

From: Bob Scott - CTL
SCOTT RC

Date: 11-Mar-1994 14:26

TO: Bob Scott - CTL

(SCOTT RC)

Subject: PQ Neurotoxicity

*for Benham
John*

PARAQUAT NEUROTOXICITY

For a number of years Zeneca has been aware of suggestions in the press and scientific literature that PQ may be a neurotoxic chemical. It has further been suggested that human exposure to PQ could result in chronic neurological impairment. The main area of concern was the erroneous linking of PQ with early onset of Parkinsonism coupled with the observation that the structures (though not the physicochemical properties) of PQ and the chemical MPTP, which does cause Parkinsonism, were very similar. More recently, studies in the scientific literature have presented evidence that PQ can penetrate into the brain (of rats) and produce neurotoxic effects and also elicit long term effects in behaviour when dosed at very low levels (to mice) several days after birth.

In order to understand the significance of these allegations/findings Zeneca initially critiqued the available literature, examined the database from mammalian toxicology studies done to Regulatory guidelines and human exposure/epidemiology studies. The conclusion was that there was no evidence that PQ is a neurotoxic chemical in animals and more importantly, even after many years of continuous occupational exposure, in man (Scott RC, 1992, CTL/L/4668).

Zeneca decided to initiate a research project at CTL to investigate the ability of PQ to interfere with normal CNS function and specifically, in the first instance with the brain (stimulated by the publications mentioned above).

In addition a second project is about to commence which will compare the neurotoxic potential of MPTP (and its toxic metabolite MPP+) with PQ; specifically in relation to dopamine systems which are affected in Parkinson's Disease.

We do not intend to study the developmental behavioural effects of PQ in the near future. Collaboration in this area is being fostered on a longer term basis with the experts at the MRC (although our own in-house skills could be applied if necessary).

Current research studies

In order for PQ to be neurotoxic it must enter the brain. Investigators in Rome have reported that, following systemic (i.p.) administration to rats of MLD doses, PQ does enter the brain, causing significant behavioural changes and brain cell death which was detected by 24h. Studies have been carried out in CTL to investigate these claims.

We failed to demonstrate behavioural changes, attributable to PQ, associated with neurotoxicity. Moreover, we have not found any pathological changes in the brain. Indeed, we believe that the changes reported in the literature were

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We failed to demonstrate behavioural changes, attributable to PQ, associated with neurotoxicity. Moreover, we have not found any pathological changes in the brain. Indeed, we believe that the changes reported in the literature were

fixation artefacts and not PQ-induced.

We have, however, found that PQ can enter the brain, to a limited extent, but only in brain areas which have an incomplete blood brain barrier.

Our studies have also quantified the amounts of PQ in the various regions of the brain. A number of studies in the literature have reported that PQ can be neurotoxic following direct injection into the brain. These studies have allowed us to calculate a NOEL for PQ-induced behavioural and pathological changes in the brain. We have found in our studies that the amounts of PQ in the brain following systemic administration of an MLD dose are well below the NOEL for PQ effects in the brain following direct injection.

By extrapolation, we would expect that lower levels of PQ given systemically, would produce no abnormal behaviour or brain cell death.

Further Investigations

The above studies are nearing completion. Further studies will examine the effect of lower doses.

It is anticipated that this programme to more fully understand various aspects of PQ's neurotoxic potential will continue for the next few years.

R C Scott
Product Toxicologist