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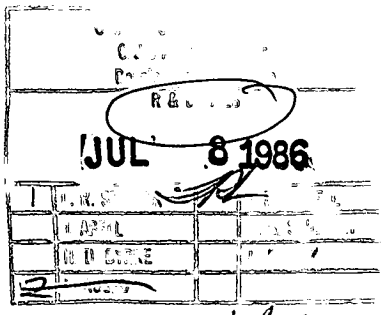


July 2, 1986

all RTS were sent their own ce's 9pp write + central files

ICI's Paraquat Document
Parkinsons Disease

7/15/86 Fresno Region 3. J. D. Whitehead
Memphis, TN 4. B. W. Kirby
Rolling Meadows, IL 5. M M Donley
6. R H Lindemann

Mr. T. B. Hart
Imperial Chemical Industries Ltd. (ICI)
Plant Protection Division
Fernhurst, Haslemere
Surrey, England GU27 3JE

Dear Dr. Hart:

Dr. R. D. White of Chevron Environmental Health Center reviewed the Paraquat Document on Parkinsons Disease prepared by ICI. His comments on the attached paper strengthened our position that there is no scientific or epidemiological evidence to link Paraquat and Parkinsons Disease. We would appreciate your inclusion of Dr. White's comments in the ICI paper.

Very truly yours,

Desmond Byrne/jca
H. D. Byrne, Manager
Registration & Regulatory Affairs

JCW:sag

Attachment

cc: R. D. Cavalli
J. A. Feldman
J. E. Ford
L. R. Stelzer
R. D. White

[redacted]

cc: Joe White sent 6/4/04

PARAQUAT - PARKINSONS DISEASE

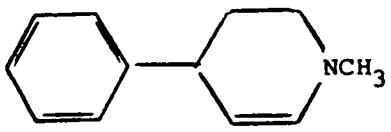
Des 6/03

INTRODUCTION

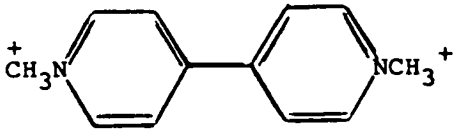
The biochemical disturbances associated with Parkinsons Disease are now fairly well understood. Depletion of monoamine neurotransmitters, in particular dopamine, within the substantia nigra of the brain stem appears to be important in the disease process. However, despite this understanding, it was only as recent as three years ago that a chemical agent capable of inducing a Parkinsonsian like syndrome was discovered.

Langston, J.W. et al (Reference 1) and Lewin, R. (Reference 2) separately reported that a relatively simple pyridine (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine - MPTP) could induce a Parkinsonian-like syndrome in humans and some animals. Later Snyder's group at John Hopkins University, Baltimore (Reference 3) demonstrated the presence of receptor sites for the metabolite of MPTP within the brain and defined the structure/activity relationship for neurotoxicity.

The whole story was reviewed more recently by Lewin in Science (Reference 4) and this review was followed by articles in the popular press, in particular Newsweek magazine. The findings in themselves are of great interest in the aetiology of Parkinsons Disease, but speculation about paraquat being able to induce the disease has also arisen. The reason for the speculation is the apparent similarity in chemical structures between MPTP and paraquat (see below).



MPTP



PARAQUAT

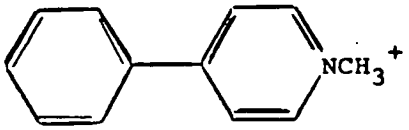
The aim of this document is to review all available scientific and epidemiological evidence on paraquat's potential to induce this disease or disease-like syndrome.

STRUCTURE-ACTIVITY RELATIONSHIP AND PARKINSONS DISEASE

Although the structures of MPTP and paraquat may appear to be similar, they are chemically very different. Firstly MPTP is uncharged and lipophilic: paraquat is charged and non-lipophilic. Secondly MPTP is a monoamine, whereas paraquat is a diamine.

The importance of charge on the molecule is reflected in the bioavailability of chemicals within the brain. It is well-known that lipophilic molecules cross the so called 'blood-brain barrier' far more readily than non-lipophilic ones. Paraquat, for example, does not readily enter the central nervous system (References 5, and 6), which explains why brain damage is not usually a feature of acute paraquat poisoning, unless the dose and plasma concentration are very large. MPTP is, however, lipophilic and therefore will cross the 'blood-brain barrier' readily.

MPTP undergoes metabolism within brain cells to a charged, non-lipophilic molecule - MPP+ (1-methyl-4-phenyl-pyridinium ion), the structure of which is shown below. It is MPP+, which is the primary neurotoxin.



MPP+

When MPP+ is given parenterally then it does not cross the blood-brain barrier readily and does not exert neurotoxic effects in animal models (Reference 7).

The importance of the monoamine structure has been shown by Snyder's group (Reference 3). The high affinity of the brain membrane for MPP+ indicates a specific monoamine uptake system into brain cells, particularly those of the substantia nigra. It is extremely unlikely that a diamine, such as paraquat, will interfere with this uptake system.

ANIMAL STUDIES While rodents are poor models for MPTP induced Parkinson's Disease,

In general animal toxicity studies are not designed specifically to examine small regional areas of the brain, such as the substantia nigra. ~~However~~ it is worth noting that when paraquat is fed to rats or mice over their life-time, no brain damage detectable by light microscopy was seen (References 8, 9). Nor were any features suggestive of Parkinsons Disease observed in these studies.

EPIDEMIOLOGICAL EVIDENCE

The review article by Lewin and the media articles all draw attention to epidemiological evidence on the incidence of Parkinsons Disease. Professor Barbeau of Quebec showed that the regional incidence of Parkinsons Disease was non-uniform, and not uniform as had previously been thought and that there was a strong correlation between people with genetically determined enzyme deficiency and the disease. It is very difficult to draw any more conclusions from this study.

However the Science article (Reference 4) stated that "In a Canadian study, the correlation between disease incidence and level of pesticide use was very strong - 0.967". It did not go on to say that a similarly high correlation was found between the incidence of Parkinsons Disease and industrial areas and wood processing regions. Clearly the association is far more complex than simply considering pesticide use. In fact, using Barbeau's results for the incidence of Parkinsons Disease and the paraquat regional sales figures in Canada, ICI has been unable to determine any correlation between paraquat usage and the incidence of Parkinsons Disease.

Since paraquat is not metabolised in mammals, the suggestion by Lewin (Reference 4) that an enzyme deficiency will affect man's ability to detoxify paraquat and may thus be susceptible to Parkinsons Disease is completely erroneous.

SUMMARY

Parkinsonian-like symptoms have been found to be associated with exposure to a pyridine-based chemical - MPTP. Although the structures of MPTP and paraquat appear to be similar, there are important differences.

Firstly MPTP is a non-charged lipid soluble chemical, whereas paraquat is charged and water soluble. This means that MPTP can enter the brain readily, whereas paraquat does not.

Secondly paraquat is a diamine and MPTP is a monoamine. The presence of a specific monoamine transport system within the brain has been identified and the chemical structure of monoamines is important in determining neurotoxicity. It is extremely unlikely that toxicologically significant levels of paraquat will enter the brain following exposure associated with use of the product and it is extremely unlikely that paraquat in the brain will be accumulated by the monoamine transport system. There is therefore no scientific reason why paraquat should be capable of increasing susceptibility to Parkinsons Disease or causing a Parkinsonian-like syndrome.

Animal studies involving chronic exposure confirm that paraquat levels in the brain are low and brain damage does not occur.

There has been a limited amount of epidemiological evidence to show that the geographical incidence of Parkinsons Disease is non-uniform. The incidence is higher in areas involving pesticide use, industrial pollution and wood processing. There has never been any correlation between the disease incidence and paraquat use. In fact available evidence indicates that there is no such correlation.

Therefore there is no scientific nor epidemiological evidence to link paraquat with Parkinsons Disease and the apparent similarity in the chemical structure between MPTP and paraquat is toxicologically irrelevant.

One important point that can be added is that pq poisoned people don't demonstrate Parkinsonism signs. Also, for what it is worth, the Malaysian epidemiology studies did not report any clinical findings of Parkinsonism.

Also, Parkinson signs have not been reported to be associated w people that spray the chem.

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TBH/NMW
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