

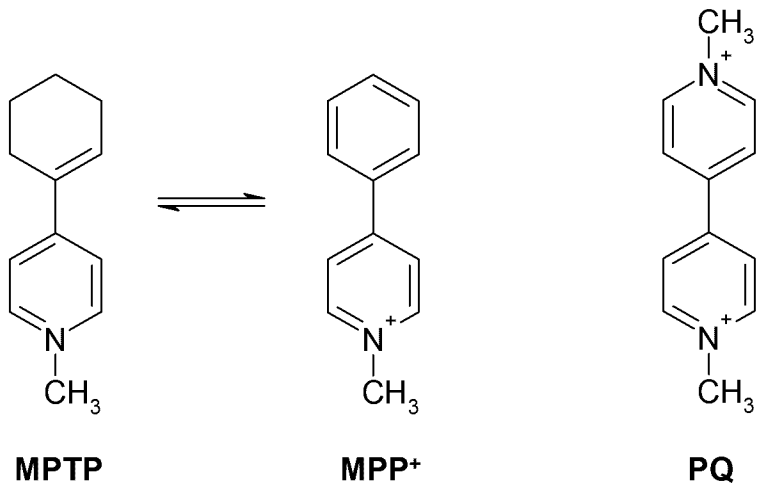
syngenta

Memo

To	M Clapp, J Doe, W Kobel, D Evans, V Anthony, M Loomes, J Street, J McFarland, J Barnes D Vitolo, I Wheals	Date:	31/08/01
Copy To		Number of pages:	1/2
Concerning	CONFIDENTIAL PARAQUAT AND PARKINSON'S DISEASE		

I attended a meeting from the 25 – 27 August on Parkinson's disease because a number of papers were to be presented on the relationship of pesticides (and paraquat in particular) with the development of Parkinsonian symptoms.

The possible relationship of paraquat (PQ) exposure to the incidence of Parkinson's disease has been a topic of discussion since the late 1980's when MPTP/MPP⁺ were shown to cause severe Parkinsonian symptoms in young adults who self administered a synthetic form of heroin contaminated with MPTP.



The facile structural relationship of MPP⁺ to PQ immediately led some scientists to speculate that PQ may cause similar pathology to MPP⁺ and there have been several publications associating the incidence of Parkinson's disease to the use of pesticides, rural environments and specifically PQ use. These have not amounted to a serious threat to our business because of the very soft epidemiological relationships and the lack of evidence that PQ causes brain lesions in experimental animals by systemic routes of exposure.

The situation has now changed. Over the last two years there have been several publications and abstracts from a group of scientists led by Deborah Cory-Slechter from the University of Rochester. Her group now collaborate with Donato (Dino) DiMonte at the Parkinson's Institute in San Francisco, directed by J William Langston, the clinician who first described MPTP toxicity in humans. This is a group of ostensibly respectable scientists, although they are obviously motivated to make the 'most' of their data in order to attract additional funding and possibly because one or more of the group genuinely believes the interpretation they are putting on their data.

- In short, they have shown that:
- (1) High doses of PQ given subchronically, combined with the fungicide MANEB, causes adverse biochemical changes in the brains of mice that are consistent with Parkinson's disease. There are also neurophysiological changes and behavioural changes consistent with Parkinsonian disease.



- (2) They have now shown that mice exposed to PQ, or PQ and MANEB are more susceptible to rechallenge with PQ and MANEB than 'naive' mice.
- (3) Exposing 5 day old pups to PQ (very low doses of 0.1mg/kg, ip) for a few days sensitised the mice, as they mature, to a rechallenge with PQ and MANEB.
- (4) Relatively low doses of PQ (1mg/kg) given ip to mice cause a 'progressive' loss of neurones in the area of the brain (substantia nigra) associated with Parkinson's disease.

These authors are carrying out additional studies using pregnant dams and lower doses.

Originally Dr Corey Slechter described her studies as developing a model for the interaction of chemicals and was not specific that the combination of PQ and MANEB was actually a threat to the health of agricultural workers or consumers. She is now implying that because of:

- (1) the use of PQ as a desiccant on cotton (leading to farm animal exposure)
- (2) occupational exposure leading to contamination of workers and their families, and
- (3) exposure to PQ in residential areas from spray drift

the risk to humans from PQ will have to be reassessed. It seems likely she will be combining PQ with other pesticides and chemicals in future studies.

It was not just the words that were used which was disturbing, but the tone of the discussion. Also, it was apparent that the audience were genuinely interested, and some appeared already convinced that this was a real issue for human health.

I am sure that we have to be proactive if we are going to contain this issue and take the necessary steps to ensure that a rational risk assessment will prevail.

I have asked Mike Clapp to set up a senior steering group, which will oversee Syngenta's technical response to this issue. This will be chaired by Mike and from Health Assessment, Nicola Wallis (our medically qualified Head of Pathology) and myself will be involved. If GRA and NAFTA would like to be represented I would appreciate suggestions on who these members should be. This will be a small group that will meet occasionally and more regularly by teleconference.

I hope you will agree that we need to join our regulatory/science expertise at a senior level to ensure that this issue is given the attention and resources that are required.

Lewis L Smith
Global Head, Health Assessment & Environmental Safety