UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUN 30 1989

007303

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Pyridate - Review of Registrant's Safety Evaluation Assessment of Pyridate; Evaluation of the Registrant's Reply to EPA Comments Concerning a Mutagenicity Study (UDS Assay); and Review of a Metabolism Study

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FROM: Yiannakis M. Ioannou, Ph.D., Section Head
Review Section I, Toxicology Branch II (HFAS)
Health Effects Division (H7509C)
J M Ioannou 6/21/89

TO: Robert J. Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (H7505C)

THRU: Marcia van Gemert, Ph.D., Branch Chief
Toxicology Branch II (HFAS)
Health Effects Division (H7509C)
Marcia van Gemert 6/28/89

MRID Nos.: 409862-01 and 409718-01

Registrant: Agrolinz, Inc., Memphis, Tennessee

Action Requested

Review and comment on the Registrant's account of "Pyridate safety evaluation", evaluate the Registrant's reply to EPA comments on a mutagenicity study (unscheduled DNA synthesis assay); and review a rat metabolism Study.

Conclusions and Recommendations

A. Pyridate Safety Evaluation - The registrant presented a brief account on pyridate safety evaluation. This account is based on all available data on pyridate submitted to the Agency and reviewed by Toxicology Branch. Based on the available data (acceptable acute, subchronic, chronic toxicity and oncogenicity, terotogenicity, reproduction, mutagenicity and metabolism studies) we agree with the Registrant's contention that pyridate appears to have a high margin of safety. However, since the data base for pyridate

is not complete (mouse oncogenicity not submitted; 1-year chronic toxicity dog, under review) a final assessment for pyridate safety cannot be made at present.

B. Mutagenicity Study - Registrant's Response to EPA's Comments. A Mutagenicity Study, titled " in vivo - in vitro Rat Hepatocyte Unscheduled DNA Synthesis Assay" was recently reviewed (12-05-88) by Toxicology Branch and classified as unacceptable due to several deficiencies concerning mainly the following points.

1. Only male rats were used for the assay.

2. No information was provided as to the absorption of pyridate from the GI tract at high enough concentrations to cause cytotoxicity of the target cells.

3. No documentation was provided to show that storage of slides coated with Kodak NTB2 emulsion for 3 days was sufficient time to develop enough nuclear grains from a weakly positive chemical.

In the present reply, the Registrant addressed all 3 points raised by the Agency and satisfactory explanations and/or additional information were provided so that all issues raised by the Agency are now resolved. The study is thus upgraded to Acceptable.

Rat Metabolism Study. The Registrant submitted a comprehensive metabolism study with pyridate in rats. The study was reviewed by Dynamac and the DER is attached. Briefly the conduct of the study and the major findings were as follows:

Male and female Sprague-Dawley rats were administered single oral (gavage) doses of ^{14}C-Pyridate (radiopurity greater than 97%) at levels of 20, 200, or 600 mg/kg body weight. A multiple exposure study was also conducted at a dose level of 20 mg/kg/day of nonradioactive Pyridate for 14 days followed by a single oral administration of ^{14}C-Pyridate. The absorption, distribution, metabolism, and excretion of Pyridate were investigated at selected time points. Metabolites were isolated (from urine) and identified using a variety of acceptable analytical techniques.

Results

At single oral dose levels of 20 and 200 mg/kg, Pyridate was rapidly absorbed through the gastrointestinal tract distributed to all major tissues examined and greater than 93 percent of the administered dose was excreted in urine and feces within 96 hours, in both sexes. The major portion of Pyridate-derived

radioactivity (approximately 80%) was excreted in the urine. No significant difference in excretion was seen between the single dose levels of 20 and 200 mg/kg and the multiple dose of 20 mg/kg/day. At the high dose of 600 mg/kg, the percent of Pyridate excreted in the urine and feces was approximately 68 percent within 24 hours and 87 percent within 96 hours.

Pyridate distribution in the major tissues was studied at selected time points after oral administration of 20, 200, or 600 mg/kg of Pyridate to male and female rats. At all dose levels tested, the highest concentration of Pyridate (as percent of administered dose) was found in the kidney, liver, and plasma. Clearance of radioactivity from these tissues was almost complete within 24 hours with the 20 and 200 mg/kg dose levels (less than 0.1% of the dose remaining in these tissues); however, with the dose of 600 mg/kg, clearance from all tissues was slow with significant concentrations still remaining in these tissues at the 24-hour time point although, clearance was almost complete by 96 hours. These results suggest that the high dose (600 mg/kg) was either more slowly absorbed from the gastrointestinal tract and/or more slowly metabolized (due possibly to saturation of metabolizing enzymes) as compared to the dose levels of 20 or 200 mg/kg.

The sponsor reported the isolation and identification of Pyridate metabolites from rat urine. Using thin layer chromatography (TLC) and different solvent systems, three metabolites were isolated from urine. Two of the metabolites were identified (using authentic standards) as CL-9673 (the hydrolysis product of Pyridate), and CL-9673-O-glucuronide. These two metabolites accounted for 35-69 percent of the radioactivity in urine. A third metabolite (representing 26-37 percent of the radioactivity in urine) was identified (using mass spectrometry) as the hydroxylated derivative of CL-9673. None of the radioactivity in the urine cochromatographed with the parent compound, Pyridate.

Conclusions

Based on results presented here, it appears that Pyridate, when administered orally to male or female rats at dose levels of 20 or 200 mg/kg, (single doses), or at 20 mg/kg, multiple exposure, is rapidly absorbed from the gastrointestinal tract, distributed to all major tissues examined metabolized and cleared from all tissues rapidly so that 24 hours postdosing only very low concentrations are present in these tissues. Most of the Pyridate-derived radioactivity is excreted in the urine (> 80%) and consists of three Pyridate metabolites identified as CL-9673, CL-9673-O-glucuronide and the hydroxylated derivative of CL-9673.

At the dose level 600 mg/kg (single oral dose), Pyridate appears to be absorbed at a slower rate than lower dose levels, distributed to the same tissues as lower dose lavels, and eliminated from these tissues at a slower rate.

Classification: Core-Guideline