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

007108

APR - 4 1989

MEMORANDOM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: DEF, (6)(a)(2) Submission, Positive Oncogneic Response in Mouse Oncogenicity Study (2-Year)

TO: Robert Taylor PM-25
Registration Division (TS-767)

FROM: Robert P. Zendzian PhD 3/29/89
Senior Pharmacologist
SACB, HED (TS-769)

THROUGH: Albin Kocialski Ph.D. ABK 4/4/89
Head
Registration Standards and Special Review Section

Reto Engler Ph.D.
Chief
Science Analysis and Coordination Branch

Compound; DEF — Tox Chem #864

Registration #3125-282 — Registrant; Mobay

Accession #N/A — Tox Project #9-1131

Action Requested

Respond to a (6)(a)(2) submission from the registrant which reports a positive oncogenic response at the terminal sacrifice of a two-year mouse oncogenic study of DEF (Tribufos). Further the registrant request an extension of the due date for submission of the final report from Feb 1989 to July 1989.

Conclusions

The information submitted is considered indicative of a positive oncogenic response in the mouse. This is a legitimate (6)(a)(2) action. The request for a due date extension is considered reasonable.

Discussion

The registrant reports by letter that;

"In this study, male and female CD-1 mice (50/sex/dose) were

exposed over their lifetime (2-years) to technical grade DEF (tribufos) in the diet at concentrations of 0, 10, 50 and 250 ppm. The preliminary histopathology results have revealed an increase on the incidence of adenocarcinoma/carcinoma in situ within the small intestine of both male and female mice at the highest treatment group. In addition, an increase in the incidence of hemangiosarcoma in the liver of male mice plus alveolar/bronchiolar neoplasia in the lungs of the female mice was also observed at the highest treatment level."

A copy of the letter and table is attached which shows a significant response of intestinal and liver tumors. The information available was examined by Dr. Slaughter (Pathologist) who concluded that this was indictive of a positive oncogenic response in intestine and liver. Dr. Slaughter commented that the tumors observed in the intestine were rare in the CD-1 strain of mice.

Attachment

Ltr, Moby to Taylor re DEF® Tribufos Defoliant , Submission of Data Persuant to 6(a)(2) of FIFRA as Amended 2/3/89

One-liner DEF

Attachment to Mr. John Thornton's
Letter to Mr. Robert Taylor, dated
February 3, 1989

PRELIMINARY NEOPLASTIC LESIONS IN THE DEF TWO-YEAR MOUSE (50/SEX/DOSE GROUP) STUDY
STUDY NUMBER 86-271-01

	MALES				FEMALES			
	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
SMALL INTESTINE, ADENOCARCINOMA	0	0	0	9*	0	0	0	4
SMALL INTESTINE, CARCINOMA IN SITU	0	0	0	2	0	0	0	2(1 RECUT)
LIVER, HEMANGIOSARCOMA	1	1	4	7*	1	2	2	1
OTHER SITES, HEMANGIOSARCOMA	1	0	2	0	1	0	3	1
LUNG, NODULES	13	12	11	16	8	10	5	17*

* STATISTICAL EVALUATION: SAS INSTITUTE INC., CHI-SQUARE/FISHER'S EXACT TEST $P \leq 0.05$

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9-1131

Mobay

Bayer MOBAY

Mobay Corporation
A Bayer USA INC. Company

Agricultural Chemicals Division

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February 3, 1989

Mr. Robert J. Taylor
Product Manager (25)
Environmental Protection Agency
Registration Division (TS-767C)
401 M Street, S.W.
Waterside Mall
Washington, D.C. 20460

Subject: DEF® Tribufos Defoliant
Submission of Data Pursuant to 6(a)(2) of FIFRA, as Amended

Dear Mr. Taylor:

Mobay is currently conducting a mouse oncogenicity study (EPA Guideline 83-2) in response to the Agency's data call-in notice, dated January 21, 1985. The final report is due to be submitted to the Agency in February 1989.

We have been advised that this study has revealed a positive oncogenicity response at the high dose, a dosage which equals or exceeds the maximum tolerated dose and which is accompanied by other clinical symptoms. As a result, we have determined that this finding should be reported to the EPA under FIFRA 6(a)(2) despite the fact that the report is not yet completed.

In this study, male and female CD-1 mice (50/sex/dose level) were exposed over their lifetime to technical-grade DEF (tribufos) in the diet at concentrations of 0 (control), 10, 50 and 250 ppm. The preliminary histopathology results have revealed an increase in the incidence of adenocarcinoma/carcinoma in situ within the small intestine of both the male and female mice of the highest treatment group. In addition, an increase in the incidence of hemangiosarcoma in the liver of male mice plus alveolar/bronchiolar neoplasia in the lungs of female mice was also observed at the highest treatment level. These results are summarized in the attached table.

DEF, or a metabolite, appears to induce irritation to the intestine of the tested animals. Furthermore, preliminary data from three recently completed mutagenicity studies (i.e. an Ames, a Chromosomal Aberration, and an UDS assay) are negative. Therefore, it is possible that the tumorigenic effects noted could be a result of a secondary (i.e. epigenetic) mechanism. Thus, we will be conducting additional research in this area.

As a result of the above findings, we will contract the services of a consultant to conduct a peer review of the histopathology findings. This will obviously delay the generation of the final pathology report which, in turn, will result in a delay of the final study report until possibly July, 1989. Therefore, we request an extension in the February deadline for this study until July, 1989.

Yours very truly,

MOBAY CORPORATION
AGRICULTURAL CHEMICALS DIVISION

John S. Thornton

John S. Thornton, Manager
Registrations
Research and Development

JST:MKT:brh

Enclosure

cc: Laboratory Data Integrity Program
Office of Compliance Monitoring (EN-342)

cc: Ms. M.A. Cherny
Manager Product Registration
Rhone-Poulenc AG Company
2 T.W. Alexander Drive
Research Triangle Park, North Carolina 27709