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April 8, 1976

Donald P. Morgan, M.D., Ph.D.
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Dear Dr. Morgan:

We have reviewed your draft, "Recognition and Management of Poisoning by Paraquat, Diquat and Morfamquat (Dipyridyls)." Enclosed is a copy of our paraquat medical brochure which has recently been revised. If you feel that appropriate sections of this brochure apply to the organization of your draft, please take the liberty of using them.

Since we do not manufacture any of the chemicals you have listed in the organochlorine draft, we suggest that you contact the respective manufacturers for review of this section.

Following are our comments regarding your draft on dipyridyls. The major portion of these comments concern the medical treatment and toxicology of paraquat.

1. Chemical Structure, Page 1 - Chevron Chemical Company markets 4 paraquat formulations in the U.S. These are listed on Page 1 of the enclosed paraquat medical brochure. The remaining paraquat products on your list are not sold in this country. All of the concentrated paraquat formulations sold in the U.S. contain 21.07 weight % cation.

2. Chemical Structure, Page 1 - The following is a list of the Chevron diquat formulations sold in this country. Each product contains 18.9 weight % cation.

   Chevron Weed Killer Concentrate D
   Ortho Diquat 2 Spray
   Ortho Diquat Herbicide Concentrate
   Ortho Diquat Water Weed Killer
   Ortho Reglone

3. Chemical Structure, Page 2 - To the best of our knowledge no morfamquat products are marketed in the U.S.

4. Toxicology, Page 2 - We are not aware of any direct binding, per se, of paraquat to biological chemicals or compounds within the living system. It is known that the lung, through an energy dependent mechanism, is capable of actively removing paraquat from the blood. Lung levels of paraquat can exceed those of the plasma, however, after a period of time paraquat is released, passes back into the plasma and is excreted.

5. Toxicology, Page 2 - Serious paraquat poisoning in human beings generally occurs only following ingestion or parenteral administration. There is one published case describing a worker who applied paraquat concentrate to his scrotum and underwear for several days as an alleged cure for pubic lice. This incident resulted in absorption of sufficient paraquat to cause systemic poisoning and death. No signs or symptoms of systemic involvement have been reported when paraquat is used according to label directions.

6. Toxicology, Page 2 - You may want to consider, before discussing the clinical events of paraquat poisoning, that the course of poisoning differs depending upon the amount of chemical ingested. If the dose is large (i.e., 6-8 oz.) the lungs, kidneys, liver, and adrenals may be severely affected initially, followed by possible fatal pulmonary edema within 24-72 hrs. Ingestion of smaller doses generally follows the discussion on Pages 2-3 of the draft. We are not aware of the development of hematuria or diffuse toxic pneumonitis on day 3 or 4 following ingestion of paraquat. We would appreciate any information you can provide us regarding this matter.

7. Toxicology, Page 3 - The histopathological changes that occur in the lung as demonstrated in laboratory animals following paraquat ingestion, initially involves swelling, vacuolization and cell organelle derangement in the type I and II epithelial cells of the alveoli. In some cases these cells may separate from the basement membrane and add further congestion within the alveolar spaces. The other events you have listed in the draft may then follow.

8. Toxicology, Page 3 - We are not aware that cranial nerve palsies are a part of the syndrome of paraquat poisoning. Again, we would appreciate any information you may have available concerning this condition.

9. Symptoms and Signs, Page 3 - Skin contact with concentrate may result in severe skin irritation. No reports, other than the above mentioned case, of systemic poisoning in man are known following dermal exposure to either concentrate or spray mist.

10. Symptoms and Signs, Page 3 - Liquid concentrate in the eyes may cause severe inflammation which develops gradually, reaching its maximum after 12-24 hours. Healing may be slow but even in severe cases recovery is usually complete.

11. Symptoms and Signs, Page 3 - Since the size of agricultural spray droplets are too large to pass into the deep lung spaces, inhaled particles are deposited on the mucosa of the upper respiratory tract. Local irritation may result as evidenced by nosebleeding, sorethroat, headache, or coughing if exposure is excessive.

12. Signs and Symptoms, Page 4 - Basically, this section is a repeat of the toxicology summary on Page 2. Perhaps these two sections could be combined rather than repeated.

13. Confirmation of Diagnosis, Page 4 - Please refer to the enclosed paraquat medical brochure, Page 13, for information regarding paraquat analysis.

14. Treatment, Page 4 - Recommended first-aid treatment for skin contact with paraquat concentrate is to wash the exposed area thoroughly with soap and water. If large areas of skin or the scrotum are involved, the patient should be hospitalized.

15. Treatment, Pages 4-6 - If paraquat has been ingested, we recommend that vomiting be induced immediately. This should be repeated several times and the individual hospitalized as soon as possible.

    There is evidence that the recommended treatment regimen for paraquat poisoning, Pages 4-7 of the medical brochure, has been effective when started within 24 hours after ingestion. Again, please feel free to use this section or parts of it if you think it will be of value.

16. Treatment, Page 6 - Use of superoxide dismutase has not proven to be effective for the treatment of paraquat poisoning. This enzyme has been tried in a number of cases and has met with questionable results. It may be premature to mention use of superoxide dismutase until further laboratory investigations have been conducted to determine its efficacy. It should also be mentioned that superoxide dismutase is not a drug and does not have an IND petition for use in this country. For this reason, in addition to only a few available chemical houses that sell this enzyme, it is difficult for the attending physician to obtain and use this compound.

17. Treatment, Page 7 - You may also want to include as Item 7, monitoring the patient's BUN and creatinine levels since these may serve as early indicators of systemic involvement.

Should you have any questions regarding these comments, please feel free to contact me. I will be happy to review any future drafts on this subject.

Very truly yours,

Original Signed
J. E. FORD

Jon E. Ford, Ph.D.
Environmental Toxicologist

JEF:flm
Enclosure

bcc: Mr. J. N. Ospenson
Mr. J. A. Spence