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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Pesticide Petition Nos. 4G3047/5G3217 - Pyridate Herbicide - Evaluation of the Response by Gilmore, Inc. to EPA Comments Pertaining to the Multigeneration Reproduction Study in Rats (EPA Experimental Use Permit Nos. 42545-EUP-1/42545-EUP-2)

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Registrant: Gilmore, Inc., Memphis, TN

Conclusions: Based on the evaluation of additional data submitted by the sponsor, Toxicology Branch I (TB-I) has determined that the NOEL for systemic and reproductive toxicity is established at 216 ppm (10.8 mg/kg/day), the analytical concentration of Pyridate in the diet. The LEL (depression of body weight gains of pups and maternal animals) is established at the analytical concentration of 1350 ppm (67.5 mg/kg/day). The study is upgraded to Core-Minimum classification.

TB-I has evaluated additional data and supplementary comments submitted by Gilmore, Inc., concerning a multigeneration reproduction study with Pyridate Technical in Wistar rats, which was initially given a Core-Supplementary classification due to a number of deficiencies involving primarily reporting of data.

All issues raised by the Agency are presented below (for the record) followed by the registrant's response and/or evaluation of new pertinent data for resolving these issues.

1. Stability of Pyridate - Data on Pyridate stability submitted earlier by the sponsor have suggested that Pyridate was unstable in the diet at room temperature so that losses up to 73 percent were reported in a 72-hour period. The issue of Pyridate stability was also raised (by the Agency) in a number of other chronic feeding studies with this chemical. For resolving this issue, the sponsor provided the Agency with extensive data on Pyridate stability. Further evaluation by TB-I of the submitted data resulted in the following conclusions:

   a. Pyridate in the diet is partially hydrolyzed at room temperature to give the metabolite CL-9673. This hydrolysis product has been shown to be the major Pyridate metabolite in animal and plant metabolism studies.

   b. The rate of hydrolysis of Pyridate in the diet at room temperature is proportional to the time of exposure to room temperature. Thus, after 24 hours, 77 percent of Pyridate is recovered in the rat diet while approximately 15 percent is present as the hydrolysis product CL-9673; at 72 hours after mixing with the diet only 54 percent is present as Pyridate while 34 percent is in the form of Cl-9673; at 120 hours, 42 and 47 percent is present in the diet as Pyridate and CL-9673, respectively. At the temperature of 3 °C the rate of Pyridate hydrolysis is considerably lower than at room temperature at all time points examined.

2. Summary Tables for Ophthalmoscopic Examination of the $F_1$ Generation - The sponsor submitted data on the ophthalmoscopic examination of the $F_1$ parent rats. No ocular lesions were seen in any of the animals of the control and treated groups. We thus consider this issue resolved.

3. Provide Summary Tables of Gross Pathology Data from all Generations - Evaluation of the data submitted by the sponsor revealed that there were no differences in the incidence of macroscopic lesions between the treated and control groups of all parent rats and all three generations of pups. We thus consider this issue resolved.

4. Provide Histopathology Summary Tables and Individual Animal Incidence of Lesions for Liver, Kidney, Pituitaries and Thyroid for all Generations - The sponsor presented data for the control and high-dose groups (2500 ppm) for all tissues requested. Review of these data revealed that the incidence of microscopic lesions was for the most part comparable between the control and the high-dose group. Numerically higher incidence of histopathological lesions was observed in the high-dose group as follows:

   a. Kidney: Focal tubular nephrosis - 3/20 vs. 6/20 for the control and high-dose groups, respectively, for $F_1$ parent male rats.

   b. Liver: Focal aggregates of the res cells and necrotic hepatocytes - $F_0$ parent male rats - 2/20 vs. 4/20 for the control and high-dose groups, respectively; $F_2$ parent male rats - 4/20 vs. 6/19 for the control and high-dose groups, respectively.

   We do not consider these histopathological changes to be of biological significance and thus we consider this issue resolved.

5. Provide Summary Tables and Individual Animal Data for Congenital Defects for all Litters - In their response, the sponsor stated that "no congenital defects were observed in either of the two litters in each of the generations. Therefore, no individual animal data can be given." However, based on the historical control data that the sponsor provided it is evident that for this strain of rats a number of congenital defects occur naturally at different incidence rates. Upon further request, the sponsor

submitted additional data for resolving this issue. Basically, the new response reiterates that no congenital defects were seen in any of the litters and that the higher background incidence of such defects observed in the historical controls was attributed to the fact that these historical controls were from teratogenicity rather than reproduction studies. Additionally, the sponsor submitted data on clinical observations for all litters during lactation. Analysis of these data did not reveal any differences between the litters of the treated and control groups. Thus, we consider this issue resolved.

6. Translate into English the Analytical Data on Pyridate - The sponsor provided the English translation of the analytical data for Pyridate Technical as requested. We thus consider this issue resolved.

7. Describe the Procedure Used in Establishing the Percent Recovery of Pyridate in Diet Preparations - The sponsor has presented data showing how the recovery of Pyridate from the diet was established. The HPLC system used for the study was slightly different from the procedure reported here. Howeve , it does not appear that these changes had any effec on the recovery of Pyridate from the diet as reported earlier. For the present response, the recovery reported was between 104 and 110 percent, as compared to 80 to 85 percent recovery reported earlier for this and other chronic toxicity studies. Based on the sponsor's response and the presentation of supplementary data on Pyridate recovery from the diet, we consider this issue resolved.

8. The Authors reported that "Because of holidays and workload the autopsy of the $F_1$ parent rats and of the $F_2b$ young was postponed 4 to 5 weeks." We request that the authors provide us with information as to how those animals were handled prior to autopsy - We consider the response given by the sponsor to be satisfactory and thus we consider this issue to be resolved.

Based on the analysis of the newly submitted data on Pyridate stability, TB-I is satisfied that losses in Pyridate in the diet reported earlier by the sponsor were in error and that such losses were accounted for by monitoring the hydrolysis product of Pyridate, CL-9673. However, the total amount of Pyridate Technical received by the test animals at each of the dose levels tested was approximately 46 percent lower than the target concentrations* (i.e., 46% of Pyridate was in the form of the hydrolysis product CL-9673). Thus, the dose

* This is a conservative estimate based on the fact that throughout the study animals were offered diet on Fridays to last until Monday thus, exposing the test article to room temperature for 72 hours

levels tested should be lowered by 46 percent to represent actual concentrations of Pyridate received by test animals. The dose levels of 80, 400, and 2500 ppm (4, 20, and 125 mg/kg/day) thus become the analytical dose levels of 43, 216, and 1350 ppm (2.2, 10.8, and 67.5 mg/kg/day).

Based on the aforementioned justifications, the LEL for systemic toxicity (depression of maternal body weight gains) is con- is considered to be:

Nominal Concentration - 2500 ppm (125 mg/kg/day)
Analytical Concentration - 1350 ppm (67.5 mg/kg/day)

The NOEL is considered to be:

Nominal Concentration - 400 ppm (20 mg/kg/day)
Analytical Concentration - 216 ppm (10.8 mg/kg/day)

The LEL for reproductive toxicity (depression of pup body weight gains) is considered to be:

Nominal Concentration - 2500 ppm (125 mg/kg/day)
Analytical Concentration - 1350 ppm (67.5 mg/kg/day)

The NOEL* is considered to be:

Nominal Concentration - 400 ppm (20 mg/kg/day)
Analytical Concentration - 216 ppm (10.8 mg/kg/day)

Based on the evaluation of the newly submitted data, and the justifications and/or clarifications submitted by the sponsor, TB-I is upgrading the classification of this study to Core-Minimum.

* The NOEL for the RfD will be based on the analytical concentration of 216 ppm (10.8 mg/kg/day)