Pesticides in well water increase risk of Parkinson's disease

Although first described over 100 years ago the causes of Parkinson's disease are still not clear. However, several lines of evidence implicate exposure to pesticides. ***Nicole Gatto, Myles Cockburn, Jeff Bronstein, Angelika Manthripragada*** *and* ***Beate Ritz*** *review the area and report on their most recent findings.*

Parkinson's disease (PD) is a degenerative disorder of the central nervous system that often impairs the sufferer's movement, speech, and other functions. It is characterized by muscle rigidity, tremor, slow movement and, in extreme cases, a loss of movement. The primary symptoms result from decreased stimulation of the motor cortex of the brain by the substantia nigra, important for controlling movement. This is normally the result of reduced levels or activity of the neurotransmitter dopamine which is made in the substantia nigra. Additional symptoms of PD may include impaired ability to think and reason and subtle language problems. Examination of the brain tissue of PD patients reveals some characteristic features such as abnormal structures known as Lewy bodies in neurons of the substantia nigra. Proteasome complexes, required to degrade unwanted proteins in cells are less active causing protein aggregates to build up inside cells.

The causes of PD are unclear but certain risk factors are known. For example, head trauma is known to increase the likelihood of developing PD and, in a small percentage of cases there may be a genetic component and in other cases exposure to environmental agents such as pesticides.

The link with pesticides

Animal studies

Over the last decade and a half, evidence has accumulated that exposure to certain environmental contaminants such as pesticides can produce the characteristics of PD in animal models of the disease. Treatment of rats with rotenone causes degeneration of some of the dopaminergic neurons (in the nigrostriatal pathway – are these going from the substantia nigra to ?) associated with reduced movement and rigidity in some rodent models, and rat nigral neurons [are these neurons of the substantia nigra?] accumulate inclusions similar to the characteristic Lewy bodies seen in PD. Paraquat has been widely used to study parkinsonism in animals. When mice are exposed to a combination of paraquat and maneb they exhibit changes in their dopaminergic neurons similar to that seen in PD [is that correct?]. Diethyldithiocarbamate inhibits proteasome activities in cell cultures, can enhance 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity in mice, and is a potent inhibitor of several enzymes such as aldehyde dehydrogenase [what is the significance of these observations? They won't make sense to the readers without a bit of explanation]. These observations demonstrate that pesticide toxicity to the dopaminergic system may be induced by single agents. However, these agents may act at different points and may enhance each others activity resulting in neurotoxicity through a 'multiple hit' process. [is this right?]

Human population studies

Studies of human populations from many countries throughout the latter part of the twentieth century reported regional differences in PD mortality rates, prompting speculations about environmental risk factors for PD. Studies in industrialized countries described excesses of disease and/or mortality from PD in rural compared to urban regions, while in developing countries, similar contrasts were not observed. While none of these studies allowed a specific environmental agent to be identified, many authors suggested that pesticides might be causing or exacerbating PD in rural environments. A possible explanation for the discrepancies between industrialized and developing countries may be that prior to 1990, 75% of all pesticides worldwide had been applied in industrialized countries; the US had applied four to five times more herbicides than non-industrialized nations. Thus, increases in PD rates due to pesticide exposures would be expected to occur earlier in industrialized countries than in developing countries.

Epidemiology studies [title OK?]

The earliest mainly hospital-based case-control studies of PD investigating pesticide exposures from occupational and non-occupational sources reported inconsistent results, with risk estimates ranging from negative to highly positive (0.6 to 5.8) for exposure to any pesticide. Few of these studies were considered population-based [is this a cohort study?] or enrolled incident cases [is this a case-control study?]

While case-control studies are the favoured approach for studying causes of rare diseases in human populations and provide much greater efficiency than cohort studies, their validity hinges on the appropriate choice of study site, control subjects, and exposure assessment/definition. A wide variety of pesticide exposure definitions have been employed in prior case-control studies, ranging from residential (living on farms or using well water) to occupational use (having worked on farms or applied pesticides). Most importantly, the predominant method of exposure assessment relied on self-reporting, that is a subject's recall of past pesticide use. This method is questionable, because recall of chemical usage in the distant past is likely to introduce substantial bias and in a case-control study setting, it is not possible to rule out the possibility that Parkinson's sufferers recall exposures differently than healthy controls because they are motivated to try to identify causes of their disease. This can lead to contradictions in studies. More recent case-control studies have employed more refined methods of exposure assessment and these have consistently suggested that pesticide exposures heighten the risk of developing PD. Most of these studies have identified risk increases less than two-fold; occasionally risks are found to be greater for certain subgroups, for example, by age or genetic variant. However, most are still unable to study the relationship between PD and individual pesticides.

Two occupational cohort studies which have reported on PD risk from specific pesticide use are the small orchardist study and the large Agricultural Health Study (AHS), a collaboration of the National Cancer Institute and National Institute of Environmental Health Science. The orchardist cohort identified only one case of physician diagnosed PD out of 310 subjects. Thus, these researchers evaluated risk due to pesticide exposures for 'parkinsonian signs at exam' rather than clinical PD, and reported a two-fold risk for 'parkinsonism' among exposed subjects, but no increase in risk was found for any specific pesticide or class of pesticides reported in a self-administered questionnaire. The AHS study recently reported results for licensed private pesticide applicators in Iowa and North Carolina. Among the almost 80,000 cohort members enrolled at baseline, 83 prevalent PD cases were identified [what is 'prevalent PD case'?], and another 78 self-reported incident PD cases [what is 'incident PD case'?] were added from among 56,001 subjects re-interviewed five years later. Incident PD was found to be associated with cumulative days of pesticide use reported at enrollment. This study also presented results for 47 different individual agents, but unfortunately, exposure to most of the agents examined was not common enough to provide sufficient statistical

power for a compound-by-compound analysis. Considering only chemicals with four or more exposed cases, effect estimates greater than or equal to 1.4 were reported for three herbicides and two fumigants with prevalent PD, and for five herbicides, two insecticides, two fungicides, and one soil fumigant with incident PD [what were the pesticides?]. Because the AHS collected detailed information on pesticide use at baseline from licensed pesticide applicators, the issue of differential recall bias did not arise for incident cases but may have influenced the analyses of prevalent cases. For a subset of applicators who completed a supplemental questionnaire, elevated risks were also seen with maneb/mancozeb (OR=2.1) and paraquat (OR=1.4) use, but these results were based on no more than four and 10 exposed cases, respectively. Thus, even in this heavily pesticide-exposed agricultural cohort of licensed pesticide applicators, statistical power was limited by the small number of incident cases identified during the short follow-up.

Contaminated well water studies

In the United States, the Safe Drinking Water Act of 1974 regulates the quality of the public drinking water supply, yet wells on private property that are not part of the public drinking water system are not subject to the same regulations, and therefore are not similarly monitored or held to the same water quality standards. Furthermore, many private wells are shallow (less than 15-20 metres) and at risk of contamination from nearby pesticide applications.

Ingesting contaminated drinking water can expose humans to pesticides. And many studies provide support for an association between drinking well water and PD. However, all existing studies have relied on participants to report their well water consumption and have used broad 'ever'/'never' exposure categories. To date no study has attempted to specify pesticide exposure levels by assessing or estimating the relative contamination of well water with specific pesticides.

New study

Our goal was to investigate whether consumption of water from private wells in areas with documented historical agricultural pesticide use was associated with an increased risk of PD among residents of the Central Valley of California, an area well-known for its intensive agriculture. We recruited Parkinson's sufferers and healthy controls from three agricultural counties, Fresno, Tulare, and Kern Counties in the Central Valley of California, between January 2001 and January 2007. They had to have lived in California for at least five years prior to diagnosis or interview. Three hundred and seventy nine cases were recruited and confirmed as having probable or possible PD. The study also had 341 matched healthy controls. Participants provided a history of their lifetime residential addresses including what type of water supply was present at each address (public supply, private well, filtered water, bottled water, other).

Since the early 1970's in the State of California, any commercial application of restricted-use pesticides and, since 1990, all commercial uses of pesticides regardless of toxicological profile must be reported to the California Department of Pesticide Regulation (CA DPR). Pesticide Use Reports (PUR) include the pesticide active ingredient, the weight applied, the crop and acreage of the field, the application method, date and location of application referenced to the Public Land Survey System (PLSS), a nationwide grid that parcels land into approximately one square mile sections. California Department of Water Resources (CDWR) land use maps allow identification of the location of specific crops within each PLSS grid section and to locate the pesticide application even more precisely.

High levels of possible well water contamination with methomyl, chlorpyrifos and propargite resulted in ~70% - 90% increases in risk of Parkinson's disease

Pesticide exposure was estimated from applications to agricultural crops combining the data on residential historical addresses, PUR data and the land-use maps. Additionally data on well water consumption was used to estimate exposure to potentially pesticide-contaminated water. We focused on pesticides that had been applied in an area within a 500m radius around each home address reported by participants.

The PUR data contains information on over 600 pesticide formulations and their active ingredients. We limited our analysis to those that had previously been detected in California groundwater or were designated as having the potential to pollute groundwater based on the CA DPR Groundwater Protection List. We also selected four additional pesticides identified by other states as being a concern to groundwater, as well as three chemicals of special interest for PD [which ones?], but whose chemistry did not necessarily qualify them as potential groundwater contaminants.

GIS modeling was used to determine which pesticide could have contaminated a subject's well water. Taking account of years of residence at each address annual cumulative exposure levels for the 1974-1999 period were estimated for each pesticide. Statistical modeling was then used to estimate how exposure to pesticides from well water consumption is related to disease risk ('relative risk') and 95% confidence intervals (95% CI), which indicate the reliability of the estimates. Other factors that are independently associated with PD risk including age, sex, education, race/ethnicity, family history of PD and smoking were taken into account in the relative risk estimates.

Our study participants were predominantly Caucasian, over the age of 65, and without a family history of PD. In our population, 27.1% of all subjects reported private well water as their drinking water source some time during the 1974-1999 period. Cases were more likely to have consumed water from private wells than controls, and reported drinking well water on average 4.3 (of the 26) years longer than controls.

The study found that drinking private well water thought to be contaminated with diazinon, methomyl, chlorpyrifos, propargite or dimethoate was associated with an elevated risk of PD. High levels of possible well water contamination with methomyl, chlorpyrifos and propargite resulted in ~70%-90% increases in risk of Parkinson's disease compared to residents without such exposures from well water. For paraquat, the well water contamination and ambient risk estimates were generally small and uninformative, which may be because exposure to paraquat may require coinciding maneb exposure to increase PD risk. Paraquat was included in the study because previous work has linked it to PD, but its physical properties including low water solubility and high adsorption make it less likely to contaminate groundwater. Thus, we expected lower well water risk estimates for this pesticide compared to others examined in this study.

The PD risk associated with a combined exposure to pesticides in presumably contaminated well water and from other ambient environmental sources of pesticides was greater than the risk from the otherambient environmental sources of pesticides alone. These results suggest that while exposure to the selected pesticides in the environment alone increases the risk of PD (20-50%), exposures from consumption of potentially contaminated well water may confer an additional, independent risk. We also found that the association between PD risk and the water soluble or organophosphate (OP) pesticides investigated in this study is not dominated by one or two specific chemicals, but rather that exposure to a number of these pesticides in water may increase PD risk. Carbamate and OP pesticides are suspected to be involved in the development of PD, for example, by disturbing redox processes that inhibit antioxidant enzymes thus enhancing lipid peroxidation and oxidative stress or inhibiting the proteasome or mitochondrial function in neurons.

Studies spanning two decades have examined the association between well water exposure and PD risk. Many of these studies were small, that is they included fewer than 100 cases; all relied on self-reported well water consumption to define 'ever'/'never' exposure groups, and none

attempted to assess levels of general or specific pesticide contamination in well water. The majority of these studies reported small relative increases in PD risk from ever being exposed to well water (ORs ranging from 1.02 – 2.8), and several found no associations, or even reported protective associations, perhaps due to the absence of a toxic agent in the well water consumed in these study populations. Some of the wells may not have been located in areas where agricultural chemicals could have contaminated them.

Some of the associations reported here may not reflect a contribution of the particular pesticide to PD risk, per se, but that the pesticide we suspected to have contaminated the well water acted as a surrogate measure for another unidentified pesticide. Exposure to mixtures of chemicals is a problem inherent in the assessment of exposure in humans. Among the 26 pesticides purposefully selected for our study, several were generally co-applied. For the six pesticides we individually examined, for example, among subjects who were ambiently exposed to chlorpyrifos at their residences, 80% were also exposed to diazinon and 91% to paraquat; of subjects ambiently exposed to paraquat 73% were also exposed to diazinon, 82% to methomyl and 80% to propargite. Thus, it was impossible to estimate the effect for one chemical alone.

It is also possible that well water in rural locations may be contaminated with multiple agricultural and industrial agents and metals, in addition to pesticides. To our knowledge, no previous study of PD has estimated pesticide residue contamination historically in drinking water; we are the first to implement a semi-quantitative approach to estimating pesticide exposure. Our well water pesticide exposure estimates do not exclusively reflect exposure from water ingestion alone because the suspected contamination was derived from data on applications in proximity of wells supplying water to residences, and these same chemicals were likely also air and soil contaminants. However, we did adjust for ambient pesticide exposure in our models, and found the associations for most chemicals remained after adjustment.

Our study is unique among those that have examined PD risk from well water consumption in that we utilized existing historical California PUR data, which we combined with land use maps to derive pesticide application rates for the study area over an extended period. Thus, our well water pesticide exposure measure is an estimate derived from our GIS models; we did not sample well water to directly measure actual current or historical pesticide levels.

Our study represents a significant improvement over other previous studies in that we did not have to rely on study subjects' recall of their own pesticide use to derive exposure estimates, a procedure criticized for its potential to introduce differential exposure misclassification bias if cases and controls recall differently. An additional strength of our current study is that all of our PD diagnoses were clinically confirmed by a study movement disorder specialist, and thus we expect our results to be affected by disease misclassification only minimally.

In conclusion, our study, the first of its kind to apply a semi-quantitative approach to estimating pesticide exposure in well water, contributes evidence that consumption of well water potentially contaminated with pesticides may play a role in the etiology of PD.

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