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

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Date: February 9, 2009

SUBJECT: Paraquat. Review and Interpretation of Special Ferret Toxicity Studies.

PC Code: 061601
Decision No.: 397930, 397089, 397656
Petition No.: N/A
Risk Assessment Type: None
TXR No.: 0055097
MRID No.: 47474201, 47474202

DP Barcode: D354431, D355033, D355034, D355431
Registration No.: 82557-1, 66222-130, 82542-3
Regulatory Action: Product Registration
Case No.: N/A
CAS No.: 1910-42-5
40 CFR: N/A

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I. Conclusions

A special toxicity study comparing the ability of a lethal dose of several paraquat formulations to induce an emetic response in the ferret has been submitted to the Agency and has been evaluated. This study was flawed because emetic response was not correlated to mortality and morbidity, which are the endpoints necessary for evaluation of potential adverse effects in humans.

Therefore, this study provides no useful information regarding the comparative safety of different paraquat formulations.

II. Action Requested

Generic paraquat dichloride formulations [including 82557-1 (Sinon USA, Inc), 82542-3 (Source Dynamics, LLC) and 66222-130 (Makhteshim Agan of North America, Inc)] currently have time-limited restrictions on their registrations that may be removed pending a decision by OPP that their products still differ only in ways that would not significantly increase the risk of unreasonable adverse effects on human health and the environment from Gramoxone Inteon (EPA Reg. No. 100-1217), a formulation introduced by Syngenta in 2005 that employs new alginate technology and is claimed to be less toxic (when ingested) than any previous formulations produced by Syngenta or any other registrant. To support such a decision, the Herbicide Branch in RD has asked HED to review the new ferret data (MRIDs 47474201, 47474202) submitted by Makhteshim Agan of North America, Inc. and Sinon USA, Inc. to determine if the new data causes the Agency's previous conclusions to change. No other data was received.

III. Background

The "me too" herbicides Paraquat SL Herbicide™ (EPA Reg. No. 82557-1, Sinon USA, Inc.) and Parazone™ 3SL (EPA Reg. No. 66222-130, Makhteshim Agan of North America (MANA), USA) were registered based on Gramoxone® Max (EPA Reg. No. 100-1074, Syngenta USA). All of these formulations had 43.8% of the active ingredient (a.i.), paraquat dichloride. Syngenta re-formulated paraquat-containing herbicides with Alginate Wall Technology (AWT), also called a "trigger gel", which Syngenta claims reduces paraquat absorption and toxicity as a result of gelling under the acidic conditions of the stomach. EPA granted registration of a new formulation, Gramoxone INTEON™, utilizing AWT with a paraquat dichloride concentration of 30.1%, on August 17, 2005 (Reg. No. 100-1217). Subsequently, Syngenta voluntarily cancelled registration of all non-AWT (non-INTEON™) paraquat formulations, including 100-1074. Registrations of Paraquat SL Herbicide™ and Parazone™ 3SL were granted by EPA under time-limited conditions until September 1, 2008, and have been extended to the present following submission of amendments by MANA and Sinon to remove the time limitation. Removal of the time limitation is predicated on evaluation by OPP of existing information and any new data that can be used to determine whether these "me too" products cause unreasonable adverse effects on human health compared to Gramoxone INTEON™. Adverse effects (mortality and morbidity) on human health in response to paraquat occur most often after deliberate oral ingestion in suicide attempts, and can be reduced by vomiting, which can decrease the ingested dose. For this reason, paraquat is commonly formulated with an emetic agent. MANA and Sinon submitted a non-guideline, acute (four hour) study (MRID 47474201) using the ferret as a model of the human emetic response (retching and vomiting) to compare three formulations (Gramoxone INTEON™ , Paraquat SL Herbicide™ , and Parazone™ 3SL). This study showed no statistically significant differences in the emetic response of ferrets to these formulations four hours following administration. Based on this study, MANA and Sinon claim that because there are no statistically significant differences among these formulations in the emetic responses of ferrets following acute administration, there are no substantive differences among these

formulations that would indicate differences in propensity to cause adverse effects in human health.

IV. Results/Discussion

New data was provided by MANA and Sinon (MRIDs 47474201 and 47474202) that investigated the ability of Gramoxone INTEON™ , Paraquat SL Herbicide™ and Parazone™ 3SL to induce an "emetic response" (vomiting and retching) in ferrets at a dose of 0.5 mL/kg (169 mg/kg Gramoxone Inteon™ , 245 mg/kg Paraquat SL, 249 mg/kg Parazone™) administered orally by gavage. A positive control of 0.64-0.65 mg of emetic and a negative control of water vehicle were also included. The emetic response endpoints investigated were mean times of onset of retching, mean times of onset of vomiting, and the hourly mean number of emetic episodes observed within four hours following administration. No significant ($p \leq 0.05$) differences among the paraquat formulations were observed at any of these endpoints, and emetic episodes were increased for all paraquat formulations compared to the emetic control. These results indicated that no differences existed among the paraquat formulations, and that paraquat itself increases emetic activity. HED reviewed this study , and agrees that the ferret is an appropriate model organism. The dose chosen was adequate to observe emetic effects, was justified based on the dose range-finding study (MRID 47474202), and was relevant to human exposures. However, HED disagrees with the use of emetic episodes (vomiting plus retching) as the endpoints, since it is vomiting (and not retching) that reduces the ingested paraquat dose. Re-analysis of the vomiting data showed no significant ($p \leq 0.05$) differences in the incidence of vomiting among controls or formulations at 15 minutes, indicating data were too variable to detect an effect at this time. After 1 hour, the only difference was increased vomiting in Gramoxone Inteon™-treated animals compared to the vehicle control. After 4 hours, vomiting was significantly increased for all formulations compared to vehicle and emetic controls, and there were no differences among the formulations. Thus, the use of a vomiting by HED compared to 'emetic episodes' by the registrants (retching plus vomiting) resulted in the same conclusion (e.g. no differences in emetic behavior among paraquat formulations and potentiation of the emetic response by paraquat). However, it is important to note that it is unknown how emetic behaviors correlated to mortality and morbidity, which are the endpoints of interest for determining the relative safety of different paraquat formulations.

The major deficiency of this study was that emetic behavior was not correlated to mortality and morbidity. Thus, it was not possible to use this study as a stand-alone to ascertain if the different formulations would differ substantially in the propensity to cause adverse effects in humans. Other deficiencies were that blood levels of paraquat were not measured and that sub-lethal doses were not investigated. In the absence of blood levels, it was unknown to what extent the incidence of an emetic response (vomiting plus retching) or vomiting alone would reduce the absorbed dose, since the productivity of vomiting may vary considerably. Also, the paraquat formulations tested contained different concentrations of paraquat (30.1-43.8%), and the differences in the formulations (e.g. ± AWT) may differently affect absorption. The use of one, ferret-lethal dose (0.5 mL/kg) for a short period of time (4 hours) did not allow investigation of mortality and morbidity over time at sub-lethal doses. Thus, *since sub-lethal and borderline-lethal doses were not included, and observations for mortality and morbidity were not conducted*

over a longer period of time, it was not possible to ascertain from this study whether or not these paraquat formulations differ in propensity to cause mortality or morbidity.

MRID Summary Table

Study Type	MRID or Literature Reference	Comments
Acute (4 hours), non-guideline main study in ferrets.	47474201	Gramoxone Inteon™, Paraquat SL Herbicide™, and Parazone™ 3SL, emetic (positive control), water vehicle (negative control). One dose. Endpoints: vomiting and retching.
Sub-Acute (14 days), non-guideline dose range- finding study in ferrets.	47474202	Gramoxone Inteon™ and Paraquat SL Herbicide™ at 0.1, 0.25, 1 mL/kg. Endpoints: vomiting, retching, gross path., mortality.

V. References.

Merkel, D. Paraquat SL Herbicide (Firestorm), Gramoxone Inteon and Parazone 3SL: Evaluation of Emesis Induced in the Ferret by Three Paraquat Dichloride Formulations Containing an Emetic. Project Number: 23206, 10/010/04, P927/SIN/02. Unpublished study prepared by Product Safety Laboratories. MRID 47474201.

Merkel, D. (2008) Paraquat SL Herbicide (Firestorm), Gramoxone Inteon and Parazone 3SL: Evaluation of Drug-Induced Emesis in the Ferret Preliminary Dose-Range Finding Study: Two Commercial Paraquat Dichloride Formulations. Project Number: 22585, 927/SIN. Unpublished study prepared by Product Safety Laboratories. 14 p. MRID 47474202.