Parkinson's Disease and Pesticide Use in Australia

A. General Introduction

Parkinson's Australia (PA) is concerned about the relationship between the occupation of farming and the risk of Parkinson's disease (PD). There is a growing literature strengthening the link between certain farm chemicals and PD. Some members of PA are involved in giving seminars to rural Parkinson's groups and are often surprised and alarmed at the high numbers of farmers with PD. Unfortunately there is little or no epidemiology on this issue in Australia. The prevalence of PD in Australia is quoted at around 280/100,000 which is similar to other industrialised countries such as the USA, Germany and Spain. Other countries with less intensive agriculture have a much lower incidence.

In the literature three particular chemicals appear to be associated with PD and these are paraquat, maneb (manganese based, banned in Australia but we use mancozeb) and rotenone but many others have never been tested. In Australia, paraquat, 2,4D amine and glyphosate are heavily used in broad acre farming. In fruit and grape growing areas fungicides such mancozeb are heavily used. The herbicide, termed "Spray Seed" (paraquat/diquat) is also extensively used and is considered to be very toxic even by the farm consultants.

Paraquat has received the most attention and some members of PA have been discussing this issue with the APMVA and have had input into the paraquat web site. There is considerable literature linking paraquat to PD and some references are listed. With any of the farm chemicals related to PD: ***It is the repeated low level chemical exposure over a long period of time in susceptible people, which is probably the issue for Parkinson's disease which is very difficult to measure.***

There are some recent epidemiological studies relating paraquat use to an increased chance of developing Parkinson's disease and some are listed below.

B. Epidemiology

i) Epidemiology (paraquat specifically)

Costello, S., Cockburn, M., Bronstein, J., Zhang, X. & Ritz, B. (2009) Parkinson's disease and residential exposure to maneb and paraquat from agricultural applications in the central valley of California. Am J Epidemiol, 169 (8), 919-926.

Tanner, C. M., Kamel, F., Ross, G. W., Hoppin, J. A., Goldman, S. M., Korell, M., Marras, C., Bhudhikanok, G. S., Kasten, M., Chade, A. R., Comyns, K., Richards, M. B., Meng, C., Priestley, B., Fernandez, H. H., Cambi, F., Umbach, D. M., Blair, A., Sandler, D. P. & Langston, J. W. (2011) Rotenone, paraquat, and Parkinson's disease. Environ Health Perspect, 119 (6), 866-872.

Animal models give a clearer picture of the relationship between paraquat and specific neurological damage as occurs in Parkinson's disease.

ii) Animal Models

Brooks AI, Chadwick CA, Gelbard HA, Cory-Slechta DA & Federoff HJ (1999): Paraquat elicited neurobehavioral syndrome caused by dopaminergic neuron loss. Brain Res 823, 1-10.

Kuter K, Nowak P, Golembiowska K & Ossowska K (2010): Increased reactive oxygen species production in the brain after repeated low-dose pesticide paraquat exposure in rats. A comparison with peripheral tissues. Neurochemical Research 35, 1121-1130.

Ossowska K, Smialowska M, Kuter K, Wieronska J, Zieba B, Wardas J, Nowak P, Dabrowska J, Bortel A, Biedka I, Schulze G & Rommelspacher H (2006): Degeneration of dopaminergic mesocortical neurons and activation of compensatory processes induced by a long-term paraquat administration in rats: implications for Parkinson's disease. Neuroscience 141, 2155-2165.

Ossowska K, Wardas J, Smialowska M, Kuter K, Lenda T, Wieronska JM, Zieba B, Nowak P, Dabrowska J, Bortel A, Kwiecinski A & Wolfarth S (2005): A slowly developing dysfunction of dopaminergic nigrostriatal neurons induced by long-term paraquat administration in rats: an animal model of preclinical stages of Parkinson's disease? Eur J Neurosci 22, 1294-1304.

Patel S, Singh V, Kumar A, Gupta YK & Singh MP (2006): Status of antioxidant defense system and expression of toxicant responsive genes in striatum of maneb- and paraquat-induced Parkinson's disease phenotype in mouse: mechanism of neurodegeneration. Brain Res 1081, 9-18.

Shimizu K, Matsubara K, Ohtaki K, Fujimaru S, Saito O & Shiono H (2003): Paraquat induces long-lasting dopamine overflow through the excitotoxic pathway in the striatum of freely moving rats. Brain Res 976, 243-252.

While some animal models have been criticised in the past as using unrealistic doses most of the more recent papers relating paraquat to specific substantia nigra damage have used doses similar to the NOEL (no adverse effect level) and still result in specific damage.

iii) Paraquat Crossing the Blood Brain Barrier

A number of studies have shown that paraquat enters the central nervous system via a neutral amino acid transporter and causes cellular damage via oxidative stress.

Chanyachukul T, Yoovathaworn K, Thongsaard W, Chongthammakun S, Navasumrit P & Satayavivad J (2004): Attenuation of paraquat-induced motor behavior and neurochemical disturbances by L-valine in vivo. Toxicol Lett 150, 259-269.

Shimizu K, Ohtaki K, Matsubara K, Aoyama K, Uezono T, Saito O, Suno M, Ogawa K, Hayase N, Kimura K & Shiono H (2001): Carrier-mediated processes in blood--brain barrier penetration and neural uptake of paraquat. Brain Res 906, 135-142.

iv) Relating farm use of paraquat to animal models.

A paper published in 1988 gives some clue to a likely mechanism. Lindquist NG, Larsson BS, Lyden-Sokololowski A. Autoradiography of [^{14}C] paraquat of [^{14}C] diquat in frogs and mice: accumulation in neuromelanin. *Neuroscience Letters*, 93: 1-6.

Only low levels are taken up into brain tissue but accumulate in melanin containing nerve cells. ***"At 4 days after the administration the radioactivity had decreased in most tissues, but the concentration was still high in pigmented nerve cells."*** The substantia nigra dopaminergic cells are the main pigmented cells in question.

While the epidemiological link is not conclusive because of the difficulties in measuring exposure over a 20 to 30 year period there are a number of animal studies showing that paraquat causes specific substantia nigra dopaminergic neuron degeneration as seen in Parkinson's disease at low doses.

C. Chemical Regulation

To be able to acquire farm chemicals farmers have to obtain a chemical users certificate. In discussion with farmers this is very easy to obtain. Larger properties that employ staff appear to comply more stringently to the regulations as they have a duty of care/responsibility under workers compensation legislative requirements. Chemical contractors appear to have better awareness, use appropriate protection and are required to maintain documentation of usage. A small operator can easily obtain a chemical usage certificate and is only responsible to themselves and can basically do as they please with respect to chemical handling. This appears to be the "at risk" group and some of the chemical handling practices conveyed to members of PA are extremely disturbing.

One major issue that makes research into the use of restricted chemicals difficult is the lack of documentation. There is no way of obtaining data on the sale and use of any farm chemical. If this data was available it would be useful in determining regional use and relating this to a range of possible rural health problems. This is not to suggest that all health problems are related to chemicals as smoking, obesity and alcohol consumption are much bigger risk factors for most conditions but farmers are a particularly vulnerable group with respect to chemically induced health problems. Since we are referring to restricted chemicals this documentation should already be collected and should be made available.

D. The Issues for Australia

a) We must recognise that all pesticides, herbicides and fungicides are designed to affect and destroy living processes and must be treated with great respect. This is not always the case in some farming communities.

b) We need an extensive advertising campaign to constantly remind farmers of farm chemical toxicity and the long term consequences of their inappropriate use to themselves and neighbours (for example spray drift).

c) Risks associated with farm chemicals need to be taught and reinforced at agricultural high schools.

d) We need a register of the sale of restricted chemicals so their distribution and use can be mapped and the epidemiology studied in relation to health and land degradation.

e) We need ongoing monitoring of domestic water tanks for specific chemicals when farmers are concerned with spray drift. Since recent publicity some members of PA have been asked by farmers on how to have this conducted.

f) We should plan to have chemical free regions around rural townships.

g) More research on chemical toxicity of specific farm chemicals needs to be conducted to assess the impact on the land, fauna and possible impact on humans.

h) We need more comprehensive data on the prevalence of PD in rural Australia.

E) Conclusion

While chemicals are a necessary requirement for modern intensive farming there is enough evidence in the literature to implicate specific chemicals in the development of PD and probably many other conditions. The next big research development will be the interaction of environmental chemicals and a person's genetic makeup. This is highlighted in the recent publication in October by a large team of very respected scientists.

Goldman et al, (2012) Genetic Modification of the Association of Paraquat and Parkinson's disease. Movement Disorders, 27(13):1652-8.

This paper shows that if you have a variation in a protective enzyme termed glutathione-S-transferase (GST) and 20% of the population have this variation in the USA then you are nine times more likely to develop PD if you use paraquat.

It is the repeated low level chemical exposure over a long period of time in susceptible people, which is probably the issue for Parkinson's disease.