CASWELL FILE

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

JUN 11 1990

MEMORANDUM

SUBJECT: Tribufos (DEF), Protocol for 21-day Dermal Toxicity Study

TO: Luminello, PM-50
SRRD (H7508C)

FROM: Robert P. Zendzian Ph.D. 6/5/90
Senior Pharmacologist
SACB, HED (H7509C)

THROUGH: Albin Kocialski Ph.D. APPROVED 6/6/90
Head
Registration Standards and Special Review Section

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

Compound; Tribufos (DEF) Tox Chem #864 MRID #N/A

Registration #2145 Registrant; Mobay Tox Project #0-1199

Action Requested

Review the protocol for a 21-day dermal toxicity study.

Response

A copy of this submission was received directly from the registrant on April 12, 1990 (hand carried). During the week of April 15 I telephoned the registrant and advised that the protocol was acceptable. Subsiquently we received a 6(a)(2) notice about retinal damage at the 12 month sacrifice of a chronic rat study on this compound. I called registrant on May 11th and learned that the dermal study was in the 2nd week of dosing. We were able to add direct eye examinations and special histopathology to the study.

In the future it is strongly advised that requests for protocol reviews be hand carried to the operating division IMMEDIATELY upon receipt. Under the proceses used here it would have been impossible to respond to this type of situation.

Mobay

263,705

2145

Bayer MOBAY

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April 11, 1990

Document Processing Desk (RS-DEF)
Office of Pesticide Programs - H7504C
Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Subject: DEF® Technical, EPA Reg. No. 3125-96
21-Day Dermal Toxicity Study in Rabbits

Dear Sir:

In our List B Phase 2 response, we indicated that a 21-day dermal toxicity study was needed and committed to do the study within the two years allotted by the Agency.

In preparation to fulfill this data requirement, we have recently concluded two short-term studies. The rational for selecting the dosages for the 21-day dermal toxicity study, based on these short-term studies, is contained in the enclosed entitled "Repeated Dose Dermal Toxicity (21-day) Study with Technical Grade Tribufos (DEF) in Rabbits." We have also enclosed our protocol for the 21-day dermal toxicity study.

We would appreciate the Agency's comments on the enclosed and protocol rational for selecting the dosages. If further information is required, please contact me at (816) 242-2255. If informal contact with our toxicologist is desired, please contact Dr. G.K. Sangha at (913) 897-9243.

Yours very truly,

MOBAY CORPORATION
AGRICULTURAL CHEMICALS DIVISION

John S. Thornton, Manager
Registrations
Research and Development

JST:MKT:brh
Enclosures:
(1) Repeated Dose Dermal Toxicity (21-day) Study with Technical Grade Tribufos (DEF) in Rabbits (2 copies)
(2) Protocol for Study No. 90-125-FP (2 copies)

cc: Robert J. Taylor
Product Manager (25) (w/encl)

Dr. Robert P. Zendzian
Health Effects Division (H7509C) (w/encl)

Ms. M.A. Cherny
Rhone-Poulenc (w/encl)

Repeated Dose Dermal Toxicity (21-day) Study with Technical Grade Tribufos (DEF) in Rabbits

In preparation for the 21-day dermal toxicity study with technical grade tribufos (DEF) we have recently concluded two short-term studies. Based on these studies, we have selected dosages of 2, 10 and 25 mg/kg/day.

Rationale for Dose Selection

In the first study, groups of three rabbits/sex/dose were administered five daily topical applications of undiluted tribufos (10, 50 or 250 mg/kg/day). The following results were obtained:

250 mg/kg/day - 100% mortality in both sexes;

50 mg/kg/day - muscle fasciculations and severe inhibition of plasma (76%) and erythrocyte (73%) cholinesterase activities;

10 mg/kg/day - no clinical signs; 43% and 44% inhibition of plasma and erythrocyte cholinesterase, respectively.

No sex-related differences were apparent at any dose. Since the lowest dose tested was not a NOEL, a second short-term study was conducted.

A vehicle was used in the second study for technical considerations associated with the administration of very small volumes of the test substance. A combination of males and females (2 or 3/dose) received five daily doses of tribufos at 0, 2, 10 or 50 mg/kg/day in polyethylene glycol 400 (1 ml/kg). The following results were obtained:

dose	n	clinical signs	percent inhibition*	
			PChE	RChE
0	3	none	8	-2
2	3	none	15	1
10	2	muscle fasciculations	34	38
50	3	2 deaths; severe toxic signs in the survivor	88	78

*Relative to the pretreatment value.

By comparing the results of these two studies, in particular the cholinesterase data, it is evident that the vehicle did not alter the toxicity of the test substance.

Based on these results, the following dosages were selected for the 21-day study: 2, 10 and 25 mg/kg/day, to be administered in polyethylene glycol 400 (1 ml/kg).

The low dose (2 mg/kg/day) should not produce any evidence of toxicity.

The high dose (25 mg/kg/day) should produce clear evidence of toxicity (including clinical signs and subtantial inhibition of plasma and erythrocyte cholinesterase).

Satellite groups of recovery control and high-dose animals (5/sex/dose) will be included for post-treatment examinations.