REVIEWER

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

007043

FEB 24 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Pesticide Petition Nos. 4G3047/5G3217 - Pyridate Herbicide - Review of Additional Data Submitted by Gilmore, Inc. in Response to EPA Comments Pertaining to Mouse Oncogenicity Study (EPA ID Nos. 42545-LE/ 42545-LG/8F3603)

TOX Chem No.: 716A
Project No.: 9-0618
Record No.: 237460

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Registrant: Gilmore, Inc., Memphis, TN

MRID No.: 409394-01

Action Requested

Gilmore, Inc. is requesting that the mouse oncogenicity study with Pyridate is upgraded from Core-Supplementary to a Core-Minimum classification based on the additional information submitted by the registrant.

Conclusion

Based on the evaluation of additional data submitted by the registrant and taking into consideration the registrant's explanations and/or clarifications of several issues, Toxicology Branch I (TB I) has determined that in the present response the registrant failed to resolve two major issues concerning the analysis of diet samples for Pyridate concentrations and, more importantly, the unusually high number of tissues not examined for histopathological lesions.

The study remains classified as Core-Supplementary.

Background

Gilmore, Inc. submitted and TB I reviewed two long-term studies conducted in mice with technical Pyridate and titled:

A. Eighty-Week Chronic Toxicity Study in Mice.

B. 104-Week Life Span Carcinogenicity Study in Mice.

Upon evaluation, a number of deficiencies were found in both studies (as specified in the attached memorandum dated December 5, 1986, from Y.M. Ioannou to R.J. Taylor and titled "Review of Chronic Toxicity, Carcinogenicity, Reproduction, and Teratology Studies in Support of Tolerances on Corn, Wheat, and Rice). As a result, the Agency classified both studies as Core-Supplementary, with the possibility of upgrading both studies to a Core-Minimum classification if the specified deficiencies were resolved by the registrant.

Review of Additional Data

With this submission the registrant made an attempt to address the issues raised by the Agency on both studies. All issues raised by the Agency are presented below (for the record) followed by the registrant's response and the Agency's evaluation of new pertinent data and/or comments for resolving these issues.

A. Eighty-Week Chronic Toxicity Study in Mice

Deficiency 1

> No clinical chemistry measurements were reported in the present study, although such measurements are required for a chronic toxicity study according to the EPA or OECD Guidelines.

The sponsor has clarified the fact that this study, which was conducted concurrently with the 104-week feeding oncogenicity study, was intended to serve as an interim sacrifice for the oncogenicity study and not as a standard chronic toxicity study. Clinical chemistry parameters were not measured in this interim sacrifice due mainly to the fact that Pyridate did not have any adverse effects on such parameters in the corresponding subchronic and/or chronic toxicity studies in rats.

Based on the fact that the study was conducted concurrently with the 104-week feeding oncogenicity study under identical conditions (same strain of mice, same dose levels, etc.), we accept this as an interim sacrifice and not as a standard chronic toxicity study. Thus, we consider this deficiency resolved.

Deficiency 2

> No urinalysis measurements were reported in the present study although such measurements are required for a chronic toxicity study according to the EPA Guidelines.

In their response, the sponsor reported that urinalyses were not performed in this study for the same reasons as specified for deficiency 1.

The Agency considers this justification acceptable and thus this issue is considered resolved.

Deficiency 3

> The registrant should provide us with individual histopathology incidence tables.

The sponsor submitted all individual animal histopathology data as requested. Based on a cursory examination of these data, there were no apparent discrepancies between these data and the histopathology data submitted with the original report in summary incidence tables. Thus, the incidence of the major histopathological lesions (summarized in the attached DER) remains unchanged.

This issue is considered resolved.

Deficiency 4

> The attached analytical data on Pyridate should be translated into English.

The sponsor submitted the English translation of the analytical data on Pyridate (see attached).

We consider this issue resolved.

Deficiency 5

> Provide us with the analytical procedure used in determining the recovery of Pyridate in diet preparations.

The Agency raised this issue with the chronic toxicity, oncogenicity, and reproduction studies in rats with Pyridate technical. The sponsor submitted and the Agency accepted the procedures used for determining the recovery of Pyridate in diet preparations for the rat studies. In their present response, the sponsor noted that the procedure used for the mouse study was, with minor exceptions, similar to the procedures used in the rat studies. Although the procedure submitted with this response is the one used for the extraction of Pyridate from rat diet preparations, the Agency is satisfied that the procedure used for determining the percent recovery of Pyridate in mouse diet preparations was appropriate.

We thus consider this issue resolved.

Deficiency 6

> Explain why analysis of Pyridate levels in the diet was conducted

in some cases every 5 months instead of 2 months as stated in the text of the report.

The sponsor stated in their response that due to a freezer breakdown, only 8 out of 14 batches of diet were analyzed for Pyridate levels. The bulk of the diets (mixed with Pyridate) for each dose group were reportedly stored in separate freezers and they were not affected by the breakdown. However, if that were the case, the sponsor should explain why new samples from the stored diets were not analyzed unless, all analyses were carried out at the completion of the study, in which case the main purpose of analyzing the diet has been defeated since diet concentrations deviating from target levels could not be adjusted during the course of this study. In fact, throughout the study, there were several occasions when Pyridate levels in the diet were significantly lower than the target concentrations (for example, diets fed to the animals between June 1 and November 19, 1981 were considerably lower than the intended levels for all dose groups - 35, 38, and 23 percent lower than target concentrations in the low-, mid-, and high-dose groups, respectively; however, diets prepared on November 19, 1981 were also of considerably lower levels than intended - 30, 28, and 23 percent for the low-, mid-, and high-dose groups, respectively, thus indicating that no attempt was made to adjust these diets to target levels.

Based on the aforementioned discrepancies, we are requiring that the sponsor provide the Agency with all the original records showing exactly when the diets were prepared, when the samples for analysis were taken, and especially when the analysis of each sample was performed.

We thus consider this issue unresolved pending more information and/or justifications from the sponsor.

Deficiency 7

The authors should explain why so many organs/tissues were lost either due to autolysis and cannibalism or lost during autopsy and processing.

Comments by the sponsor and the Agency on this deficiency are discussed under deficiency 6 of the 2-year carcinogenicity study (similar deficiency).

B. Two-Year Dietary Carcinogenicity Study in Mice

Deficiency 1

> The authors should describe the procedure employed in estimating the recovery of Pyridate in diet preparations.

The registrant's response to this deficiency has been evaluated already as shown under deficiency A1 above. Thus, this deficiency is considered resolved.

Deficiency 2

> Explain why analysis of Pyridate levels in the diet was conducted in some cases every 5 months instead of 2 months as stated in the text of the report.

The registrant's response to this deficiency has been evaluated as shown above (see Deficiency A6). The additional data and/or clarifications provided by the registrant were deemed inadequate. Thus, this deficiency remains unresolved.

Deficiency 3

> Individual histopathology incidence tables for male and female mice should be submitted.

The sponsor submitted the histopathology data as requested by the Agency. Comments on the evaluation of these data are included in the discussion of deficiency 6 below.

This deficiency is considered resolved.

Deficiencies 4 and 5

> Complete Table 12 (page 60) by providing the number of animals examined for lesions for: Abdominal cavity, nasal cavity, hematopoietic system, and mediastinal lymph nodes.
>
> Complete Table 9 (pages 42 to 50) by providing the number of animals examined for each specified observation.

The sponsor submitted the requested data, thus resolving these two deficiencies.

Deficiency 6

> A number of tissues were lost according to the authors, due to "autolysis or cannibalism, loss during autopsy; loss during fixation or processing." Thus, fewer types of some tissues were available for macroscopic and microscopic examination.

This deficiency was common in both studies (80-week chronic toxicity and 104-week oncogenicity) and thus comments made below apply to both studies.

In their response, the sponsor made the following points:

1. Lost tissues (during dissection and/or processing) were mainly of very small size that are not easily seen in the mouse.

2. None of the tissues lost had any lesions, otherwise they would have been seen since they would be of bigger size and/or of different color.

3. Mice undergo postmortem autolysis faster than other animals (because of higher metabolism rates).

4. Mice are more cannibalistic than rats.

5. The conclusions as to the negative oncogenic potential of Pyridate will not change even if all the lost tissues were considered to have developed tumors or tumorlike lesions.

Based on the submission by the sponsor of all the requested histopathology data (individual animal data and/or summary histopathology incidence tables), TB I has reevaluated these data and in conjunction with the missing tissues the following comments can be made:

1. Missing tissues were reported in all dose groups, in male and female mice.

2. Even large tissues such as liver and lung were missing in some cases or somehow they were not examined.

3. The number of tissues of small size lost for each dose group was unusually high, in some cases reaching up to 70 percent, as shown below.

Tissue[2/]	Percent of Tissues Not Examined[1/]							
	Dose (ppm)							
	Males				Females			
	0	200	1000	5000	0	200	1000	5000
Adrenals	2	12	4	2	10	10	2	8
Brain	2	2	0	0	2	8	2	0
Eyes	4	2	2	0	4	14	2	0
Liver	2	2	0	0	2	6	0	0
Lung	4	6	2	0	2	6	0	0
Mammary gland	-	-	-	-	14	10	6	2
Ovaries	-	-	-	-	16	34	14	26
Peripheral nerve	28	8	6	14	16	16	24	26
Pituitary	38	36	26	36	18	28	20	16
Thymus	56	54	42	60	32	52	40	40
Thyroid	22	18	24	10	14	22	24	18
Gall bladder	52	61	58	70	38	60	30	52
Axillary lymph nodes	20	26	12	22	18	26	10	8

1/Tissues were lost due to autolysis and cannibalism or lost during autopsy and processing.
2/50 mice were tested/dose group/sex.

4. Based on the available histopathology data, Pyridate does not appear to be oncogenic in male and female mice. However, in view of the large number of tissues that were lost during this study and thus not examined, the oncogenic potential of this chemical in mice cannot be known with certainty.

   Thus, this deficiency remains unresolved.

TB I concludes that this study remains classified as Core-Supplementary based on the fact that the sponsor did not adequately resolve the issues concerning 1) analysis of samples for Pyridate concentrations in the diet (as discussed under Deficiency A6) and 2) the unusually high number of tissues lost because of autolysis and cannibalism, or lost during autopsy and processing and thus not examined for histopathological lesions (as discussed under Deficiency B6).

Attachments

53040:I:Ioannou:HED-01:KENCO:02/07/89:02/21/89:de:VO:CT