Polychlorinated Biphenyls and Neurodegenerative Disease Mortality in an Occupational Cohort

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Background: Production of polychlorinated biphenyls (PCBs) ended in the United States in the 1970s, but PCBs persist in the environment and are detectable in the blood of approximately 80% of Americans over age 50. PCBs decrease dopamine levels in rats and monkeys. Loss of dopamine is the hallmark of Parkinson disease, a neurodegenerative disease. There are no epidemiologic studies of PCBs and neurodegenerative disease.

Methods: We conducted a retrospective mortality study of 17,321 PCB-exposed workers to determine whether mortality from Parkinson disease, dementia, and amyotrophic lateral sclerosis was elevated compared with the U.S. population. All workers had a least 90 days employment in 1 of 3 electrical capacitor plants using PCBs from the 1940s to the 1970s. PCB serum levels from a sample of these workers in the 1970s were approximately 10 times the level of community controls.

Results: We found no overall excess of Parkinson disease, amyotrophic lateral sclerosis, or dementia in the PCB-exposed cohort (standardized mortality ratios [SMRs]-1.40, 1.11, and 1.26, respectively, and number of deaths-14, 10, and 28 respectively). However, sex-specific analyses revealed that women had an excess of amyotrophic lateral sclerosis (SMR-2.26; 95% confidence interval [CI] = 1.08–4.15; 10 deaths). Furthermore, among highly exposed women (defined by a job-exposure matrix), we found an excess of Parkinson disease (SMR-2.95; 95% CI = 1.08–6.42; 6 deaths) and dementia (SMR-2.04; 95% CI = 1.12–3.43; 14 deaths).

Conclusions: Our data are limited due to small numbers and reliance on mortality rather than incidence data, but are suggestive of an effect of PCBs on neurodegenerative disease for women. The literature does not offer an explanation for why women would be more affected than men by PCB exposure for these outcomes.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

Editors' note: *A commentary on this article appears on page 2.*

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Most occupational exposure to polychlorinated biphenyls (PCBs) stopped in 1977, when the production of PCBs and their use in electrical capacitors and transformers were banned in the United States. Nevertheless, large numbers of capacitors and transformers still in use contain PCBs. In 1985, the Environmental Protection Agency estimated that 1.4 million transformers with PCBs would remain in use in the year 2000.[1]

Leaks from capacitors and transformers, and poor handling of wastes in production facilities, have led to widespread dispersion of PCBs into the environment.[2] PCBs, particularly those PCB congeners that are more highly chlorinated, persist in the environment and in the fatty tissues of humans. A typical mixture of congeners used in industry in the 1940s and 1950s (Aroclor 1254, 54% chlorine by weight) has been estimated to have a half-life in the body of 4.8 years.[3]

Many U.S. residents have detectable PCBs in their serum, particularly older Americans.[4] Among individuals age 50 years and older, several of the heavily chlorinated PCBs (PCB 153, 180, 187) are detectable in the serum of 80% or more of the population (86%, 89%, and 84%, respectively, after weighting the sample to estimate the national population).[5] Others investigators[6] found a similar high prevalence of PCBs in the blood of 1000 breast cancer cases and controls on Long Island in the late 1990s.

Loss of dopaminergic cells in the brain is the hallmark pathologic sign of Parkinson disease. Several studies indicate that exposure to PCBs decreases dopamine levels in rats and monkeys.[7,8] This has led to speculation that PCBs might be linked to Parkinson disease in humans. There have been 2 small autopsy studies of PCB levels in the brains of patients with Parkinson disease compared with controls.[9,10] One[9] reported a modest increase in PCB levels in the substantia nigra of the Parkinson disease brains versus controls brains, whereas the other[10] found increased PCB levels in the caudate nucleus of Parkinson disease brains versus control brains.

Parkinson disease is 1 of several neurodegenerative diseases marked by the death of neurons in the central nervous system. Dementing disorders (including Alzheimer disease) and amyotrophic lateral sclerosis (ALS; also known as motor neuron disease) are among the more common of the remaining neurodegenerative diseases. There is evidence that Parkinson disease and Alzheimer disease may have overlapping underlying pathology and sometimes share clinical symptoms.[11] In addition, in at least 1 population, a pattern of

joint occurrence of ALS, Parkinson disease, and Alzheimer disease has been observed.[12]

The National Institute for Occupational Safety and Health (NIOSH) has assembled 3 cohorts that were occupationally exposed to PCBs at plants that produced electrical capacitors from the 1940s to the 1970s.[1,13] Serum PCB levels from the 1970s are also available for a sample of workers at 2 of these plants.[3,14–16] At 1 plant at which nonexposed community controls were also tested at the same time, PCB levels in the serum of workers were approximately 10 times higher than in that of controls, and the most highly exposed workers had levels approximately 50 times higher than controls.[15]

These 3 cohorts, totaling 17,321 people with at least 90 days of employment, represent the largest existing cohort of PCB-exposed workers. We have studied mortality from neurodegenerative diseases in this cohort using analyses based both on underlying cause and on multiple causes in which any mention of neurodegenerative disease on the death certificate is included in the analysis. Two of the neurodegenerative diseases (Parkinson disease and Alzheimer disease) are often nonfatal but of sufficient importance to be mentioned on the death certificate as a "contributory cause" or "other significant condition." To our knowledge, this is the first study of neurodegenerative disease among workers with high levels of PCB exposures.

METHODS

All 3 plants studied here produced electrical capacitors. Capacitor manufacturing involved placing bales of foil and paper film in metal capacitor boxes, which were filled with PCBs. PCB oils are viscous, and so either the oils were heated before filling the capacitors or the filled capacitors were heated in an oven to facilitate penetration of the paper in the bales. Filled capacitors were then soldered shut, degreased, leak-tested, painted, packed, and shipped. Leak testing involved subjecting the capacitors to a heat test when possible cracks were spotted. The highest levels of PCBs, both air concentrations and surface levels, were expected to be found close to the ovens. PCBs vaporized due to the heat from the oven area, and then either the vapors condensed and settled on surfaces or the vapors adsorbed directly to surfaces within the facility, providing exposure opportunity to workers in the plant whose job tasks did not involve direct contact with liquid PCBs.

Brown et al[13,17] studied 2 plants (plant 1 in New York and plant 2 in Massachusetts), but restricted their study to the most highly exposed workers and excluded some solvent-exposed workers (plants 1 and 2, n = 2588 included). PCBs were used at plant 1 from 1946 through 1977 and at plant 2 from 1939 through 1976. PCBs at both plants included Aroclor 1254 (54% chlorine), Aroclor 1242 (42% chlorine), and Aroclor 1016 (41% chlorine), with less chlorinated PCBs used more recently. (Aroclor is a commercial name representing a specific mixture of PCB congeners). Sinks et al[1] studied 3588 workers with at least 1 day of employment at a third plant in Indiana, where PCBs were used in 1957 through 1977. Aroclor 1242 was used through 1970, and Aroclor 1016 was used in 1971 through 1977. We have modified these cohorts to include all workers with 90 or more days of employment (plant 1, n = 6947; plant 2, n = 7564; plant 3, n = 2810).

The 3 cohorts combined totaled 17,321 workers, of whom 14,976 were hourly workers (86%). We excluded 415 workers because their follow up ended before 1960 (the year when U.S. mortality rates for neurodegenerative diseases were first available) or because they were missing key data such as birth date. Our final analytic cohort numbered 16,906.

These cohorts have been updated for mortality through 1998 through the National Death Index. Prior follow up was through 1982 for plants 1 and 2 and June 1986 for plant 3.

Here we focus only on neurodegenerative disease mortality. U.S. mortality rates for Parkinson disease, ALS, and dementia (divided into cerebrovascular and noncerebrovascular, the latter including Alzheimer disease) as underlying causes were specially created for this study for the years 1960 through 1998 to use as nonexposed comparison rates. No rate files could be made before 1960, the earliest date for which electronic mortality data are available. Parkinson disease was defined as ICD-9 code 332 (1978–1998), ICD-8 code 342 (1969–1977), and ICD-7 code 350 (1960–1968). ALS was defined as ICD-9 code 335.2, ICD-8 code 348.0, and ICD-7 code 356.1. Noncerebrovascular dementia was defined as ICD-9 code 331.0 (Alzheimer disease), ICD-9 codes 290.0–290.3 (senile and presenile dementia), ICD-8 codes 290.0–290.1 (senile and presenile dementia), and ICD-7 codes 304–305 (senile and presenile psychoses, including Alzheimer disease). Cerebrovascular dementia was defined as ICD-9 code 290.4 (arteriosclerotic dementia), ICD-8 codes 293.0 and 293.1 (psychosis associated with cerebral arteriosclerosis or other cerebrovascular disturbance), and ICD-7 code 306 (psychosis with cerebral arteriosclerosis). Cerebrovascular dementia was separated from other dementia because of the likelihood that neuronal death in these causes is due to the underlying cerebral vascular disease.

U.S. mortality rates per 100,000 in 1998 for Parkinson disease, ALS, and noncerebrovascular dementia (as defined previously) were 7.8, 1.8, and 14.8, respectively, for men and 3.3, 1.4, and 17.6, respectively, for women.

In addition to analyses using U.S. rates, we also used state rates for Indiana, New York (excluding New York City), and Massachusetts (plant-specific analyses were then combined) as a way of considering possible variations in regional rates.

In addition to analyses using underlying cause, "multiple-cause" mortality rates using any mention of the neurodegenerative disease on the death certificates were also created for 1960 through 1998.[18] Any mention of Parkinson disease or dementia on the death certificate occurs about twice as often as a listing of Parkinson disease or dementia as the underlying cause. ALS on the other hand is almost always fatal, and there is little difference between underlying and multiple-cause analysis.

Life-table analyses were conducted using the NIOSH PC Life Table Analysis System[19] comparing neurodegenerative disease mortality rates in the cohort with those in the U.S. population (or state-specific populations for some analyses), stratified by age, calendar time, sex, and race. In these

analyses, we calculated standardized mortality rate ratios (SMRs). Person-time in these analyses began after 90 days of exposure or in 1960, when rates were first available, whichever came later. Person-time ended at time of death, time of loss to follow up, or end of the study (31 December 1998), whichever was earlier.

Work history data from the 3 plants were collected in the mid-1970s. Use of PCBs stopped in 1976 through 1977. Plant-specific semiquantitative job-exposure matrices were created to enable a ranking of intensity of exposure for all workers across all 3 plants and across time.[20] The job-exposure matrices were developed using work history records, air samples from the mid-1970s (n = 157) available at all 3 plants, a history of process changes, job descriptions, and plant layouts. This was done separately for inhalation and dermal exposures in each plant using the same scaling for exposure scores across plants and across each of these 2 types of exposures so that exposure estimates could be combined across plants and across exposure types. An average of inhalation and dermal exposure scores was used to create the final plant-specific job-exposure matrices, because both routes of exposure were likely to be equally important. In the analysis of the combined cohort (3 plants together), each plant-specific job-exposure matrix was applied only to workers at that specific plant. However, because the exposure intensity units were comparable across plants, we were able to conduct an exposure–response analysis of the combined cohort.

The job-exposure matrix for each plant was developed in 4 steps.

1. All job codes were assessed for PCB exposure using "exposure determinants" such as time period, Aroclor mixture used, process temperature, plant location, and duration of tasks.
2. Jobs with similar exposure determinants were categorized together, resulting in exposure categories (33, 29, and 20 exposure categories for plants 1, 2, and 3, respectively).
3. For each exposure category, scores for exposure intensity (high—medium—low—baseline) and frequency (continuous—intermittent) were assigned separately for inhalation and dermal exposures. For frequency, continuous frequency was assigned a "1," whereas intermittent frequency was assigned a "0.5". Dermal exposure intensity took into account the potential for dermal exposure in each job, ie, opportunity for skin contact with PCB liquids. Inhalation intensities were quantified based on the plant's PCB air concentrations.
4. Scores for intensity and frequency were then multiplied together to get a final score for each plant-specific exposure category (and thereby for each plant-specific job within that category).

The job-exposure matrices for each plant were then further modified to reflect eras of stable PCB-type exposure conditions in which exposure levels were assumed to have remained relatively constant based on known process changes over time.

PCBs measured in blood for a sample of approximately 200 workers at each of 2 plants in the late 1970s[3,14] were compared with cumulative exposure scores calculated by the job-exposure matrices. Cumulative exposure estimated by the job-exposure matrices correlated reasonably well with the more highly chlorinated PCBs (with longer half-lives) measured in the blood samples in the late 1970s at the end of exposure (approximately r = 0.50–0.60 depending on the congener and the plant). However, one would not necessarily expect very high correlations between serum and estimated cumulative exposure. Serum levels measured at 1 point in time will not necessarily reflect cumulative exposure, especially for workers with longer exposure.

It should be noted that the exposure scores estimated by the job-exposure matrix do not have interpretable units, eg, such as parts per million in the air. Indeed, because they represent an average of inhalation and dermal exposure, there are inherently no common units for these exposures. Instead, they are simply scores that permit a relative ranking of workers by their exposure level.

Of the 17,321 workers, 2% had work histories with at least 1 job code that could not be linked to a known job and therefore for which no exposure level could be estimated (median percent of employment time in an unknown job code for these workers was 11%). For these workers, time in an unknown job code contributed toward duration of exposure, but not toward cumulative exposure.

The job-exposure matrix enabled us to analyze the data by cumulative exposure level, in addition to comparing the exposed workers as a whole to the U.S. population. Because of the small number of observed deaths from neurodegenerative disease, we elected to divide the cohort into low and high cumulative exposure groups. We chose a cut point a priori based on equally dividing multiple-cause Parkinson disease deaths (Parkinson disease being our original primary a priori cause of interest). The resulting cut point of 500,000 cumulative exposure units divided the observed Parkinson disease deaths (using multiple cause) in half (n = 13 in each category), thereby ensuring approximately equal statistical power in each category for this outcome.

RESULTS

The cohort was 50% men and 99% white; 26% had died by the end of follow up in 1998. The average year of birth was 1934, the average first year of exposure was 1960, the average length of exposure was 5.3 years, and the average length of follow up was 35 years. Men and women did not differ greatly regarding year of birth (means 1935 and 1933 for men and women, respectively) or year of first exposure (means 1961 and 1959 for men and women, respectively), and both men and women had the same mean length of exposure (5.3 years). We observed 253,000 person-years for men and 272,000 person-years for women. Plants 1, 2, and 3 contributed 206,000, 234,000, and 85,000 person-years, respectively.

Table 1 shows the SMRs for the underlying-cause and multiple-cause data. Analyses for cerebrovascular dementia are omitted because there was only 1 death from this cause

TABLE 1. SMRs (95% CIs) for Neurodegenerative Deaths and Death From All Causes Using Underlying and Multiple-Cause Data

	Low Exposure		High Exposure*		Total	
	SMR (95% CI)	Observed Deaths	SMR (95% CI)	Observed Deaths	SMR (95% CI)	Observed Deaths
Underlying Cause Data						
Parkinson disease	0.97 (0.36–2.12)	6	2.06 (0.89–4.07)	8	1.40 (0.76–2.34)	14
ALS	0.94 (0.35–2.05)	6	1.49 (0.41–3.83)	4	1.11 (0.53–2.03)	10
Dementia/Alzheimer disease†	1.00 (0.53–1.71)	13	1.63 (0.91–2.69)	15	1.26 (0.84–1.82)	28
All causes	0.91 (0.87–0.94)	2521	0.99 (0.94–1.05)	1279	0.93 (0.90–0.96)	3800
Multiple-cause data						
Parkinson disease	0.82 (0.44–1.40)	13	1.25 (0.66–2.13)	13	0.99 (0.65–1.45)	26
ALS	0.97 (0.39–1.99)	7	1.27 (0.35–3.25)	4	1.06 (0.53–1.89)	11
Dementia/Alzheimer disease†	0.82 (0.53–1.22)	24	1.35 (0.91–1.94)	29	1.05 (0.78–1.37)	53
All causes	0.89 (0.87–0.91)	6161	0.94 (0.91–0.98)	3218	0.91 (0.89–0.92)	9379

*High exposure defined as >500,000 cumulative exposure units using the job-exposure matrix.
†Excludes cerebrovascular dementia.

(underlying cause) and because noncerebrovascular dementia was of greater a priori interest. Hereafter, we use "dementia" to refer to noncerebrovascular dementia.

There were no marked increases for any neurodegenerative disease for the cohort as a whole, or for either the high- or low-exposure group, when we examined either underlying-cause or multiple-cause data. However, there was a consistent pattern of higher underlying-cause SMRs for the high-exposure group than for the low-exposure group. Also, among those with 30 or more years since first exposure (potential latency), there were excesses of Parkinson disease and dementia deaths (SMR = 2.50; 95% confidence interval [CI] = 1.08–4.93; 8 deaths) and dementia (1.73; 0.97–2.85; 15 deaths); ALS did not show a similar excess for this subgroup.

Table 2 shows sex-specific analyses. Men did not show any marked excesses for either underlying- or multiple-cause mortality. Among women, on the other hand, there were notable excesses for ALS overall (2.26; 1.08–4.15) and among the high-exposure group for Parkinson disease (2.95; 1.08–6.42) and dementia (2.04;1.12–3.43). Multiple-cause

TABLE 2. SMRs (95% CIs) for Neurodegenerative Deaths, by Sex, Using Underlying and Multiple-Cause Data

	Low Exposure		High Exposure*		Total	
	SMRs (95% CIs)	Observed Deaths	SMRs (95% CIs)	Observed Deaths	SMRs (95% CIs)	Observed Deaths
Underlying Cause Data						
Men						
Parkinson disease	1.34 (0.43–3.12)	5	1.09 (0.13–3.92)	2	1.25 (0.50–2.58)	7
Dementia/Alzheimer disease†	1.56 (0.68–3.08)	8	0.42 (0.01–2.36)	1	1.20 (0.55–2.29)	9
ALS	0.00 (0.00–1.08)	0	0.00 (0.00–3.10)	0	0.00 (0.00–0.80)	0
Women						
Parkinson disease	0.41 (0.01–2.31)	1	2.95 (1.08–6.42)	6	1.57 (0.63–3.24)	7
Dementia/Alzheimer disease†	0.63 (0.20–1.48)	5	2.04 (1.12–3.43)	14	1.29 (0.78–2.01)	19
ALS	2.04 (0.75–4.44)	6	2.69 (0.73–6.88)	4	2.26 (1.08–4.15)	10
Multiple-cause data						
Men						
Parkinson disease	1.13 (0.57–2.02)	11	0.61 (0.13–1.77)	3	0.96 (0.52–1.60)	14
Dementia/Alzheimer disease†	1.09 (0.58–1.86)	13	0.71 (0.19–1.81)	4	0.96 (0.56–1.54)	17
ALS	0.00 (0.00–0.93)	0	0.00 (0.00–2.54)	0	0.00 (0.00–0.68)	0
Women						
Parkinson disease	0.32 (0.04–1.17)	2	1.82 (0.87–3.35)	10	1.03 (0.53–1.80)	12
Dementia/Alzheimer disease†	0.63 (0.32–1.14)	11	1.59 (1.03–2.34)	25	1.09 (0.76–1.51)	36
ALS	2.15 (0.86–4.43)	7	2.34 (0.64–6.00)	4	2.21 (1.11–3.96)	11

*High exposure defined as >500,000 cumulative exposure units using the job-exposure matrix.
†Excludes cerebrovascular dementia.

mortality showed a similar pattern, but SMRs were somewhat diminished.

We carried out additional analyses for underlying cause among women using state rates for each state-specific cohort to account for any important variations in rates by state. Results for all 3 plants combined were similar to results using U.S. rates. The SMRs (95% CIs) for Parkinson disease, ALS, and dementia were 1.70 (0.68–3.50), 2.12 (1.01–3.89), and 1.40 (0.84–2.19), respectively. For the same outcomes in the high-exposure group, SMRs were 3.05 (1.12–6.63), 2.50 (0.68–6.41), and 2.11 (1.16–3.35), respectively.

Small numbers generally precluded direct comparisons of the high-exposure and low-exposure groups, with the exception of dementia for which numbers were the largest. For dementia among women (19 deaths as underlying cause), Poisson regression controlling for age (<65, 65–69, 70–74, 75–79, 80–84, 85+, no deaths before age 60) found a rate ratio of 3.15 (1.11–8.94) for high-exposed versus low-exposed. This rate ratio was quite similar to the ratio of SMRs for dementia between high- and low-exposed women was quite similar (2.04/0.63 = 3.24).

Several supplemental analyses are not shown. Analyses by duration of exposure showed a similar but slightly less pronounced pattern compared with analyses by cumulative exposure. This is not surprising because these 2 measures are correlated (duration of exposure is a component of cumulative exposure, which is calculated as level of exposure multiplied by duration of exposure). Other analyses restricted to the hourly cohort showed the same pattern as the overall results; again, this finding is not surprising because hourly workers represent 86% of the combined cohort. Analyses lagging exposure (discounting recent exposure) gave results similar to overall results, which was anticipated given that most workers had no recent exposure.

DISCUSSION

This is the first published study of workers exposed to PCBs in relation to neurodegenerative disease. The total cohort showed no excess of neurodegenerative disease mortality compared with what would be expected based on the U.S. population. However, our data do show mortality excesses of ALS among women and of Parkinson disease and dementia (other than cerebrovascular dementia) among women in the high-exposure group. We know of no reason why PCB-exposed women should be more at risk for neurodegenerative disease than PCB-exposed men. U.S. mortality rates for ALS and Parkinson disease are 15% to 40% higher for men than women, whereas for dementia, mortality rates for women are approximately twice that for men.

Estrogen might potentiate the effect of an exogenous toxin such as PCBs. There is some evidence of a sex difference in the effect of PCBs on dopaminergic neurons (loss of which is the hallmark of Parkinson disease), recently available in preliminary unpublished data. Investigators in New York data (Richard Seegal, personal communication, May 2005) have studied exworkers at 1 of the electrical capacitor plants included in this study. These investigators found a strong inverse relationship (r-square = 0.64) between current serum PCBs and dopamine transport density (a marker of substantia nigra neuronal death) as measured by single photon emission computed tomography imaging of the brain among 12 female ex-workers, but no relationship among a larger number of male ex-workers (r-square = 0.01).

There is indirect evidence of an interaction of postmenopausal estrogen and another environmental agent (caffeine) in relation to Parkinson disease in epidemiologic studies[21,22] and in animal studies.[23] In both types of studies, estrogen appears to eliminate the protective effect of caffeine.

Other possible explanations for differing results by sex are that there are increased serum PCBs in women due to increased storage in body fat or that job exposures for women were higher than for men. However, NHANES data[4] for the general U.S. population generally show women with the same or slightly lower PCB levels than men for the heavier PCB congeners, and our own analyses of these national data[5] for people over 50 confirms this pattern. Regarding occupational exposures, we know of no evidence suggesting the women had higher exposures than men when they worked in the same job categories.

The small number of neurodegenerative disease deaths in this cohort limits inferences about causality. Furthermore, mortality is not the end point of preference for assessing a PCB link with neurodegenerative disease; it would be preferable to have data on disease incidence. There is evidence from Europe and the United States in the 1990s that death certificates underreport Parkinson disease by 25% to 35%.[24–26] Regarding Alzheimer disease, 2 U.S. reports from the late 1980s and early 1990s based on a state Alzheimer disease registry and on next-of-kin reports suggest that only approximately 30% of Alzheimer disease is recorded on death certificates.[27,28] However, for U.S. patients with clinically well-characterized Alzheimer disease, this figure increased to 75%,[29] and a Scottish study of well-characterized nonvascular dementia reported a figure of 90%.[30] For ALS, incidence and mortality rates are virtually the same, diagnoses are usually straightforward, and little underreporting on death certificates would be expected. In general, underreporting of Parkinson disease or Alzheimer disease would not necessarily bias SMRs unless it was differential between the exposed and the nonexposed U.S. population. Furthermore, underreporting would not bias comparisons of rates between high- and low-exposed workers unless it was differential between these 2 groups. Although scenarios for such differential underreporting can be imagined, there are no strong a priori reasons to suspect serious biases in this regard in our results. If underreporting were nondifferential, it would be expected to bias effect measures to the null.

Our data are suggestive of an effect of PCBs on neurodegenerative disease for women. However, further investigation will be required to determine why women and not men would be susceptible to neurodegenerative disease from PCB exposure.

If this association is a true one, it would represent one of the relatively few documented associations between chemical toxins and neurodegenerative diseases. Lead has been associated with ALS in 1 study,[31] as have nonspecific pesticide exposures

in men in another.[32] Pesticide exposure across numerous studies has been associated with Parkinson disease, although this association is not consistent and no specific pesticide has been clearly implicated.[33] Nonspecific pesticide exposure has also been associated with Alzheimer disease in 1 study.[34]

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