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CASWELL FILE

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

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MAY 20 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Metribuzin
4-amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one (SENCOR Technical): Review of additional information submitted by the registrant.

Caswell No: 033D
HED Project No: 1-1094
MRID No: 418355-01

FROM: Timothy F. McMahon, Ph.D., Toxicologist 5/8/91
Review Section I, Toxicology Branch II
Health Effects Division (H7509C)

TO: Lois Rossi/PM Team 74
Registration Division (H7505C)

THRU: Yiannakis M. Ioannou, Ph.D., Section Head 5/9/91
Review Section I, Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia Van Gemert, Ph.D., Branch Chief 5/10/91
Toxicology Branch II
Health Effects Division (H7509C)

Registrant: Mobay Corporation

Action Requested: Review of the Registrant's response to Agency review of a rabbit teratology study with 4-amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one (SENCOR Technical), required for California registration.

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Discussion and Conclusions:

Initial review of the registrant's report, "Teratology Study in the Rabbit with SENCOR Technical (Metribuzin)" (MRID#412492-01), revealed a number of deficiencies which resulted in a core supplementary classification of this study. In order to properly evaluate the original study, the Agency requested the following information from the registrant:

1) litter incidence data for fetal skeletal abnormalities listed in Table VI of report

2) historical control data for the skeletal abnormalities listed in Table VI of report

3) necropsy findings on does not listed in Appendix D

4) results of histological examination of maternal tissues, if any

5) times and dates of sacrifice for all maternal rabbits

The registrant's response to these concerns are addressed below.

1) litter incidence data for fetal skeletal abnormalities listed in Table VI of report

These data were requested as the litter is considered the experimental unit for developmental toxicity studies, and was not provided for assessment of skeletal abnormalities observed in the developmental toxicity study. The registrant supplied information on litter incidence for all values presented in Table VI of the original report. Evaluation of these data as submitted showed that the litter incidence for the skeletal abnormalities listed in Table 6 of the initial review (attached) were not significantly different between dose groups, with the exception of the litter incidence for irregular spinous process of the scapula, in which the litter incidence increased from 0 in controls to 5 in the 85mg/kg/day dose group.

2) historical control data for the skeletal abnormalities listed in Table VI of report

These data were requested as there was not proper historical control data with which to evaluate the significance of the skeletal abnormalities observed in the developmental toxicity study. The registrant responded to this request by supplying historical control data from 19 studies with the American Dutch rabbit on the skeletal abnormalities flagged in Table VI of the original report. Evaluation of these data showed that the historical incidence of the skeletal abnormalities listed in Table 6 of the review was adequate to explain the incidence of these abnormalities, with the exception of the irregular spinous process, which fell outside the historical control range (0-5 fetal incidence).

3) necropsy findings on does not listed in Appendix D

These data were requested in order to properly evaluate potential maternal toxicity of test article administration. The registrant supplied necropsy data for those does not listed in Appendix D of the original report. Evaluation of these data did not alter the original conclusions of test article toxicity to maternal rabbits in this study, as the additional data submitted were for does in which no findings were present at necropsy.

4) results of histological examination of maternal tissues, if any

These data were requested in order that maternal toxicity might be more carefully evaluated, However, the registrant stated that these data were not generated in this study. As this is not a required aspect for a developmental toxicity study, this response is considered adequate.

5) times and dates of sacrifice for all maternal rabbits

These data were requested as a significant difference in mean fetal body weight was observed between fetuses of control rabbits and those in the 30 mg/kg/day dose group which could have been due to differences in sacrifice times for maternal rabbits or differences in insemination times, i.e. differences in gestation time. However, data submitted by the registrant showed that the times of insemination and sacrifice were equivalent between dose groups of maternal rabbits. In addition, it was stated on page 10 of the review that the lower mean fetal body weight observed in the 30 mg/kg/day dose group as compared to control was within historical control range as supplied by the registrant.

Based on the additional information supplied by the registrant in support of the developmental toxicity study with SENCOR technical, this study is upgraded from core supplementary to core minimum data. In addition, the Developmental toxicity NOEL and LEL are stated as follows:

Developmental toxicity NOEL= 30 mg/kg/day
Developmental toxicity LEL= 85 mg/kg/day (increase in irregular spinous process)

TABLE 6

Developmental Toxicity of SENCOR Technical: Skeletal Examination[a]

Dose group (mg/kg/day)	0	10	30	85
Observations[a] #pups(litters) examined	85 (15)	84 (14)	86 (14)	77 (14)
skull:				
incomplete ossification	17(10)	31[b](11)	38[c](11)	16(7)
enlarged fontanelle	13(10)	30[c](11)	36[c] (11)	16(7)
sternebrae				
unossified 5th sternebra	6(3)	5(2)	19[b](8)	6(5)
scapula				
irregular spinous process	- (0)	5(3)	1(1)	6[b](5)
pubis				
incomplete ossification	8(5)	10(7)	27[c](6)	3(2)
appendages posterior-IO Talus	3(3)	9(4)	23[c](6)	6(2)

[a] Data are taken from Table VI, pages 23-24 of registrant report., and represent number of fetuses affected. ( )=litter incidence

[b]significantly different vs control by pair-wise comparison ($p < 0.05$).

[c]significantly different vs control by pair-wise comparison ($p < 0.01$)