indicated that the risk of PD was 30% less amongst coffee drinkers and 60% less amongst smokers (Hernán *et al* 2002).

18. Abuse of the drug 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) has been shown to result in acute parkinsonism in addicts. This last observation raised concerns that exposure to certain pesticides may also lead to PD, since the metabolite of MPTP is structurally and toxicologically similar to certain pesticides such as rotenone and paraquat. As a result, a number of toxicological and epidemiological studies have been carried out to investigate the possible association between pesticide exposure and PD.

Evaluation of the literature

19. There is an extensive epidemiological literature on this subject. The MRC review, which considered studies up to 2003, reported on 49 epidemiological studies which investigated the possible association between pesticide exposure and PD. The majority of these (38 studies) were case-control studies which considered either the relationship between pesticides in general and PD, or specified exposure either to fungicides, herbicides or insecticides. In addition there were three cohort studies, and a further eight descriptive studies which formally examined the relationship between pesticides and PD (three mortality studies, three prevalence studies, one incidence study and a case series). Finally several meta-analyses of case-control studies have been carried out to examine associations between PD and agricultural employment and aspects of rural living (Priyadarshi *et al*, 2000, 2001).

20. The Council also conducted its own literature search in order to identify studies published from 2003 to 2007. Two further cohort studies and two further case-control studies were found, together with two reports relating to an on-going European multicentre case-control study (the 'Geoparkinson study').

21. In order to evaluate this large dataset and to consider the case for prescription, the Council has focussed on a number of specific questions. First, is there convincing evidence, derived from a number of high quality studies, to indicate an increased risk of PD which was more than doubled in those with pesticide exposure? Second, can the exposure of interest be defined, not only in terms of its level and duration but also, importantly, in terms of the specific compound(s) involved? As noted above, the term 'pesticide' covers a large number of substances which may be classified as either insecticides, herbicides or fungicides, or alternatively in terms of whether they are organochlorine-based or organophosphate-based. In addition, a number of different compounds are contained within each of these groups. The authors of the MRC review noted the biological implausibility of the same or similar effects occurring across all substances referred to as 'pesticides'. Thus the specific nature of the exposure in any particular study is of central importance. Finally, how far may the results of certain studies reflect the influence of other potential risk factors, notably rural living and well-water consumption, for which there would appear to be evidence of an association with PD and which may act as confounders? Several study designs were found in relation to these questions.

Cohort studies

22. In cohort studies individuals with exposure to a particular causative agent, in this case pesticides, are identified, and their subsequent incidence of the disease in question, (PD), is compared to that in an unexposed control population, and a direct estimate of relative risk (RR) is calculated.

23. The largest cohort study, carried out in Denmark, (Tüchsen & Jenson 2000), followed a cohort of over two million men and women for a 13 year period and reported a 'standardised hospitalisation ratio' (SHR) for PD based on the observed versus expected[3] number of admissions to hospital where PD was the primary diagnosis. A statistically significant higher risk of PD was found for male self-employed farmers (SHR 1.30, 95% CI[4] 1.03-1.63) and female self-employed farmers (SHR 1.49, 95% CI 3.1-4.35), although for other occupations involving pesticide use, such as horticulturalists, fruit growers and landscape gardeners, risks were non-significant. In addition, statistically significant risks were also identified for a range of other occupations such as lawyers, psychologists, welfare staff, transport staff and laundry workers where pesticide exposure was presumably absent or very low.

24. An American study, (Petrovitch *et al* 2002), utilised a cohort of nearly 8000 Hawaiian men of Japanese origin, born between 1900 and1919 who were enrolled in a study of genetic and environmental risk factors for cardiovascular disease. During the follow-up period, which ran from enrolment in 1965 until the end of 1996, there were 116 diagnosed cases of PD. After adjustment for age the incidence of PD was found to increase significantly with increasing number of years of plantation work. In those employed in such work for more than 20 years the risk was double that in those who had never worked in plantations. The authors note, however, that no distinction could be made between different types of plantation work involving different types of pesticides and that for 15% of the population no exposure information was available.

25. A further study, (Ascherio *et al* 2006), employed a cohort of more than 143,000 participants enrolled in an on-going USA Cancer prevention study. At nine year follow-up 413 newly diagnosed cases of PD were found. Those who reported regular, current or past exposure to pesticides or herbicides at enrolment had a statistically significant increase in risk of PD (RR 1.7, CI 1.2-2.3).

26. In each of the above studies PD was confirmed by physician diagnosis. However, although this is more reliable than self-report of disease, it does not necessarily imply accuracy of case definition since diagnostic criteria may vary between physicians and, as noted above, misdiagnosis has been shown to be common. In addition, strict adherence to physician-based diagnosis may sometimes lead to an underestimation of cases. In the Ascherio study, for example, 20% of subjects reporting PD refused confirmatory access to their medical records and were thus excluded from the analysis. The authors noted that those refusing record access tended to report higher levels of pesticide exposure and a subsequent analysis which included those subjects resulted in a slightly higher RR of 1.8 (CI 1.4-2.4).

---

[3] Expected on the basis of background rates for economically active individuals.

[4] A 95% confidence interval (CI) represents a plausible range in which the true population value lies, given the extent of statistical uncertainty in the data. A lower confidence limit >1 suggests a positive association that is unlikely to arise simply by chance (less than 1 chance in 20).

27. In contrast to the use of medical diagnosis, two cohort studies (Baldi; Lebailly *et al* 2003; Kamel *et al* 2006) based incidence of PD during follow-up entirely on patient report, with no medical confirmation. In the study by Baldi the cohort consisted of 1507 elderly people assembled from the electoral roles, primarily in order to study functional ageing. Over a six year period 24 cases of PD were reported. Levels of former pesticide exposure were determined according to an expert panel's classification of job categories. In men, the relative risk of PD associated with pesticide exposure was 5.63, although the CI was wide (1.47-21.58). Moreover the relative risk reduced to 2.39 (CI 1.02-5.63) following adjustment for smoking and educational level. No significant association between PD and pesticide exposure was identified in women.

28. Kamel *et al* (2007) studied a cohort of 22,915 licensed pesticide applicators who were a subset of a cohort enrolled between 1993 and 1997 in a US agricultural health study. Self-reported PD (prevalence) and detailed information on pesticide exposure was obtained at enrolment. At follow-up, between 1999 and 2003, 68% of the cohort were interviewed and 78 new incident cases of PD, (self-report of physician diagnosis) were identified. The prevalence of PD at enrolment was not associated with any measure of previous pesticide exposure. The incidence of PD at follow-up showed a tendency to increase with increasing cumulative lifetime days of exposure measured at enrolment. However, the association with PD was statistically significant, and indicated a doubling of risk only in terms of the highest quartile exposure category versus the lowest quartile (Odds Ratio 2.3, CI 1.2-4.5, where the highest quartile was represented by >397 lifetime days of use and the lowest quartile by 0-64 lifetime days of use). None of the other investigated exposure measures (ever used pesticides, personally mixing pesticides, personally applying pesticides, use of personal protective equipment, incident of pesticide medical care) were significantly associated with incidence of PD.

29. In summary, four of the five cohort studies reported a statistically significant association between pesticide exposure and PD. However, the findings were not consistent in terms of identifying an increased risk in all exposed groups, or an increased risk which was exclusively confined to pesticide exposed groups. Three studies reported a doubling of risk although, of these, the studies of Kamel and Baldi, which were reliant on self-reported rather than physician-confirmed diagnosis, had a greater potential for reporting bias (a tendency, for example, for anxious pesticide users to report more symptoms). Two studies, those of Kamel and Petrovitch, suggested a higher risk with longer duration of exposure, although no studies provided information on the type of pesticides likely to have been used.

Case-control studies

30. In case-control studies patients who have been diagnosed with the disease in question, in this case PD, are identified, and their past exposure to possible causal agents, including pesticides, is compared with that of controls who do

not have the disease. From this an odds ratio (OR) is calculated, which is similar to a relative risk for rare outcomes.

31. A number of factors need to be taken into account when interpreting and comparing the results of these studies. As in the case of the cohort studies diagnostic criteria for PD have varied and the potential for diagnostic misclassification cannot be discounted. In addition, exposure classification was inevitably retrospective and potentially subject to errors of recall. In most studies exposure assessment was relatively crude in terms of the substance(s) involved, usually defined simply as 'pesticides' or sometimes more specifically as fungicides, herbicides or insecticides. Few studies distinguished between different pesticide compounds. Most collected some details of exposure duration but tended to use this information to classify patients as exposed or non-exposed, with only a minority of studies investigating possible relationships between cumulative dose and effect. Few reported any assessment of the likely exposure levels. In general, approaches to exposure assessment varied considerably between studies.

32. Methods of data collection were broadly similar, with the majority of studies employing interviews with patients or carers. However, the nature of PD is such that it is difficult for the case-control status of the interviewee to be concealed from the interviewers. In addition, it was often unclear whether the patient was aware of the study hypothesis. This absence of 'blinding' could lead to an overestimate of effect (if, for example, an interviewer probed more carefully for a history of pesticide exposure in cases than in controls, or if motivated cases searched their memories more carefully to recall a past exposure to pesticides than controls did). A minority of studies employed a postal questionnaire, which helped to overcome the problem of interview bias but which tended to result in lower response rates.

33. Studies also varied in terms of the extent to which potentially confounding exposures were taken into account. For example, while the majority of studies used age and sex as matching criteria in control selection, few studies adjusted for the protective effect of smoking in design or analysis.

34. Finally, the authors of the MRC review noted the relatively small sample sizes in many studies, and questioned whether such studies had sufficient power to detect important effects.

35. These various factors may explain the inconsistency in the findings of the case-control studies. In 34 studies where exposure to 'pesticides' (as opposed to specific compounds or groups of compounds) was considered as the exposure category, ORs ranged from 0.75-7.0. (Appendix I). Thirteen of these studies reported an OR which was greater than 2.0. Notably, however, those with larger ORs tended to be small with wide CIs, reflecting a large measure of statistical uncertainty in the true size of effect. A meta-analysis (Priyadarshi *et al* 2000) which included nineteen studies published between 1989 and 1999, indicated a relative risk which was almost doubled (combined OR 1.94, CI 1.49-2.53). However, meta-analysis involves the combination of the results of

a number of studies of similar design in which the assessment of exposure and outcome is also judged to be similar. Interpretation is problematic and less satisfactory when, as in this case, analysis combines the results of studies with different definitions of exposure and which involve several different agents.

36. A similarly inconsistent picture emerged from those studies with separate analyses relating specifically to fungicide, insecticide or herbicide exposure (Appendix II). Five studies focussing on fungicides found no association between exposure and PD, although one, among winegrowers, (Baldi *et al* 2003), in which subjects were predominantly exposed to fungicides but also to some insecticides and herbicides, reported an OR of 2.2 (CI 1.1-4.3).

37. Evidence relating to herbicide exposure was similarly rather weak, with only five of eleven studies reporting a statistically significant association, of which three reported an OR greater than 2.0.

38. Of those ten studies focussing on insecticides, five indicated a statistically significant association between PD and exposure, with four reporting an OR greater than 2.0. In addition, a study which investigated combined exposure to insecticides and fungicides (Duzcan *et al* 2003) reported an OR of 4.52 (CI 1.83-11.2).

39. The availability of such a large dataset and a high degree of inconsistency in the results presents certain difficulties of interpretation. However, studies varied in methodological quality, some providing only limited information on exposure and, in particular, many failing to make adjustments in their analysis for other important risk factors. In addition, many of the studies had small sample sizes, the majority (32 studies) having fewer than 150 cases. The focus below, therefore, is on those studies which appear to be stronger methodologically and on those which attempt to examine exposure-response relationships and thus provide some information on levels of exposure at which effects may occur.

40. Of those studies considered to be methodologically stronger in terms of both exposure assessment and appropriate adjustment for other risk factors, the largest was the multicentre 'Geoparkinson study' (Dick, Seaton, *et al*, 2007), carried out in five European countries, including Scotland. The study included 959 cases of parkinsonism, of which 797 were diagnosed as PD according to the UK Parkinson's Disease Society criteria, and 1989 controls. The adjusted OR for the association between diagnosed PD and pesticide exposure was 1.25 (CI 0.97-1.61), rising to 1.29 (CI 1.02-1.63) when other forms of parkinsonism were included. Subsequent classification in terms of average annual intensity of exposure, derived from a detailed exposure assessment, yielded ORs (all parkinsonism) of 1.13 (CI 0.82-1.57) for low exposure versus no exposure, and 1.41 (CI 1.06-1.88) for high exposure versus no exposure. For diagnosed PD only, ORs were 1.09 (CI 0.77-1.55) and 1.39 (CI 1.02-1.89) respectively. High exposure constituted a median level of 0.019 Occupational Exposure Limit (OEL) units, (range 0.003-0.89), where 0.5 units was equivalent to having worked for 240 days per year at 50% of the UK OEL for the total number of years exposed. In this study risk factors with an OR of more than

two were a family history of PD and a history of loss of consciousness due to accident. Earlier analysis of the data from this study which defined exposure simply in terms of job category showed no association between PD and occupations involving agriculture, fishery or farming (Dick, Semple, *et al* 2007).

41. Other studies judged to be of good quality were those of Semchuk *et al* (1992) in Canada, Seidler *et al* (1996) in Germany and Firestone *et al* (2005) in the USA. Semchuk *et al*, although a relatively small study involving 130 cases and 260 controls, included separate analyses of exposure to herbicides, insecticides and fungicides as well as an analysis of dose-response relationships. Following adjustment for other risk factors, an overall risk of PD with exposure to pesticides yielded an OR of 2.25 (CI 1.27-3.99). However in subsequent analyses of separate groups of pesticides the OR exceeded two only in the case of herbicides (OR 3.06, CI 1.34-7.00). No dose-response relationships in respect of exposure duration were identified, although increased risks were reported with exposure at older ages (46-55 years for insecticides, older than 26 for herbicides). However, the authors noted that very few of their subjects had experienced occupational exposure to pesticides, a factor which might suggest relatively low exposures.

42. Seidler *et al* focussed on cases diagnosed before the age of 65 years (relatively early onset PD) and included 380 cases and 755 controls. The overall increased risk of PD for pesticide exposure was 2.06 (CI 1.62-2.62), although when herbicide and insecticide exposure were considered separately ORs were both less than doubled (1.97 and 1.77 respectively). In each case, however, there was a significant positive trend between risk of PD and exposure duration measured in 'dose-years', assessed by years of exposure combined with category of use (graded as rarely, special circumstances or regular). Presumably those reporting 'regular' exposure were more likely to be occupationally exposed, although the authors note that there was no difference in frequency of farming or agricultural work between cases and controls.

43. Firestone *et al* studied 250 cases and 388 controls, focussing on subjects resident in an urban area. Separate analyses were conducted for those cases (156) reporting occupational as opposed to home-based exposure. No statistically significant increased risk was seen for exposure to pesticides in general or for herbicides or fungicides separately. However, an increased but non-significant risk (OR 2.07, CI 0.67-6.38) was found for the occupational title 'pesticide worker', thus indicating occupational and presumably higher exposure. In addition, a significantly increased risk associated with parathion exposure was noted (OR 8.08, CI 0.92-70.85), based on 6 cases. No increased risks associated with other specific compounds (diazinon, malathion, paraquat) were observed. There was no significant trend with either duration of employment in years or cumulative exposure as measured by number of days exposed per year.

44. Five further studies carried out dose-response analyses. Gorell *et al* (1998) studying 144 cases and 464 controls found a significantly increased risk associated with exposure to herbicides and insecticides. Importantly, in

separate analyses of those occupationally and residentially exposed this association remained only in those occupationally exposed. In addition, for those with more than 10 years exposure to insecticides the OR was 5.81 (CI 1.99-16.97), as compared with an increased but non-significant risk in those with less than 10 years exposure (OR 2.39 CI 0.89-6.40).

45. Liou *et al* (1997), studying 120 cases and 240 controls, also found a statistically significant association between duration of pesticide exposure and PD. However, the association was strongest when paraquat exposure of more than 20 years duration was considered separately. In this study no distinction was made between occupational and residential exposure and there was no indication of exposure level. The remaining three studies, (Chan *et al* 1998, Jiménez-Jiménez *et al* 1992, Zayed *et al* 1990) found no significant associations between duration of exposure to any pesticides and an increased risk of PD.

46. Epidemiological studies which have focused on specific compounds are relatively rare. Original observations of the similarity between the metabolite of MTPT and the herbicide paraquat and the insectide rotenone have prompted a number of studies which investigated the association between PD and exposure to these two compounds. The study by Liou *et al* noted above remains the only one to identify a statistically significant association, namely between PD and paraquat exposure (OR 3.22, CI 2.41-4.31).

47. Overall the results of the case-control studies show an inconsistent but frequently less than doubled risk of PD in relation to pesticides in general, with some studies suggesting that certain classes of pesticides, notably insecticides and herbicides, may have a specific role. However, there is no strong evidence base relating to any particular compound. The evidence relating to risks to exposure level and duration is similarly rather weak. The results of one study (Gorell *et al*) suggested an increased risk with increased duration of exposure, notably occupational exposure which exceeds 10 years. However, these results were not supported by those of other studies that had examined dose-response relationships.

Case-control studies relating to other risk factors

48. A number of studies have identified other risk factors associated with PD, which may be correlated with pesticide exposure, notably rural living, farming and well water consumption. The data, while not wholly consistent, are sufficient to warrant suspicion that these may have a role to play in the causation of PD as independent risk factors and potential confounders. There is currently a dearth of studies which have investigated exposure to pesticides in non-rural areas, such as exposure associated with pesticide manufacture or with urban usage in parks and gardens, which might help to clarify this question.

49. Twenty-three case-control studies investigated the association between PD and rural living, nine of which reported a significant association with six reporting

an OR that was more than doubled. A meta-analysis of sixteen of these studies, (Priyadarshi *et al* 2001), found a combined OR of 1.56 (CI 1.17-2.07). It should be noted, however, that the definition of rural living varied considerably between studies.

50. Twenty studies investigated farming, including living on a farm or exposure to farm animals, as an independent risk factor. Five studies reported a significant association between PD and farming of which four reported an OR greater than two. However, meta-analysis (of 12 studies) yielded a lower combined OR of 1.42 (CI 1.05-1.91). The study by Firestone, (noted above) focussing on urban residents occupationally exposed to pesticides, provides a possible comparator here. For those with the title 'pesticide worker' an OR of 2.07 was reported, although this did not reach statistical significance, suggesting, rather than confirming, a slightly increased risk independent of factors associated with rural living.

51. Twenty-eight studies investigated well-water consumption as a possible risk factor. Nine studies reported a significant association, with five reporting an OR more than two. Meta-analysis of 18 studies yielded a combined OR of 1.26 (CI 0.96-1.64). A recent study, (Wright and Keller-Byrne 2005), which investigated each of these factors found no association between farming or pesticide use (occupational or residential) and PD, but a significant association (OR 7.1 95% CI 2.3-22.1) between PD and well water exposure for more than 40 years versus no well water use. Again, however, the sample size was small. In the considerably larger Geoparkinson study, which reported on well-water exposure as a risk factor, an OR of 1.23 (CI 1.00-152) was found.

Descriptive studies

52. Eight descriptive studies which formally examined the relationship between pesticide exposure and PD were identified in the course of the MRC review. As the authors of the review noted, these studies, which analysed routinely collected data, cannot by themselves provide evidence for a causal association between an exposure and a disease, but rather they provide hypothesis-generating data or additional evidence to support data derived from other purpose-designed studies. In this case evidence from descriptive studies tended to mirror the inconsistency found in the cohort and case-control studies discussed above.

53. A number of studies of this type fall under the heading of 'ecological studies' in that the outcomes and exposures were routinely collected statistics available at a geographical level (e.g. county) but not as paired observations in individuals. Correlations between group averages are sought. However, findings from this type of study give relatively weak evidence on causation since items that are correlated at population level may not be causally related in individuals. (For example PD may be more common in rural areas because countryside residents are more elderly; pesticide usage will be higher in rural areas, but the excess cases of PD may not be in the pesticide users).

54. Two such mortality studies (Vanacore *et al* 1991 in Italy; Ritz & Yu 2000 in the US) used routinely collected information on death certificates and examined associations between PD and agricultural activity in the corresponding geographical areas. Both studies reported an association between PD prevalence and agricultural use of pesticides and herbicides. By contrast Strickland *et al* (1996) in the US, employing the same methodology, found no such association.

55. Bennett *et al* (1988) surveyed the use of agricultural chemicals and the incidence of PD in an area of Canada over an unspecified number of years beginning in 1968. Although the data tended to support an association between rural living and the incidence of PD, there appeared to be no association with the use of any particular chemicals.

56. Barbeau *et al* (1987) studied nine rural regions of Canada, comparing cases of PD (identified from medical records, sales of medication and death certificates) and the sales of agricultural pesticides. A marked variation in PD prevalence rates between the regions was found regardless of the method of case identification and a significant correlation was found between pesticide use and PD prevalence, with one region consistently showing the highest prevalence of PD and the highest usage of various different pesticides.

57. Three further prevalence studies failed to support an association between PD and pesticide exposure. In a study of over three thousand rural inhabitants in the USA, Yesalis *et al* (1985) found that farm workers had a significantly lower prevalence of PD compared with non-farm workers, both during the period when they were still working and after retirement. Engel *et al* (2001) in the US, comparing exposed and non-exposed workers, found no association between PD and exposure to any specific pesticide or class of pesticides. Similarly, Sala *et al* (1999) found no increased risk of PD in workers employed at a factory producing fungicides, compared with non-workers from the same village.

58. Finally Rajput *et al* (1986) reported a case series of 21 patients diagnosed with young onset PD (before the age of 40) and noted that 19 of these patients were born and lived for their first 15 years in a small rural community. However, it was not possible to relate the development of PD specifically to pesticide use. Moreover, the small size of these communities (population 169 or less) suggested genetic factors may have played a role, particularly since the series concerned young onset PD.

Conclusions

59. A large number of studies have been carried out to investigate the possible association between pesticide exposure and PD. However, the evidence provided by these studies, while suggestive of such an association, presents an inconsistent picture. The results of the cohort studies, although indicating that employment in occupations involving pesticide exposure may increase the risk of PD, do not consistently support a doubling of risk. Similarly, while a number of the case-control studies suggest an association between pesticide

exposure and PD, only a minority have reported a two-fold risk. Moreover, very few studies have satisfactorily demonstrated a dose-response relationship. Thus, there is only very limited information about the duration or level of exposure required to produce an effect.

60. In interpreting the results of these different studies a number of factors need to be borne in mind, notably the variations in diagnostic criteria employed to identify cases of PD, inconsistency in adjustment for other potential risk factors and limitations in exposure assessment. In particular, exposure was most frequently assessed without reference to the specific pesticide or class of pesticide involved. Given the wide range of compounds subsumed under the title 'pesticide' the authors of the MRC review noted the biological implausibility of all pesticides having a similar toxicological action.

61. A number of studies have suggested an association between PD and rural living, as well as between PD and well water consumption. It is not clear how far these factors have acted as confounders in studies which identify an association between agricultural employment and PD. The role of such factors in the causation of PD is currently unclear.

62. Overall, therefore, the current evidence is suggestive of a role for some pesticides, or some element of rural living, in the causation of PD. However it is unlikely that all pesticides are implicated, a factor which may help to explain the inconsistency of the current results. At present it is not possible to identify the specific pesticides which may be involved, or the qualifying levels of such exposures, or to exclude confounding by aspects of rural living as another explanation of the findings.

Recommendation

63. The Council has concluded that at present there is insufficient evidence to recommend prescription of PD in relation to pesticide exposure in general since the results of existing studies do not consistently support a doubling of risk. In addition, it is not possible to identify the specific pesticide agents implicated in the causation of PD or to discount the possible role of other factors associated with rural living. However, this is an active area of research and the Council intends to keep the growing body of evidence on this subject under review.

Prevention

64. The contribution from work activities to the overall burden of ill health where pesticide exposure may be a contributory factor is mitigated by legal controls on workers' exposure to pesticides.

65. The Control of Substances Hazardous to Health Regulations 2002 (COSHH) apply to work with hazardous substances. These regulations require that work is not carried out with any substance liable to be hazardous to health unless a suitable and sufficient assessment has been made of the risks created by the

work and measures are taken to prevent exposure as far as is reasonably practicable. Where it is not reasonably practicable to prevent exposures they must be adequately controlled by the use of appropriate work processes, systems and engineering controls and measures, including ventilation systems, to control exposures at source. Suitable personal protective equipment may be used in addition, where adequate control cannot otherwise be achieved.

66. The UK's regulatory regimes for both agricultural and non-agricultural pesticides aim to protect people and the environment. Central to this is the prior approvals regime whereby Government must approve pesticides before they can be sold or used. Part of the approvals process includes stringent requirements for labelling of products. Provided the instructions for use on a product's label are followed using that product should pose no unacceptable risk. It is, therefore, essential that all users should carefully read the label before using or applying such products thereby helping to ensure that they are used safely.

67. Everyone who uses a pesticide has a legal responsibility to ensure that all reasonable precautions are taken to protect the health of people and safeguard the environment. Both employers and employees, who use a pesticide in the course of their business, have a duty to ensure that they give and receive sufficient instruction and guidance. In some situations the law states that users must have an appropriate certificate of competence. These measures ensure that users are competent to carry out the duties they are called upon to perform. Advice to professional pesticide users on how to meet their legal responsibilities and use pesticides safely are given in the statutory 'Code of practice for using plant protection products' and 'The safe use of pesticides for non-agricultural purposes.'

References

- Ascherio A, Honglei C, Weisskopf MG, O'Reilly E, McCullough ML, Calle EE *et al*. Pesticide exposure and risk for Parkinson's disease. Ann Neurol. 2006;60:197-203.
- Baldi I, Lebailly P, Mohammed-Brahim B, Letennur L, Dartigues J-F, Brochard P. Neurodegenrative diseases and exposure to pesticides in the elderly. Am J Epidemiology, 2003;157: 409-414.
- Baldi I, Cantagrel A, Lebailly P, Tison F, Dubroca B, Chrysostome V, *et al*. Association between Parkinson's disease and exposure to pesticides in southwestern France. Neuroepidemiology. 2003;22:305-310.
- Behari M, Srivastava AK, Das RR, Pandey RM. Risk factors of Parkinson's disease in Indian patients. J Neurol Sci. 2001;190:49–55.
- Bennett V, Rajput AH, Uitti RJ. An epidemiological survey of agricultural chemicals and incidence of Parkinson's disease. Neurology. 1998; 38:349.
- Barbeau A, Roy M, Bernier G, Campanella G, Paris S. 1987. Ecogenetics of Parkinson's disease: Prevalence and environmental aspects in rural areas. Can J Neurol Sci 14:36-41.
- Butterfield PG, Valanis BG, Spencer PS, Lindeman CA, Nutt JG. Environmental antecedents of young-onset Parkinson's disease. Neurology. 1993;43:1150–1158.
- Chan DKY, Woo J, Ho SC, Pang CP, Law LK, Ng PW, *et al*. Genetic and environmental risk factors for Parkinson's disease in a Chinese population. J Neurol Neurosurg Psychiatry. 1998;65:781–784.
- Chaturvedi S, Østbye T, Stoessl AJ, Merskey H, Hachinski V. Environmental exposures in elderly Canadians with Parkinson's disease. Can J Neurol Sci. 1995;22:232–234.
- Dick S, Semple S, Dick F, Seaton A. Occupational titles as risk factors for Parkinson's disease. Occ Med. 2007;57:50-56.
- Dick FD, Seaton A, Haites N, Semple S, Dick S, Prescott GJ, *et al*. Environmental risk factors for Parkinson's disease and parkinsonism: the Geoparkinson study. Occup. Environ. Med. 2007; 64:666-672.
- Duzcan F, Zencir M, Ozdemir F, Cetin GO, Bagci H, Heutink P, *et al*. Familial influence on Parkinsonism in a rural area of Turkey (Kizilcaboluk-Denizli): a community-based case-control study. Mov Disord. 2003;18:799–804.
- Engel LS, Checkoway H, Keifer MC, Seixas NS, Longstreth WTJ, Scott KC, Hudnell K, Anger WK, Camicioli R. Parkinsonism and occupational exposure to pesticides. Occup Environ Med. 2001; 58:582-589.
- Fall P-A, Fredrikson M, Axelson O, Granérus A-K. Nutritional and occupational factors influencing the risk of Parkinson's disease: a case-control study in southeastern Sweden. Mov Disord. 1999;14:28–37.
- Falope ZF, Osuntokun BO, Ogunniyi A. Risk factors for Parkinson's disease in Nigerian Africans: a case-control study. J Trop Geograph Neurol. 1992;2:177–180.
- Firestone JA, Smith-Weller T, Franklin G, Swanson P, Longstreth WT, Checkoway H. Pesticides and risk of Parkinson's disease. A population-based case-control study. Arch Neurol. 2005;62(1):91–95.
- Golbe LI, Farrell TM, Davis PH. Follow-up study of early-life protective and risk factors in Parkinson's disease. Mov Disord. 1990;5:66–70.

- Goldman SM, Tanner C. 1998. Etiology of Parkinson's disease. In: Parkinson's Disease and Movement Disorders (Jankovic J, Tolosa E, eds). London, UK:Williams and Wilkins, 133–158.
- Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Richardson RJ. The risk of Parkinson's disease with exposure to pesticides, farming, well water, and rural living. Neurology. 1998;50:1346–1350.
- Herishanu YO, Medvedovski M, Goldsmith JR, Kordysh E. A case-control study of Parkinson's disease in urban population of southern Israel. Can J Neurol Sci. 2001;28:144–147.
- Hernán MA, Takkouche B, Caamano-Isorna F, Gestal-Otero JJ. A meta-analysis of coffee drinking, cigarette smoking and the risk of Parkinson's disease. Annal Neurol. 2002;52;276-284.
- Hertzman C, Wiens M, Bowering D, Snow B, Calne D. Parkinson's disease: a case-control study of occupational and environmental risk factors. Am J Ind Med. 1990;17:349–355.
- Hertzman C, Wiens M, Snow B, Kelly S, Calne D. A case-control study of Parkinson's disease in a horticultural region of British Columbia. Mov Disord. 1994;9:69–75.
- Ho SC, Woo J, Lee CM. Epidemiologic study of Parkinson's disease in Hong Kong. Neurology. 1989;39:1314–1318.
- Hubble JP, Cao T, Hassanein RES, Neuberger JS, Koller WC. Risk factors for Parkinson's disease. Neurology. 1993;43:1693–1697.
- Jiménez-Jiménez FJ, Mateo D, Giménez-Roldán S. Exposure to well water and pesticides in Parkinson's disease: a case-control study in the Madrid area. Mov Disord. 1992;7:149–152.
- Kamel F, Tanner CM, Umbach DM, Hoppin JA, , Alavanja MCR. Blair A. Comyns K Goldman SM, Korell M, *et al*. Pesticide exposure and self-reported Parkinson's disease in the Agricultural Health Studyt. Am J Epdemiol. 2007;165:364-374.
- Koller W, Vetere-Overfield B, Gray C, Alexander C, Chin T, Dolezal J, *et al*. Environmental risk factors in Parkinson's disease. Neurology. 1990;40:1218–1221.
- Kuopio A-M, Marttila RJ, Helenius H, Rinne UK. Environmental risk factors in Parkinson's disease. Mov Disord. 1999;14:928–939.
- Liou HH, Tsai MC, Chen CJ, Jeng JS, Chang YC, Chen SY, *et al*. Environmental risk factors and Parkinson's disease: a case-control study in Taiwan. Neurology. 1997;48:1583–1588.
- Litvan I, Bhatia KP, Burn DJ, Goetz CG, Lang AE, McKieth I, *et al*. SIC Task Force appraisal of clinical diagnostic criteria for Parkinsonian disorders. Mov Disord. 2003; 18:467-486.
- McCann SJ, LeCouteur DG, Green AC, Brayne C, Johnson AG, Chan D, *et al*. The epidemiology of Parkinson's disease in an Australian population. Neuroepidemiology. 1998;17:310–317.
- Menegon A, Board PG, Blackburn AC, Mellick GD, Le Couteur DG. Parkinson's disease, pesticides, and glutathione transferase polymorphisms. Lancet. 1998;352:1344–1346.
- Morano A, Jiménez-Jiménez FJ, Molina JA, Antolin MA. Risk-factors for Parkinson's disease: case-control study in the province of Cáceres, Spain. Acta Neurol Scand. 1994;89:164–170.
- Nelson LM, Van den Eeden SK, Tanner CM, Efird JT, Bernstein AL. Home pesticide exposure and the risk of Parkinson's disease. Neurology. 2000;54:A472–A473.
- Petrovitch H, Ross GW, Abbott RD, Sanderson WT, Sharp DS, Tanner CM, Masaki KH, Blanchette PL, Popper JS, Foley D, Launer L, White LR. 2002. Plantation work and risk of Parkinson disease in a population-based longitudinal study. Arch Neurol 59:1787- 1792.
- Preux PM, Condet A, Anglade C, Druet-Cabanac M, Debrock C, Macharia W, *et al*. Parkinson's disease and environmental factors. Matched case-control study in the Limousin region, France. Neuroepidemiology. 2000;19:333–337.

- Priyadarshi A, Khuder SA, Schaub EA, Priyadarshi SS. Environmental risk factors and Parkinson's disease: a meta-analysis. Environ Res. 2001;86:122–127.
- Priyadarshi A, Khuder SA, Schaub EA, Shrivastava S. A meta-analysis of Parkinson's disease and exposure to pesticides. Neurotoxicology. 2000;21:435–440.
- Rajput AH, Uitti RJ, Stern W, Laverty W. Early onset Parkinson's disease in Saskatchewan: Environmental considerations for etiology. Can J Neurol Sci. 1986; 13:312-316.
- Ritz B, Yu F. Parkinson's disease mortality and pesticide exposure in California 1984-1994. Int J Epidemiol. 2000; 29:323-329.
- Sala M, Sunyer J, Otero R, Santiago-Silva M, Ozalla D, Herrero C, *et al*. Health effects of chronic high exposure to hexachlorobenzene in a general population sample. Arch Environ Health. 1999; 54:102-109.
- Seidler A, Hellenbrand W, Robra B-P, Vieregge P, Nischan P, Joerg J, *et al*. Possible environmental, occupational, and other etiologic factors for Parkinson's disease: a case-control study in Germany. Neurology. 1996;46:1275–1284.
- Semchuk KM, Love EJ, Lee RG. Parkinson's disease and exposure to agricultural work and pesticide chemicals. Neurology. 1992;42:1328–1335.
- Smargiassi A, Mutti A, De Rosa A, De Palma G, Negrotti A, Calzetti S. A case-control study of occupational and environmental risk factors for Parkinson's disease in the Emilia-Romagna region of Italy. Neurotoxicology. 1998;19:709–712.
- Stern M, Dulaney E, Gruber SB, Golbe L, Bergen M, Hurtig H, *et al*. The epidemiology of Parkinson's disease. A case-control study of young-onset and old-onset patients. Arch Neurol. 1991;48:903-907.
- Strickland D, Bertoni JM, Pfeiffer RF. Descriptive epidemiology of Parkinson's disease through proxy measures. Can J Neurol Sci 23:279-284. study in China. Neurology. 1996; 39:660-664.. A case-control study of young-onset and old-onset patients. Arch Neurol. 1991;48:903–907.
- Taylor CA, Saint-Hilaire MH, Cupples LA, Thomas CA, Burchard AE, Feldman RG, *et al*. Environmental, medical, and family history risk factors for Parkinson's disease: a New England-based case control study. Am J Med Genet. 1999;88:742–749.
- Tüchsen F, Jensen AA. Agricultural work and the risk of Parkinson's disease in Denmark, 1981-1993. Scand J Work Environ Health. 2000. 26:359-362.
- Vidal J-S, Elbaz A, Clavel J, Delemotte B, Alpérovitch A, Tzouri C. Exposure to pesticides and Parkinson's disease: a community-based case-control study among a population characterised by a high prevalence of exposure. Mov Disord. 2002;17(suppl 5):S80.
- Vanacore N, Bonifati V, Fabrizio E, Modarelli FT, Meco G. Epidemiologic study of geographical correlation between consumption of herbicides and paraquat and Parkinson's disease (PD) mortality rates in Italy (period 1969 to 1987). Neurology. 1991; 41 (suppl 1):307.
- Vanacore N, Nappo A, Gentile M, Brustolin A, Palange S, Liberati A, Di Rezze S, Caldora G, Gasparini M, Benedetti F, Bonifati V, Forastiere F, Quercia A, Meco G. Evaluation of risk of Parkinson's disease in a cohort of licensed pesticide users. Neurol Sci. 2002. 2; (suppl 2):S119-S120.
- Werneck AL, Alvarenga H. Genetics, drugs and environmental factors in Parkinson's disease. A case-control study. Arq Neuropsiquiatr. 1999;57:347–355.
- Wong GF, Gray CS, Hassanein RS, Koller WC. Environmental risk factors in siblings with Parkinson's disease. Arch Neurol. 1991;48:287–289.

- Wright JM & Keller-Byrne J. Environmental determinants of Parkinson's disease. Arch Environ Occ Health. 2005;60(1):32-38.
- Yesalis III CE, Lemke JH, Wallace RB, Kohout FJ, Morris MC. Health status of the rural elderly according to farm work history: The Iowa 65+ rural health study. Arch Environ Health. 1985; 40:245-253.
- Zayed J, Ducic S, Campanella G, Panisset JC, André P, Masson H, *et al*. Environmental factors in the etiology of Parkinson's disease. Can J Neurol Sci. 1990;17:286–291.
- Zorzon M, Capus L, Pellegrino A, Cazzato G, Zivadinov R. Familial and environmental risk factors in Parkinson's disease: a case-control study in north-east Italy. Acta Neurol Scand. 2002;105:77–82.

APPENDIX I

Case-control studies: 'Pesticide' exposure and risk of PD

Study	OR (95% CI)
Ho *et al* (1989)	3.6 (1.0, 12.9)
Golbe *et al* (1990)	7.0 (1.61, 63.46)
Hertzman *et al* (1990)	6.64 (1.29, 34.12)
Koller *et al* (1990)	1.05 (0.66, 1.70)
Zayed *et al* (1990)	1.23 (0.46, 3.29)
Stern *et al* (1991)	0.79 (0.53,1.18)
Wong *et al* (1991)	1.0 (0.33, 3.06)
Falope *et al* (1992)	1.23 (0.35, 4.34)
Jiménez-Jiménez *et al* (1992)	1.34 (0.85, 2.13)
Semchuk *et al* (1992)	2.25 (1.27, 3.99)
Hubble *et al* (1993)	3.42 (1.27, 7.32)
Hertzman *et al* (1994)	1.72 (0.98, 3.03)
Morano *et al* (1994)	1.73 (0.98, 3.02)
Chaturvedi *et al* (1995)	1.81 (0.92, 3.3)
Seidler *et al* (1996)	2.06 (1.62, 2.62)
Liou *et al* (1997)	2.89 (2.28, 3.66)
Chan *et al* (1998)	0.75 (0.26, 2.22)
McCann *et al* (1998)	1.2 (0.8, 1.5)
Menegon *et al* (1998)	2.3 (1.2, 4.4)
Smargiassi *et al* (1998)	1.15 (0.56, 2.36)
Fall *et al* (1999)	2.8 (0.89, 8.7)
Kuopio *et al* (1999)	1.02 (0.63, 1.65)
Taylor *et al* (1999)	2.49 (0.53, 13.14)
Werneck & Alvarenga (1999)	1.9 (1.3, 2.9)
Nelson *et al* (2000)	1.34 (0.85, 2.10)
Preux *et al* (2000)	6.34 (0.75, 53.8)
Herishanu *et al* (2001)	1.7 (1.1, 2.8)
Vidal *et al* (2002)	1.6 (1.0, 2.4)
Zorzon *et al* (2002)	2.96 (1.31, 6.69)
Duzcan *et al* (2003)	1.01 (0.53, 1.92)
Baldi *et al* (2003)	2.2 (1.1, 4.3)
Firestone *et al* (2005)	1.01 (0.53, 1.92)
Dick *et al* (2007)	1.25 (0.97, 1.61)
Wright & Keller-Byrne (2006)	1.2 (0.3, 4.8)

APPENDIX II

Case-control studies: Fungicide, herbicide and insecticide exposure and risk of PD

Study	Exposure	OR (95% CI)
Semchuk *et al* (1992)	fungicides	1.63 (0.81, 3.29)
Hertzman *et al* (1994)	fungicides	1.04 (0.49, 2.24)
Gorell *et al* (1998)	fungicides	1.6 (0.47, 5.45)
Kamel *et al* (2001)	fungicides	0.4 (0.2, 0.8)
Baldi *et al* (2003)	mainly fungicides	2.2 (1.1, 4.3)
Firestone *et al* (2005)	fungicides	0.38 (0.07, 4.1)
Stern *et al* (1991)	herbicides	0.9 (0.6, 1.5)
Semchuk *et al* (1992)	herbicides	3.06 (1.34, 7.00)
Butterfield *et al* 1993)	herbicides	3.22 (2.51, 4.12)
Hertzman *et al* (1994)	herbicides	1.02 (0.50, 2.07)
Seidler *et al* (1996)	herbicides	1.97 (1.40, 2.79)
Gorell *et al* (1998)	herbicides	4.10 (1.37, 12.24)
Kuopio *et al* (1999)	herbicides	1.40 (0.79, 2.48)
Taylor *et al* (1999)	herbicides	1.06 (0.68, 1.65)
Nelson *et al* (2000)	herbicides	1.9 (1.05, 3.4)
Behari *et al* (2001)	herbicides	0.50 (0.28, 0.88)
Firestone *et al* (2005)	herbicides	1.41 (0.51, 3.88)
Stern *et al* (1991)	insecticides	0.5 (0.2, 1.1)
Semchuk *et al* (1992)	insecticides	2.05 (1.03, 4.07)
Butterfield *et al* (1993)	insecticides	4.22 (1.68, 10.58)
Hertzman *et al* (1994)	insecticides	0.62 (0.28, 1.3)
Seidler *et al* (1996)	insecticides	1.77 (1.28, 2.43)
Gorell *et al* (1998)	insecticides	3.55 (1.75, 7.18)
Nelson *et al* (2000)	insecticides	2.6 (1.4, 4.8)
Behari *et al* (2001)	insecticides	0.73 (0.45, 1.17)
Kamel *et al* (2001)	insecticides	1.6 (0.5, 5.2)
Duzcan *et al* (2003)	insecticides & fungicides	4.52 (1.83, 11.2)
Firestone *et al* (2005)	insecticides	0.88 (0.44, 1.76)
Hertzman *et al* (1994)	paraquat	1.25 (0.34, 4.63)
Liou *et al* (1997)	paraquat	3.22 (2.41, 4.31)
Kamel *et al* (2001)	paraquat	1.5 (0.7, 3.0)
Kamel *et al* (2001)	rotenone	1.2 (0.4 3.4)
Firestone *et al* (2005)	paraquat	1.67 (0.22, 12.76)

Report published 14th of February 2008