456F

CASWELL FILE

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

010725

JAN - 5 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Id# 053301. Fenthion: Additional information submitted in support of the dog chronic feeding study (Mobay, 1992), rat reproduction study (Bayer, 1990) and the mouse carcinogenicity study (Bayer, 1990) in response to inquiries from the California EPA or the Department of Health and Welfare of Canada.

TOX CHEM No.: 456F
PC No.: 053301
Barcode No.: D195701
Submission No.: S449663

FROM: John Doherty 12/8/93
Section IV, Toxicology Branch I
Health Effects Division (7509C)

TO: Larry Schnaubelt/Richard King
Product Manager #72
Registration Division (7505C)

THROUGH: Marion Copley, DVM, Section Head
Section IV, Toxicology Branch I
Health Effects Division (7509C)
12/27/93

I. CONCLUSION

Information provided by the registrant in response to requests by the California EPA and the Health and Welfare Department of Canada for the dog chronic dosing study, the rat multi genreation reproduction study and the mouse carcinogenicity study were inspected by Toxicology Branch. None of the information provided is considered to be a basis for altering the orignal conclusions made by Toxicology Branch I regarding these studies. No regulatory action is recommended based on this information.

II. Action Requested.

The Miles Co. (refer to letter from John S. Thornton dated August 17, 1993) has submitted three reports prepared in response to inquires from either the California EPA or the Health and Welfare Department of Canada concerning the series 83-1 chronic dog study, the series 83-4 rat multi generation reproduction study or the series 83-2 mouse carcinogenicity study. Each of these three studies was previously reviewed by Toxicology Branch I and determined to be acceptable and none of this information was requested. TB-I has perused the information submitted and the following comments apply.

III. Toxicology Branch Comments

TB-I has determined that the information provided will have no impact on the current classification of these three studies. Thus, no recommendations for regulatory action is considered appropriate based on these submissions.

Generalizations of the content of each of these submissions are described for each study as follows.

A. Mouse Carcinogenicity Study

[Original Submission: Bayer AG, Study No.: TOO20495, October 25, 1990, MRID No.: 418692-01, HED Document No.: 009536, dated June 15, 1992.

Addendum: Bayer AG, dated June 28, 1993 and authored by D.L. Van Goethem and K.H. Leser, MRID No.: 429014-03]

Issue: The California Environmental Protection Agency classified the study as unacceptable but indicated that the study "could be upgraded if evidence could be presented to demonstrate that substantially higher doses could not have been employed".

TB-I review of this study determined that the dose levels were high enough for carcinogenicity evaluation based on the high degree of ChE and AChE inhibition and because of the increase in body weight.

The Miles Company provided a response which also included effects on ChE and AChE and bodyweight increase in this study. Other parameters that were noted to be affected were increased cholesterol and liver weight. TB-I recognizes that an increase in liver weight is not generally regarded as a basis for sufficiently high dose level for carcinogenicity assessment and considered the cholesterol increase to be too inconsistent to be a definite toxicity response. The Miles Company also described the results of subacute dietary studies with the same strain of mouse. These studies indicated that the lethal range for AChE

inhibition was 150-250 ppm. The incidence of mortality during blood sampling was 80% and 30% for males and females at 150 ppm indicating this level is much too high due to stress apparently from AChE inhibition.

The report presents some interesting discussion concerning a possible but indefinite effect of fenthion at higher dose levels. The insulin levels of the mice dosed with 150, 200 and 250 ppm was elevated (actual data or quantitative measure of increase not presented) implying that fenthion increases or alters carbohydrate metabolism thus accounting for the increased body and liver weight and possibly the increased cholesterol levels at 25 ppm. Feed intake at this level was said to be decreased [redacted] suggesting some metabolic effect of treatment.

In general, the Miles Company asserts that higher dose levels would produce intolerable cholinergic symptoms and negative body weight effects thus justifying the high dose level of 25 ppm as being appropriate.

B. Dog Chronic Dosing Study.

[Original submission: Miles, Inc. Study No.: 87-274-01, July 31, 1990, MRID No.: 416328-01, HED Document No.: 009295, dated Feb 4, 1992.

Addendum: Miles Inc. report authored by W.R. Christenson and dated June 28, 1993, MRID No.: 429014-02]

Issue: The California EPA requested additional information regarding correspondence that was mentioned in the original report between the USEPA and the registrant which pertained to the rationale behind the selection of the doses for this study.

The registrant provided the requested correspondence.

The dose levels selected for the dog chronic dosing study were considered appropriate by TB-I.

C. Rat Multi Generation Reproduction Study.

[Original Submission: Miles, Inc. Study No.: 99811, December 22, 1989, MRID No.: 413486-01, HED Document No.: 008545 dated September 3, 1991.

Addendum: Miles Inc., May 25, 1993, authored by R.L. Kowalski, G.R. Clemens, V. Jasty, C.M. Troup and R.E. Hartnagel, Jr. MRID No.: 429014-01].

Issue: The Department of Health and Welfare of Canada requested the registrant to provide additional data for this study concerning the following four items:

i. Data on the homogeneity of the test article in the test diet.

ii. The group mean necropsy observations in both parental and pup generations.

iii. The individual body weights of pups on lactation days 0, 4, 7, 13 and 21.

iv. The study dates for the historical control data presented in Appendix J.

The registrant provided responses for each of the above requested information.

No new information that would cause TB-I to alter any conclusions in the original review were presented in the registrant's response to the request of the Canadian government authorities.

Note: The MRID Nos for the submissions have been added to the one liners for future references.