Exposure to pesticides or solvents and risk of Parkinson disease

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ABSTRACT

Objective: To investigate the risk of Parkinson disease (PD) associated with exposure to pesticides and solvents using meta-analyses of data from cohort and case-control studies.

Methods: Prospective cohort and case-control studies providing risk and precision estimates relating PD to exposure to pesticides or solvents or to proxies of exposure were considered eligible. The heterogeneity in risk estimates associated with objective study quality was also investigated.

Results: A total of 104 studies/3,087 citations fulfilled inclusion criteria for meta-analysis. In prospective studies, study quality was not a source of heterogeneity. PD was associated with farming and the association with pesticides was highly significant in the studies in which PD diagnosis was self-reported. In case-control studies, study quality appeared to be a source of heterogeneity in risk estimates for some exposures. Higher study quality was frequently associated with a reduction in heterogeneity. In high-quality case-control studies, PD risk was increased by exposure to any-type pesticides, herbicides, and solvents. Exposure to paraquat or maneb/mancozeb was associated with about a 2-fold increase in risk. In high-quality case-control studies including an appreciable number of cases (>200), heterogeneity remained significantly high (>40%) only for insecticides, organochlorines, organophosphates, and farming; also, the risk associated with rural living was found to be significant.

Conclusions: The literature supports the hypothesis that exposure to pesticides or solvents is a risk factor for PD. Further prospective and high-quality case-control studies are required to substantiate a cause-effect relationship. The studies should also focus on specific chemical agents.

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GLOSSARY

β-HCH = β-hexachlorocyclohexane; **CI** = confidence interval; **DDT** = dichloro-diphenyl-trichloroethane; **NOS** = Newcastle-Ottawa Scale; **OR** = odds ratio; **PD** = Parkinson disease; **RR** = relative risk.

Parkinson disease (PD) is regarded mainly as a sporadic disorder of multifactorial origin.[1] Besides age and family history, a number of potential contributing factors, such as comorbidities (e.g., diabetes, hypertension) and lifestyle habits (e.g., dietary pattern, smoking), have been identified.[2–7] Also, the role of living and working environments has been considered to be of great significance. The first demonstration that the active metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine can cause a subacute form of parkinsonism[8] aroused considerable interest in the role of some organic pollutants, such as pesticides. The same applied to solvents,[9] compounds that seem also to be responsible for earlier onset and more severe symptoms.[10] In vitro and in vivo studies have demonstrated their toxic effects on dopaminergic pathways,[11–13] and recent evidence supports gene-based susceptibility.[14]

Preliminary meta-analyses published more than 10 years ago suggested that exposure to pesticides or related proxies (e.g., rural living or farming) may be a risk factor for developing PD.[15,16] Similar findings on pesticides and related subcategories (herbicides and insecticides) have been confirmed recently.[17] This study also investigated different sources of heterogeneity in risk estimates (exposure assessment, occupational exposure, multiple adjustment, source of controls, geography). However, the effect of overall objective quality of the studies has never been considered.[15–17] Moreover, no

Supplemental data at www.neurology.org

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updated information on the risk associated with solvents, specific compounds, and proxies of exposure is available.

Since information on the etiology of PD may improve health prevention policies, the aim of this study was to investigate the epidemiologic relationship between PD and exposure to pesticides and solvents by means of a meta-analysis.

METHODS

Data reporting of the present systematic review and meta-analysis was performed in agreement with the PRISMA guidelines.[18] The protocol was approved by the ethics committee of the Parkinson Institute.

Literature search and study inclusion criteria. A literature search for all English-language manuscripts published up to late December 2011 was performed independently by the authors. Queried databases were PUBMED (accessed December 19, 2011–from 1975), EMBASE, and CINAHL (accessed December 23, 2011–from 1978).

The search strategy (appendix e-1 on the *Neurology*® Web site at www.neurology.org) included terms (free text or MeSH terms adapted to the requirements of each database) for both environmental and occupational exposure to pesticides or solvents and PD. References to eligible articles were also searched for additional reports. Both prospective and case-control original studies were eligible for inclusion. Studies addressing fetal or early-life (childhood) exposure were not candidates for a more thorough review. Investigations using mortality data (for case identification of ascertainment of PD) were also excluded because PD may be frequently underdeclared in death certificates and mortality rates in PD may be different from those in the general population. Manuscripts were reviewed independently by the authors and initially selected on the basis of the title and abstract. Any discrepancies were resolved by joint evaluation of the manuscript.

Data extraction. To be included in the quantitative analyses (meta-analysis), articles had to report at least one risk value (relative risk [RR]) or odds ratio (OR) and a precision estimate (95% confidence interval [CI]) relating exposure to organic pollutants (pesticides, herbicides, insecticides, fungicides, rodenticides, solvents) or proxies of exposure (occupation, rural living, well water drinking) to PD or enough data to calculate them. Estimates for specific single compounds (e.g., paraquat) or subgroups of compounds (e.g., organochlorines) with an established literature background were also considered. Authors of investigations were contacted for further information, as appropriate. Fully adjusted estimates were preferably included and analyzed. For case-control studies providing estimates related to different control groups, we included only risks computed for community/regional controls or healthy subjects. Any-type exposure estimates were considered when more than one risk was computed according to the type of exposure (any kind of exposure, occupational, or home-based/environmental); otherwise, we used the estimate for occupational exposure. This decision was made also because type of exposure does not seem to be a source of heterogeneity.[17] From studies providing risks according to genotype, we extracted estimates for low-risk genotype carriers. Estimates based on self-reported exposures were preferred to those derived from proxy respondents. Data from duplicate publications or by the same authors in the same cohorts were removed and only one estimate was retained in the analyses, using the highest adjustments and largest sample size. Other abstracted data included study population characteristics, adjustment variables, and potential for bias. We also reviewed the sources of funding. Any discrepancies were resolved by discussion.

Quality assessment. The quality of each study was assessed independently using the Newcastle-Ottawa Scale (NOS).[19] The NOS assigns a maximum of 9 points to studies of the highest quality according to 3 parameters of quality: selection (4 points), comparability (2 points), and exposure (case-control studies) or outcome (cohort studies) (3 points). Any discrepancies were addressed by a joint re-evaluation of the article.

Data analyses. Data from prospective and case-control studies were analyzed separately. Pooled estimates were computed when the number of studies permitted. When a study provided only separate risks for subgroups of patients (e.g., according to sex or dose exposure), the within-study pooled estimate of subgroups was included in the analyses. When studies provided estimates only for single compounds or groups of them, these risks were not pooled with those of the higher-order reference chemical category. This choice was made in order to prevent the risk associated with a single compound (or group of compounds) from leading to an imbalance in the estimation of the risk associated with the exposure to a broad and not well-defined category of compounds, regardless of the type of association with PD. Moreover, we believed that this choice would enable us to detect any differences in risk and resulting heterogeneity among different exposures.

Presence of heterogeneity between studies was assessed using Cochran Q and I^2 statistics. To compensate for potential between-study heterogeneity, we calculated a pooled risk using a random-effect model.[20] Therefore, heterogeneity in risk estimates according to study quality (NOS score) was explored by meta-regression and stratified analysis whenever the number of studies permitted. In respect to this feature, strata were arbitrarily created according to an NOS score of ≥ 7 points (highest tertile vs the others).

Since positive studies are more likely to be published than negative ones and the evaluation of a funnel plot is subjective, the Duval and Tweedie nonparametric trim-and-fill procedure was used to address publication bias among high-quality studies.[21] This method assumes that the effect sizes of all the studies distribute normally around the center of a funnel plot; if asymmetry is found, it adjusts for the potential effect of nonpublished (imputed) studies.

All analyses were performed using Comprehensive Meta-Analysis, version 2.2.064 (Biostat, Englewood, NJ), establishing the level of significance at a 2-tailed $p < 0.05$.

RESULTS

Search results. A total of 104 articles were selected for qualitative assessment,[22–40,e1–e85] and 89 were included in meta-analysis, providing data on 6 prospective investigations[22–27] and 83 case-control comparisons.[26,29–31,33–36,38,e5,e7,e9–e17,e19–e21,e23–e27,e30–e38,e42,e44–e61,e63,e64,e66–e69,e71–e74,e76,e78–e80,e82–e85] Reasons for exclusion were not enough data available for risk calculation[e29,e43]; estimates provided for cumulative (1-year increase) exposure[e22]; exposure assessed by serum evaluation[e65,e77,e81]; and duplicate data.[e32,e-7,e6,e8,e18,e28,e39,e62,e70,e75] The literature search flow is shown in figure e-1.

Characteristics of cohort and case-control studies. A summary of the evidence reported by the studies undergoing qualitative assessment is presented in table e-1. Detailed descriptive data from cohort and

case-control studies are presented in tables e-2 and e-3, respectively.

Quality assessment results. According to the NOS, the most common bias in prospective studies was the ascertainment of exposure; exposures were assessed mainly (97%) by self-administered questionnaires. Moreover, initial assessment of outcome (PD) relied on self-reported data in 50% of studies.[24–26]

In case-control studies, the most common selection bias was the inclusion of non-community controls (57%). The most common exposure biases were no secure or blind ascertainment (78%) and no definition of response rates (percentage of subjects included compared to those contacted) or different (>15%) response rates between cases and controls (85%).

Outcome results from cohort studies. In 5 studies,[23–27] the association between pesticides and PD was marginal (RR = 1.26 [95% CI 0.89–1.78]; $z = 1.297$, $p = 0.194$; $I^2 = 52.9\%$, $p = 0.075$). Two studies collected data on exposure to solvents[25,27] and both reported no association.

With respect to proxies of exposure to pollutants, 3 studies investigated the role of employment in agricultural jobs. The pooled estimate for risk of PD was RR = 1.33 (95% CI 1.14–1.56); $z = 3.555$, $p < 0.001$; $I^2 = 0.0\%$, $p = 0.964$. Only one study reported no association with rural living.[24]

Study quality did not appear to be a source of heterogeneity among studies addressing exposure to pesticides. However, heterogeneity was associated with the ascertainment of PD (for meta-regression, $p = 0.005$; figure e-2). Accordingly, risk was increased in studies in which PD relied on self-reported diagnosis confirmed by the treating neurologist.[24–26] Sensitivity analyses, based on studies recording >100 incident cases, confirmed the risk associated with agricultural jobs.[22,23] There was no publication bias.

Outcome results from case-control studies. In primary analyses including all studies (table 1), PD was associated with exposure to any-type pesticides, herbicides, insecticides, and solvents; the increase in risk ranged between 33% and 80%. No association was observed with fungicides, rodenticides, organochlorines, and organophosphates. Regarding specific chemicals, we observed about a 2-fold increase in risk for exposure to paraquat, while no association was found with exposure to dichloro-diphenyl-trichloroethane (DDT) or to maneb or mancozeb. Finally, PD was associated with any of the proxy conditions of exposure to organic pollutants investigated. The increase in risk ranged between 30% and 34%.

Mild to moderate significant heterogeneity in study results was detected for a large part of the exposures. The overall quality of the studies included appeared to be a source of heterogeneity for some of them (table 1). Higher study quality (NOS ≥ 7) was frequently associated with a reduction in heterogeneity. This was statistically significant for the exposure to solvents, paraquat, and well water drinking. However, high quality also frequently resulted in a reduction in risk of PD. In particular, exposure to insecticides, farming, and well water drinking was no longer associated with PD. Conversely, high quality resulted in an increase in risk of PD for exposure to solvents (+30%) (figure e-3).

In most cases, analyses based on high-quality studies revealed the absence of publication biases (table 2). After adjusting for publication bias, the association with pesticides was slightly attenuated. All the other relationships were confirmed.

Finally, in sensitivity analyses on high-quality studies including an appreciable number of cases (≥200), heterogeneity remained high (>40%) only for insecticides (70.4%), organochlorines (61.3%), organophosphates (77.9%), and farming (57.9%). The risks of PD remained mainly unchanged except for the risk related to rural living, which became significant (1.51 [1.13–2.03]; $z = 2.771$, $p = 0.006$; $I^2 = 0.0\%$, $p = 0.388$).

OTHER OBSERVATIONS

Exposure to multiple compounds or dose-dependent effect. All available studies focusing on a dose-dependent effect reported a higher risk for exposure to an increasing number of compounds[e98,e102,e104,e125] or for cumulative lifetime exposures.[26,37,39,e11–e13,e15,e33,e45,e50,e58,e60,e63,e68] However, a meta-analysis was not possible due to differences in the definition/quantification of exposure (e.g., days per year, dose per year, thresholds for cumulative lifetime exposure [hours or years]).

Exposure adjusted by risk genotypes. The modifying effect of genetic susceptibility on risk of PD was investigated by several research groups.[e14,e18,e38,e50,e52,e55,e68,e70,e71,e72,e80] However, the heterogeneity in pollutants (solvents, pesticides, or subgroups of chemicals) and candidate genes and the low study quality did not allow us to provide informative quantitative syntheses. Nonetheless, only 2 studies[e18,e71] identified no interaction with exposure to pesticides (glutathione S-transferases); all the others reported an interaction for both pesticides and solvents. The presence of a low-risk genotype appeared to convey only a marginal risk for positive exposure while a high-risk genotype was responsible for about a 3-fold to 14-fold increase in risk in the studies in which this was quantified.[e14,e37,e38,e50,e52,e55,e72]

Exposure to pollutants by serum evaluation. Three different research groups[e61,e77,e81] investigated the serum levels of persistent contaminants, but data (continuous or categorical variables) could not be meta-analyzed due to different formats in reporting. However,

Table 1 Risks for strata of study quality (by the Newcastle-Ottawa Scale) in case-control studies investigating the association between PD and exposures to pesticides or solvents or proxies of exposure

Exposure	Strata (NOS score)	Studies included, n	sOR (95% CI)	I^2, %	*p* Value[a]
Pesticides	Overall	51	1.76 (1.56–2.04)	67.3	0.433
	<7	33	1.88 (1.52–2.32)	72.2	
	≥7	18	1.58 (1.34–1.86)	45.1	
Herbicides	Overall	19	1.33 (1.08–1.65)	55.0	0.805
	<7	9	1.44 (0.90–2.30)	68.0	
	≥7	10	1.36 (1.11–1.66)	33.3	
Insecticides	Overall	18	1.53 (1.12–2.08)	78.8	0.245
	<7	8	2.03 (1.06–3.89)	79.7	
	≥7	10	1.31 (0.92–1.86)	79.2	
Fungicides	Overall	12	0.97 (0.69–1.38)	35.4	0.597
	<7		1.12 (0.56–1.26)	0.0	
	≥7	75	0.94 (0.61–1.43)	54.2	
Rodenticides	Overall[b]	4	0.99 (0.53–1.66)	0.0	
Solvents	Overall	16	1.35 (1.09–1.67)	35.5	0.025
	<7	10	1.26 (0.92–1.73)	44.9	
	≥7	6	1.58 (1.23–2.04)	0.0	
Organochlorines	Overall[c]	5	1.39 (0.77–2.50)	60.6	
Organophosphates	Overall[d]	7	1.27 (0.82–1.98)	68.9	
Paraquat	Overall	7	2.19 (1.48–3.26)	51.1	0.003
	<7	2	3.22 (2.42–4.30)	0.0	
	≥7	5	1.72 (1.28–2.32)	0.0	
Maneb/mancozeb	Overall[e]	4	1.49 (0.85–2.63)	13.8	
DDT	Overall[e]	5	1.03 (0.80–1.34)	0.0	
Farming	Overall	34	1.30 (1.14–1.49)	43.2	0.171
	<7	19	1.43 (1.18–1.72)	42.7	
	≥7	15	1.18 (0.98–1.43)	44.0	
Well water drinking	Overall	37	1.34 (1.16–1.55)	66.4	0.006
	<7	27	1.53 (1.27–1.84)	67.5	
	≥7	10	1.00 (0.85–1.17)	17.2	
Rural living	Overall	30	1.32 (1.15–1.51)	75.2	0.424
	<7	26	1.35 (1.16–1.58)	76.7	
	≥7	4	1.14 (0.81–1.62)	62.0	

Abbreviations: DDT = dichloro-diphenyl-trichloroethane; NOS = Newcastle-Ottawa Scale; PD = Parkinson disease; sOR (95% CI) = strata odds ratio and 95% confidence interval.
[a] The *p* value from meta-regression represents the *p* value for the *t* test between the 2 statistical analysis strata.
[b] Heterogeneity could not be assessed (NOS <7 in all studies).
[c] Heterogeneity could not be assessed (NOS ≥7 in all studies).
[d] Heterogeneity could not be assessed (NOS <7 in only one study).
[e] Not computed (no heterogeneity).

while one study[e77] reported no association between PD and increasing concentrations of 5 different organochlorine pesticides, including β-hexachlorocyclohexane (β-HCH), the others[e61,e81] observed an increased risk for exposure to β-HCH.

Sources of funding. In all the studies, the sources of funding were health or health-related institutions, private foundations (mainly PD foundations), or government or paragovernment companies. No study acknowledged the involvement of any chemicals manufacturer.

DISCUSSION Exposure to pesticides and solvents appears to be a risk factor for PD. Our evidence also

Table 2 Adjusted risks (Duval and Tweedie nonparametric trim-and-fill procedure: test for publication bias) for exposures reported in high-quality studies

Exposure	Crude OR (95% CI)	Imputed studies, n	Adjusted OR (95% CI)
Pesticides	1.58 (1.34–1.86)	5	1.39 (1.17–1.65)
Herbicides	1.36 (1.11–1.66)	No publication bias	
Insecticides	1.31 (0.92–1.86)	2	1.24 (0.89–1.72)
Fungicides	0.94 (0.61–1.43)	3	0.65 (0.40–1.06)
Solvents	1.58 (1.23–2.04)	No publication bias	
Organochlorines	1.39 (0.77–2.50)	No publication bias	
Organophosphates	1.22 (0.78–1.91)	No publication bias	
Paraquat	1.72 (1.28–2.32)	No publication bias	
Maneb/mancozeb	2.18 (1.19–3.98)	Not computed (only 2 studies available)	
Dichloro-diphenyl-trichloroethane	0.97 (0.66–1.24)	No publication bias	
Farming	1.18 (0.98–1.43)	No publication bias	
Well water drinking	1.00 (0.85–1.17)	No publication bias	
Rural living	1.14 (0.81–1.62)	No publication bias	

Abbreviations: OR (95% CI) = odds ratio and 95% confidence interval.

supports the involvement of specific compounds, such as paraquat, maneb/mancozeb family, as well as proxies of exposure. However, it could be argued that the evidence collected is still limited, or at least inconclusive, because there was no definitive agreement between cohort and case-control studies.

Indeed, most of the evidence found relied on data from case-control studies. To investigate an etiologic relationship, the use of cohort studies is preferable. However, the incidence of PD is low and usually occurs in the elderly; large populations, a large number of cases, and a long follow-up are required to achieve adequate statistical power. Accordingly, most neuroepidemiologists resort to case-control studies, which are practical and, despite their retrospective nature, have the advantage of more detailed exposure assessment.

We have also partly explained the sources of heterogeneity in individual study results. In prospective studies, differences in estimates of exposure to pesticides appeared to depend on the method of ascertainment of PD. This factor is less likely to have been a source of bias in case-control studies because, although different sets of well-accepted diagnostic criteria were used, in most cases secondary causes of PD were excluded in patients recruited at movement disorders clinics. However, we did not assess the effect of this feature and we recognize that this is a possible limitation of our study. Heterogeneity in case-control studies appeared to be due mainly to study quality and size. With respect to study quality, our results are consistent with previous suggestions.[e86] However, the issue of sample size analysis was addressed by only a few authors.[e25,e60,e66,e80] To detect an OR of 2 and an exposure frequency of 20% we calculated that at least 200 case-control pairs would be needed.

A meta-analysis investigating several sources of heterogeneity in risk estimates has recently shown that study design (case-control vs prospective), source of controls (community vs non-community controls), type of exposure (occupational vs non-occupational/others type), adjustment for potential confounders, or geographical area do not appear to be important determinants. Accordingly, no consistent explanation of heterogeneity has been provided. The only factor that appeared to contribute was the method used for exposure assessment, as the use of job title–based exposure matrix resulted in a higher risk than assignment based on self-reported exposure.[17] Unfortunately, this method could not be applied with sufficient accuracy to specific working occupations.

Despite our methodologic approach to quantitative synthesis, notable heterogeneity, probably affecting the evidence of an increased risk associated with exposure, was still present for insecticides, organochlorines, organophosphates, and farming. There are some possible explanations for this observation. With respect to farming, we observed that exposure was assessed either by open questions or by specific industry coding systems. Moreover, the choice of controls may introduce bias. Few studies have considered the effect of geography (area/region of residence; the additional criteria for "comparability" in our quality assessment process) in study design or adjustment of analyses. Regional controls may be preferable for the evaluation of direct exposure but both these and neighboring areas may affect the assessment of risk associated with this proxy measure of exposure. Insecticides are a heterogeneous class of compounds to which most organochlorines and organophosphates belong. Indeed, among organochlorines

the most frequently used insecticide is DDT and the risk associated with this compound was found to be nonsignificant. In some cases, frequency of exposure is low and there may be difficulties in recalling specific product names. Given the advanced age of patients with PD, impairment of cognitive function is possible. Although poor cognition has been considered as an exclusion criterion during recruitment in some studies, only one research group adjusted for this covariate.[e63,e68] Exposure to insecticides also appears to be closely correlated with exposure to herbicides.[16]

Finally, there may be residual confounders that we were not able to address. In some cases, data derived from proxy respondents were pooled with those reported by cases,[29,e10,e44,e51,e79,e84] probably introducing misclassification bias.[e6,e8]

Confounding also could be secondary to the use of protective equipment and compliance with suggested, or even recommended, preventive practices. Only one study addressed this issue.[26] Prevalent exposure was heterogeneous among the populations investigated and was likely to be higher in certain working categories. Inclusion bias should be taken into consideration, because in some studies selection of cases or controls was performed by linking to professional and insurance databases[26,e7,e15,e38,e39,e45,e63,e68,e77,e79,e84] or in geographical areas characterized by extensive use of pesticides. A few studies investigated the role of genetic susceptibility. Although mechanisms of action at the molecular level are largely unknown, there is a growing body of evidence progressively substantiating the hypothesis of a gene–environment interaction.[14] Finally, positive exposure was defined according to different levels (e.g., number of chemicals or times of usage over a period), types (particularly for toxin application), or durations.

The present study highlights unresolved issues with implications for health policies. From a preventive perspective, we observed that the route of exposure (e.g., inhaled or transcutaneous) and the method of toxin application (e.g., spraying or mixing) has never been investigated. Risk appears to increase as the duration of exposure increases. Since several compounds are likely to be used by the same people, different routes of exposure may act synergistically in increasing the risk. Unfortunately, it was not possible to investigate the issue of a dose–response relationship and to provide a cutoff for exposure.

The literature supports the hypothesis that exposure to pesticides or solvents is a risk factor for PD. However, further prospective and high-quality case-control studies are required to substantiate a cause-effect relationship. Although some compounds have been withdrawn from the market in industrialized countries, they are still in use in developing parts of the world. According to our review of the sources of funding, interest in this issue should come also from chemicals manufacturers. This should be emphasized because an interest in the adverse effects of specific compounds appears justified.

AUTHOR CONTRIBUTIONS

Both authors contributed to the work and approve the manuscript for submission. E. Cereda: data collection, data analysis, data interpretation, and manuscript drafting. G.P.: data collection, data interpretation, supervision, review, and critique.

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