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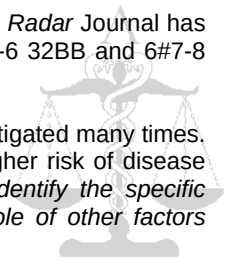
Rotenone, Paraquat and Parkinson's Disease

An association with two specific biocides is reported and given the size and design of the study, the effects could be real. A plausible cumulative mechanism is supported. However, some data also suggest a lack of support for a cumulative mechanism. Previous reports from the same study failed to find a specific risk from rotenone or paraquat.

The report is based on very large study known as the Agricultural Health Study. The *Radar* Journal has reported previous findings from this study; in the database at 7#5-6 30BB and 7#5-6 32BB and 6#7-8 31BB. Outcomes included bronchitis, colorectal cancer and depression respectively.



An association between pesticide exposure and Parkinson's disease has been investigated many times. In 2008 IIAC reviewed the evidence; database 8#1-2 4, the trend was to see a higher risk of disease associated with work with pesticides. IIAC concluded that *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.*

PD affects around 2% of the UK population over the age of 65. Clinical signs emerge only after a large proportion of damage has already occurred. The UK GP consultation case load was estimated [HSE RR608] to be 88,000 consultations where the patient thought pesticides were involved in their illness and 6,600 where the GP, when asked, thought they might be. Clearly there will be a large number of people who have some recorded evidence of concern about exposure to pesticides; some 2% of these would eventually have Parkinson's disease even if there was no causal link. Given that neuron damage is thought to be largely irreversible, any cause of neuron loss could be cited as material.

Lab work has shown how some pesticides affect some of the basic repair and metabolic functions of some cultures of neurons and affect animal behaviour in a way which is consistent with Parkinson's disease (PD). Two mechanisms are referred to as oxidation (Ox) and, inhibition of mitochondrial complex 1 (MC1). Cell cultures don't always behave in the same way as cells in living animals.

The hypothesis is therefore that risk of PD in pesticide users would be higher in those who used pesticides which act as Ox or inhibit MC1.

The researchers state that the following Ox and MC1 pesticides were used by people in this study:

Oxidative	Paraquat Permethrin Carbon disulfide Chloranil Cyhalothrin Dichlone Mercury compounds Pybuthrin
Mitochondrial Complex 1 inhibition	Benomyl Carbendazim Cyhalothrin Permethrin Pyridaben Rotenone Thiabendazole

Rotenone was withdrawn from use in the European Union in 2007, after which time most uses were voluntarily cancelled in the USA. Paraquat remains one of the most widely used herbicides worldwide.

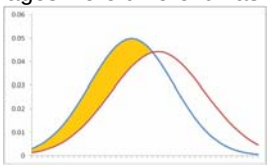
All the study participants were registered pesticide applicators, and their spouses (enrolment was from 1993 to 1997). The basic study included 84,740 people. Suspected cases were identified from self reports or from mortality information. Controls were randomly selected from age stratified groups.

Cases were validated by home visit; controls were validated by home visit. Exposure, ever use, and, days of use in working life, of 31 pesticides was determined by telephone interview with the index person or, someone who knew them well (proxy interview was used for 28 cases and 6 controls). Reported use and use reported at enrolment (~9 years earlier) were compared. For 4 pesticides (including rotenone and paraquat) exposures were found to be in agreement more than 75% of the time.

Correction was made for family history, education level and smoking.

The analyses reported here include 110 PD cases and 358 controls, all of whom provided complete information on pesticide use and application practices. Participation refusal rates were twice as high in the control group (29%) than in the case group (13%).

There was no clinical difference between PD cases in users and non-users. There was some evidence that PD was diagnosed at a younger age in those who had used oxidative stressors (59±8 vs 64±9 years) but the probability that these two ages were different was ~23%:



The blue curve represents the diagnosis age distribution for PD cases with occupational exposure to Ox, the red curve applies to those without exposure to Ox. By comparing curves, the probability that these two groups are different, can be estimated (yellow area).

Out of 8 Ox pesticides the Odds Ratio for paraquat was statistically significant; reported at 2.5 (95% CI = 1.4 to 4.7). Out of 7 MC1 inhibitors the Odds Ratio for rotenone was statistically significant; reported at 2.5 (95% CI = 1.3 to 4.7). In both cases these are adjusted for age, degree of exposure, gender and cigarette smoking. In both cases the un-adjusted odds ratios were smaller and probably not statistically significant in the case of paraquat.

There were 18 cases and 22 controls with a genetic risk for PD. In this group, paraquat and rotenone were not associated with disease. This counts against any cumulative mechanism, but the numbers are small.

Lag time between exposure and diagnosis did not change the odds ratios for paraquat or for rotenone. Again, an argument against any cumulative mechanism if it is assumed exposure is repeated.

For both groups of 8 Ox or 7 MC1 pesticides, the adjusted odds ratios showed a statistically significant association with PD. OR = 2.0 (95% CI = 1.2 to 3.6) and OR = 1.7 (95% CI = 1.0 to 2.8), respectively.

Comment

Statistically significant adjusted odds ratios for individual agents and when grouped by mechanism type, combined with a plausible mechanism suggest a causal role for the two pesticides.

Exposure recall bias was tested for and shown to be probably unimportant.

Three years ago the same authors using the same basic study population showed there to be an increased risk of PD with ever use of pesticides, but no particlar pesticide was identified. For some reason, both paraquat and rotenone have now become statsistically significant. Better case determination has been used, but so has an increased reliance on memory of exposure long after exposure ceased. It is difficult to explain why the new results should differ from the old if there really is a causal link. The numbers of exposed cases were 23 and 19 for paraquat and rotenone respectively; with numbers of that size the contribution from unknown biases could be significant.

14% of controls ever used paraquat, for rotenone the proportion was 9%. The authors don't comment whether these are the proportions that would be expected given the data collected at enrollment.

In our view, the study provides a hypothesis that should be tested deliberately rather than in retrospect. A total of 1,700 cases of PD should be expected in this cohort, exposure information has already been gathered, adding new data collected by history taking should be avoided.