

The United States Ag Health Study recently released a subset study, the “2011 Tanner FAME study” to explore whether there is an association between Parkinson’s disease and the use of paraquat. A Question and Answer on the findings and other frequently asked questions is posted below.

Q/A:

How does the 2011 Tanner FAME study relate to the Ag Health Study (AHS) that was initiated in 1993 to explore potential causes of cancer and other diseases among farmers and their families and among commercial pesticide applicators?

The Tanner study is a subset of the much larger Agricultural Health Study (AHS) that has been underway since 1993. The AHS has been extended to examine occupational and environmental factors affecting morbidity and mortality to diseases other than cancer, as well as injuries and accidents. So far, the AHS has shown that, while agricultural workers are generally healthier than the general US population, they do experience a higher rate of machine and motor vehicle accidents and have higher rates of some cancers.

Is the incidence of Parkinson’s disease among the members of the Tanner FAME study group higher than would be expected in the overall US population?

No. The incidence of Parkinson’s disease in the Tanner Farming and Movement Evaluation study (FAME) appears to be lower than in the general US population. The group being studied by the AHS includes approximately 57,300 farmers and pesticide applicators in North Carolina and Iowa and approximately 32,300 spouses of farmers. The FAME study excluded 4,900 commercial applicators. Of the remaining approximately 84,700, approximately one percent (110) have a confirmed diagnosis of Parkinson’s disease (PD). U.S. Medicare statistics indicate that more than 175 cases of Parkinson’s disease would have been expected in this population.

Have other studies supported the safety of paraquat?

Yes, there are other studies with AHS members that support the safety of paraquat use, including the following:

- Research published in November 2010 (led by Jenna Waggoner) analyzed the causes of death amongst the 6,419 of the 89,000 population who have died since the AHS was initiated. The number who died due to nervous system disorders was 190 compared with the expected 386 in the general North Carolina and Iowa populations (fewer than half of what would be expected). Based on US Centers for Disease Control data, it would be expected that approximately 30 percent of deaths due to nervous system disorders would be caused by Parkinson’s disease.
- In this latest Tanner study, past exposure to pesticides was determined retrospectively by telephone interview. In some cases, when the individual had died or was too ill to take part, the interview was conducted with a proxy. **The retrospective analysis of past exposure among patients is not considered good epidemiological practice** because it can lead to recall bias and incorrect associations between specific exposures and the development of disease.

Another relevant study was published in 2009 by Alexis Elbaz, MD, PhD in the Annals of Neurology which looked at professional pesticide users in France and found a weak association between some pesticide families and PD but was unable to detect any association with paraquat.

- This study was conducted in France among agricultural workers and those in related occupations in order to investigate the possible association of different pesticides with the occurrence of PD. Physicians determined 224 cases of PD that were contrasted with 557 PD free, but otherwise similar controls. Detailed interviews were conducted with all the participants and where possible the information verified at their places of work and checked for plausibility by experts. Overall, the study found a small but significant association between professional pesticide use and PD that increased with the number of years of exposure. This relationship was strongest with insecticides and in particular organo-chlorine insecticides where an increase in the extent of exposure and Older Onset PD in men was detected. The researchers were unable to find an association between PD and paraquat in this highly detailed study group.

Has Dr. Tanner provided additional information to help clarify the differences in the data between the 2007 study and the 2011 study?

We have recently requested additional information from Dr. Tanner and hope to hear back soon. Syngenta continuously monitors developments in the academic and scientific understanding of the health impacts of our products by closely following the literature and consulting with researchers who are investigating any new findings of scientific significance.

Is the number of paraquat-exposed Parkinson's disease cases consistent between the 2011 FAME study and the 2007 Kamel study in which Dr. Tanner participated?

No. There are actually fewer paraquat-exposed Parkinson's disease cases in the 2011 study than were reported in 2007 due to the exclusion, after closer medical examination, of earlier self-reported cases:

- 2007 TOTAL cases 25 (Incident cases 11; Prevalent cases 14)
- 2011 TOTAL cases 23 (Incident and Prevalent cases not defined)

What is the difference between "incident" and "prevalent" cases in the reporting?

In the AHS, participants were asked about their pesticide handling practices at the time they were enrolled (between 1993 and 1997.) Participants who already had Parkinson's disease at the start of the study make up the "prevalent" case population. Those participants who developed the disease at some point after the start of the study make up the "incident" case population.

The difference between the two populations can be an important source of reporting bias among the participants. This is why incidence data are used as a measure of risk over time, whereas prevalence data provide only a snapshot of a disease rate at a given point in time.

Why is it important to distinguish between incident and prevalent cases?

Reporting results separately for the incident and prevalent cases is important since response bias is possible in the enrollment phase, even when relying on incident cases, particularly if enrollment in the study could have been influenced by exposure and subsequent disease status. For example, this could occur if a farmer with exposure to pesticides and a family history of Parkinson's disease would have been more likely to participate in the study than a farmer with the same family history but no exposure to pesticide.

The 2007 study analyzed the prospective cohort data by specific pesticides. The authors noted that few prior studies had assessed exposure prospectively or had been able to separate prevalent and incident cases. They found that for paraquat, the odds ratio was 1.8 for prevalent cases and 1.0 for incident cases. This contrast in the results reinforced the need to analyze the prevalent and incident cases separately

Based on the new Tanner study do you believe that paraquat causes Parkinson's disease?

No. There is no evidence to support a causal relationship between exposure to paraquat and the development of Parkinson's disease. Neither the Tanner nor the Kamel study found a causal link between the use of paraquat and Parkinson's disease.

What do you see as the strengths and weaknesses of the new publication?

The biggest strength of the new study is the confirmation of Parkinson's disease diagnosis by movement order specialists. But there are also several weaknesses. For example, it does not distinguish between incident and prevalent cases. It includes less reliable post-enrolment exposure assessments, including some that rely on proxy informants for study subjects unable to complete interviews. The authors state good agreement between exposure recorded at the outset of the Agricultural Health Study and subsequent re-assessment as part of the Farming and Movement Evaluation (FAME) study. However, the number of Parkinson's cases differs significantly. No detail is presented which would allow the apparent discrepancy to be resolved for paraquat or the other three pesticides for which 'percentage agreement' is given in the paper.

What do you do to understand the different outcomes of the results, given that you say that explanatory details are missing?

Since the study involves individual respondents whose anonymity should not be compromised through the unofficial release of information, we may need to obtain additional study details through a Freedom of Information request.

How does the new publication's method of assessing paraquat and Parkinson's disease differ from the 2007 publication?

Due to a lack of distinction between incident and prevalent cases, the results of the 2011 study are not directly comparable with those reported in 2007. Additional interviews on past exposure (including proxy interviews) and the medical confirmation of diagnosis also may have affected the comparability of the results.

This is a reputable scientific study that shows that paraquat causes health problems. Why is paraquat still on the market?

While we take this new publication seriously, it does not show a causal link between exposure to paraquat and the subsequent development of Parkinson's disease. Epidemiological studies are complex to design and interpret, and this new study is no exception. It requires careful scrutiny to understand whether the way in which the data have been collected and interpreted fully support an association between occupational exposure to paraquat and the development of Parkinson's. What we do know is that paraquat is a valuable herbicide in both developed and developing countries, benefitting farmers, society, and the environment.

Will you be handling your paraquat products any differently following this new study?

Paraquat has been used safely around the world for many years. Existing manufacturing and formulation operations, along with end user label precautions, are already designed to minimize potential for worker exposure.

The occupational use of paraquat is highly regulated by government authorities. Paraquat is a 'Restricted Use Pesticide' in the US, available only to certified spray operators, and applicators must typically meet high standards of education and training in the use of pesticides.

The new publication cites the Centers for Disease Control 2009 Fourth National Report on Human Exposure to Environmental Chemicals stating 'Many persons with non-occupational pesticide exposures may be unaware of the presence of pesticides in their environments.' Should I be concerned about developing Parkinson's disease as a result of non-occupational exposure to paraquat?

There is negligible potential for exposure to paraquat from food or drinking water. Uses of paraquat for weed control do not result in detectable residues on agricultural commodities intended for human consumption, therefore the maximum residue levels (MRLs) for most crops in most countries are set at or about the limit of quantification (LOQ) of the residue analytical method (0.01 mg/kg or 0.01 parts per million). Paraquat binds exceptionally strongly to soil. It is immobile and therefore will not leach through soil to contaminate drinking water.

Is the link made in the Tanner paper to animal studies and toxic modes of action plausible? Doesn't it make the case against paraquat compelling?

The vast majority of animal studies referred to by the Tanner paper investigating a possible link between exposure to paraquat and the development of Parkinson's disease or parkinsonism have been carried out in one specific strain of mice (C57Bl6J). The doses, routes and duration of exposure are not relevant to human exposure scenarios for several reasons:

- The doses of paraquat used in these studies far exceed normal occupational exposure. They are typically one-quarter to one-third of a lethal dose applied repeatedly.
- In contrast to relevant routes of exposure (e.g. oral or dermal), these studies use repeated injections into the body cavity. Humans are not exposed to paraquat in this way..
- High concentrations of paraquat are administered over many weeks, to a strain of mice known to be particularly sensitive to the induction of Parkinsonian-like symptoms by an impurity (called MPTP) in illegal recreational drugs.
- When considered in the context of occupational risk, the scenario of a farm operator being exposed to equivalent high doses of paraquat used in the animal experiments does not arise.

Why is paraquat a Restricted Use Pesticide (RUP) in the US?

The US Environmental Protection Agency classified paraquat dichloride as a Restricted Use Pesticide in 1978 due to high acute toxicity to animals and people from intentional or inadvertent oral ingestion or inappropriate dermal exposure.

Under the Restricted Use classification, only certified applicators are authorized to apply paraquat dichloride end-use products. The classification is unrelated to any alleged relationship between paraquat and Parkinson's disease.