

Exhibit 50

ROUGH DRAFT
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The article in the July 19, 1985 issue of Science raised the general allegation that environmental factors, primarily pesticides, may be implicated in causing Parkinson's Disease. Paraquat was specifically named in the article because of its structural similarity to 1-methyl-4-phenyl-tetrahydropyridine (MPTP), a chemical known to cause Parkinson's Disease. There is no scientific evidence to support a causal relationship between exposure to Paraquat and development of Parkinson's Disease.

Discussed below are three topics which underlie our belief that Paraquat exposure does not cause Parkinson's Disease.

A. Pharmacokinetics of Paraquat

Paraquat, or 1,1-dimethyl 4,4-bipyridylum ion, is a divalent cation which is manufactured as the dichloride salt. With a molecular weight of 187 and a permanent charge, Paraquat is highly water soluble with a very low partition coefficient (1). These physical properties significantly influence its absorption, distribution, and elimination. Important features of Paraquat pharmacokinetics include limited absorption through either the skin (1,2,3) or the gastrointestinal tract (4,5), poor distribution into the central nervous system (6,7), and rapid elimination by the kidney (8,9,10). A neutral, lipid-soluble compound like MPTP will likely have significantly different pharmacokinetics.

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Paraquat is not metabolized by mammalian enzymes. The fraction absorbed from the gastrointestinal tract is excreted unchanged in the urine (4,5). A claim has been made that individuals with Parkinson's Disease tend to have decreased liver drug metabolizing enzymes (11). Apparently, these researchers believe a decreased ability to metabolize and excrete pesticides efficiently makes them more available to cause neurotoxic effects. Because Paraquat is not metabolized by anyone, there should be no "at risk population" based on that ^{crit~~erion~~} ~~criteria~~, if Paraquat is related in any way to development of Parkinson's Disease.

Another important aspect of Paraquat pharmacokinetics to be aware of is the active transport of Paraquat into certain cell types (12,13). The distinction between the monoamine and diamine cellular transport systems is significant in understanding the differences in the specific toxicity of paraquat and MPTP. The diamine transport system of the Type II pneumocytes has been convincingly demonstrated to be responsible for Paraquat's selective pulmonary toxicity (14,15). In close association with the pneumocytes is the capillary endothelium of the lung, which contains cells with the ability to clear many monoamine compounds from the blood, yet they are not target cells for Paraquat toxicity (16). Experimental evidence suggests that active accumulation of the monoamine, MPP+ (the end metabolite of MPTP) into the dopaminergic neurons of the substantia nigra occurs and is essential for toxicity (11,17,18). To date, there is no evidence that demonstrates the presence of a diamine transport system in the substantia nigra or that paraquat affects this specific portion of the brain. Therefore, although Paraquat

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is structurally similar to MPTP and MPP+, there are critical differences which ^aeffect the absorption, distribution, and cell-specific accumulation of these chemicals.

B. Animal Studies

There have been no published animal studies designed to specifically evaluate the effect of Paraquat on the dopaminergic neurons of the substantia nigra. However, there are numerous subchronic and chronic studies in many animal species where daily clinical observation^s have not detected signs of Parkinson's Disease. These include life-time feeding studies in mice (19) and rats (20), a one-year feeding study in dogs (21), and a three-generation reproduction study in rats (22). Also, several academic and governmental researchers have conducted experiments where the treatment and observation periods were sufficient to detect the signs of Parkinson's Disease (4,6,23,24,25). Again, no reports of unusual behavioral changes are contained in those studies.

C. Human Observations

Epidemiology studies on workers routinely exposed to Paraquat have not reported any adverse health effects due to their occupation (26,27,28,29). Obviously, none of these studies ^{was} ~~were~~ designed to answer the question, "Does Paraquat cause Parkinson's Disease?" However, several studies specifically evaluated the pulmonary effects of chronic Paraquat exposure. Based on the pharmacokinetic consideration discussed above,

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that would be the most sensitive indicator of Paraquat toxicity. No evidence of pulmonary dysfunction nor clinical observations of Parkinson-like syndrome ^{was} ~~were~~ reported in any individual in the studies.

Additionally, there have been a significant number of human paraquat poisonings worldwide since paraquat was first marketed in the early 1960s. To our knowledge, there have been no reports or observations of Parkinson-like signs either during the acute phase of the poisoning, or later in those individuals surviving the intoxication. If the association between overexposure to paraquat and the eventual development of Parkinson's Disease was strong, then it seems reasonable that promotion of the disorder would be most favorable following a high paraquat blood level. However, our surveillance of the medical literature has never identified any paraquat poisoning case report describing the finding of a Parkinson-like syndrome.

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