

Paraquat: Neurotoxicity and Parkinson's Disease

Outline of the issue -

Historically, specific acute, subchronic and developmental neurotoxicity studies have not been considered routinely necessary, or required by regulatory authorities, unless the substance was an organophosphate; inhibited cholinesterase; produced cholinergic-like toxic signs or affected morphology of the central and peripheral nervous systems. Paraquat does not affect the nervous system and as such, no specific regulatory neurotoxicity studies have been undertaken.

US EPA recently decided to make acute and subchronic neurotoxicity studies a standard regulatory requirement, and in 1999 EPA began a phased data call-in (DCI) of acute, subchronic, and developmental neurotoxicity studies. Paraquat was not a high priority but is included in later phases of the DCI. Similarly in Japan, MAFF now intend to routinely request acute and subchronic neurotoxicity studies and Syngenta will be required to fill this data gap by the end of 2006 in order to support continued approval of paraquat based products in Japan.

New studies always pose potential risk of unexpected findings at doses below current reference doses.

Paraquat has some structural similarity to the chemical MPTP which has been shown to induce Parkinson's Disease (PD) like symptoms in humans, but paraquat has markedly different properties from MPTP such that it does not readily cross the blood-brain barrier. As a consequence however, some academic researchers have used paraquat as a model to develop test system to study PD and develop potential therapies. This does not imply paraquat is in any way associated with the aetiology of the disease.

However, publications do exist citing correlation between incidence of PD and herbicide use, including paraquat and other academic researchers have sought to examine the effects of pesticides including paraquat on the central nervous system, and their potential to produce PD-like symptoms. Recent studies have focussed on the cumulative effects of pesticides, including paraquat; different developmental stages of the animal models; and development of PD hazard models, using high levels of pesticides to demonstrate changes.

In 2003 WHO commented on the epidemiological studies seeking to examine associations between PD and exposure to chemicals, including pesticides, "*associations with exposure to specific pesticides have not been shown consistently*". WHO also commented on the research examining the effects of pesticides including paraquat on the central nervous system, and their potential to produce PD-like symptoms, "*the design of these studies renders the relevance of these data questionable for the risk assessment of dietary exposure to paraquat residues*". The WHO expert panel concluded "*that the available mechanistic and other animal studies did not support the hypothesis that paraquat residues in food are a risk factor for Parkinson's disease in humans.*"

In contrast, some NGOs opposed to pesticides in general and paraquat in particular have claimed that paraquat is implicated as a causative or contributory agent in PD. They have and will likely continue to make this claim to regulatory authorities and the general public.

A high level of funding will ensure PD research will increase and focus on environmental factors such as exposure to pesticides. There are a number of well-known PD sufferers and these will ensure PD receives high media attention. Future publications may show misleading results or interpretation & it is highly likely that paraquat will continue to be drawn into the debate.

Proposed management tactics

1. Develop a regulatory database of neurotoxicity studies to support continued approval of paraquat products globally
 - Preliminary acute and sub-chronic neurotoxicity studies are scheduled to commence in 4th quarter 2004
 - The RDT supports sequentially conducting the definitive acute and sub-chronic neurotoxicity studies proactively in 2005. This recommendation will be discussed at a 4th November 2004 techno-regulatory review with final approval to be confirmed at the subsequent regulatory sciences committee meeting.

- The RDT recommends not progressing with a definitive developmental neurotoxicity study at this time as the methodology is still subject to change and there is no clear timeline of regulatory need
 - The RDT encourages proactive careful consideration of the appropriate design and timing for conduct of a future paraquat developmental neurotoxicity study
2. Monitor, understand and influence ongoing academic PD research and manage the impact on paraquat registrations by putting published findings in context of the use of paraquat as a herbicide
 - Develop and maintain an in-house capability to further our understanding of paraquat and its role in PD models, and to gain a presence in the international scientific community engaged in this PD research
 - Foster close links with the key relevant PD research groups globally to get early visibility of their research and potential publications, and create opportunity to influence these to avoid inadvertently alarmist statements or misleading conclusions based on a poor understanding of paraquat's use as a herbicide
 - Review relevant publications and advise the RDT of key findings and potential risks from anticipated future research
 3. Support regulatory authorities in dismissing the hypothesis that paraquat is a risk factor for Parkinson's Disease in humans
 - Maintain PD position statements and literature reviews and make these available to regulatory authorities as appropriate
 - Seek to demonstrate the lack of independent regulatory expert support for the hypothesis that paraquat residues in food is a risk factor for PD in the general population
 - Formally include PD in the WHO periodic re-evaluation of paraquat toxicology under JMPR in 2003
 4. Seek to demonstrate the lack of independent regulatory expert support for the hypothesis that occupational paraquat exposure is a risk factor for PD in the sub-population of people exposed to paraquat
 - Monitor, and where appropriate contribute to, national regulatory consideration of the association between PD and rural living, pesticides in general and paraquat specifically
 5. Create an international scientific consensus against the hypothesis that paraquat is a risk factor for Parkinson's Disease in humans
 - Demonstrate how low aggregate exposure of the general population to dietary residues of paraquat from food and drinking water really is by conducting and publishing a US market basket residue survey and a relevant water monitoring exercise
 - Demonstrate the difference (in orders of magnitude) between doses of paraquat causing observed, and relevant, biological effects and paraquat exposure to the sub-population in and around its occupational use as a herbicide
 - Emphasise alternative agents or risk factors that have both a hazard and exposure profile that make them a more plausible lead for targeted academic PD research