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

OCT 2 1990

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Peer Review of Tribufos

FROM: Esther Rinde, Ph.D. E. Rinde 8/14/90
Science Analysis and
Coordination Branch
Health Effects Division (H7509c)

TO: Robert Taylor
Product Manager #25
Registration Division (H7505c)

The Health Effects Division Peer Review Committee met on June 13, 1990 to discuss and evaluate the weight-of-the-evidence on Tribufos with particular reference to its carcinogenic potential. The Committee concluded that Tribufos should be classified as a Group C, Possible Human Carcinogen, and recommended that a low dose extrapolation model applied to the experimental animal tumor data be used for quantification of human risk (Q_1*). This is an interim classification, pending completion and HED review of an acceptable carcinogenicity study in the rat.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated.)

Penelope A. Fenner-Crisp	Penelope A. Fenner-Crisp
William L. Burnam	
Reto Engler	
Marcia Van Gemert	Marcia Van Gemert
Karl Baetcke	
Kerry Dearfield	
John Quest	John A. Quest
Esther Rinde	Esther Rinde

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A. 1. Peer Review Committee (contd.)

William Sette

Yin-Tak Woo

2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Robert Zendzian 5/14/90

3. Peer Review Members in Absentia: (Committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Robert Beliles

Marion Copley

Julie Du —

George Ghali

Richard Hill —

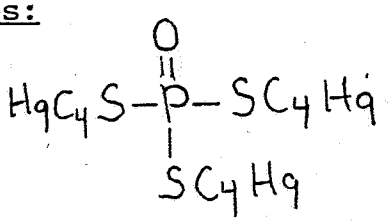
B. Material Reviewed:

The material available for review consisted of DER's, one-liners, and other data summaries prepared by Dr. Zendzian; The material reviewed is attached to the file copy of this report.

C. Background Information:

Tribufos (DEF, S,S,S-Tributylphosphorotrioate) a FIFRA 88 List B chemical, is an organophosphate cholinesterase inhibitor used as a cotton defoliant before harvesting. On Feb. 3, 1989 the Registrant sent a 6(a)(2) letter to the Agency reporting the results of a mouse oncogenicity study with Tribufos (adenocarcinoma of the small intestine in both sexes).

Structure of Tribufos:



D. Evaluation of Carcinogenicity Evidence for Tribufos:

1. Carcinogenicity Study in Crl:CD-1 (ICR)BR Mice

Reference: Oncogenicity (sic) study of technical tribufos (DEF™) with mice. R.H. Hayes, Mobay Corp. Toxicology Dept. Study #86-27101, Report #99175, June 1989, MRID 411710-01.

Tribufos was administered in the diet to groups of 50 male and 50 female mice at 0 (control), 10, 50 or 250 ppm for 90 weeks.

Neoplastic Lesions: The significant tumor sites were liver, lung and small intestine.

Liver: In male mice only there was a statistically significant increase in hemangiosarcoma at 250 ppm (HDT).

Lung: In female mice only there was a statistically significant increase in alveolar/bronchiolar adenoma at 250 ppm (HDT).

Small Intestine: There were increases in adenocarcinoma in both sexes at 250 ppm which were statistically significant in male mice only. This tumor type is considered to be rare in this strain of mice with a reported incidence of 0/50 in each of 3 studies in both sexes at the Registrant's facility (1980 to 1985).

Tumor incidences are given in Table 1 and Historical Control Data for the CD-1 mouse at Mobay Corporate Toxicology Dept. are presented in Table 2.

Compound-related non-neoplastic effects including statistically significant decreases in brain, plasma and red blood cell cholinesterase activity, were observed at all doses in both sexes. Increases in mortality which occurred late in the study (between weeks 72 and 90) in both sexes at 250 ppm were not considered to compromise the study findings. The Committee concluded that dosing was adequate for assessing the carcinogenic potential of Tribufos.

2. Carcinogenicity study in the Rat

A rat study is in progress and a preliminary report indicates that treated rats at 320 ppm (HDT) presented with blindness at the one year sacrifice.

Table 1. Tumor incidence by organ[1]. Carcinogenicity Study of Tribufos in Crl:CD-1BR Mice

Organ & Disease	MALES Dose(ppm) Cont	10	50	250	FEMALES Dose(ppm) Cont	10	50	250
Liver	50	50	50	50	50	50	50	50
Hemangiosarcoma	1/50(2) M	1/50 M	4/50(8) M	7/50(14)* M	2/50(4) M	2/50(4) M	2/50(4) M	1/50(2) M
Lung	50	50	50	50	50	50	50	50
Alveolar/bronchiolar adenoma	11/50(22) B	9/50(18) B	5/50(10) B	9/50(18) B	5/50(10) B	5/50(4) B	2/50(4) B	15/50(30)* B
Small Intestine	50	50	50	50	50	50	50	50
Adenocarcinoma, NOS	0/50 (0)	0/50(0)	0/50(0)	9/50(18)* M	0/50(0)	1/50(2) M	0/50(0)	4/50(8) M

observed/# examined; (percent incidence); B = Benign; M = Malignant; NOS = Not Otherwise Specified; *P<0.05

1. Agency statisticians (Fisher & Pettigrew) have examined this data and determined that additional analysis is not necessary.

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Table 2. Historical Control Data.

Species Mouse Strain CD-1, [Crl:CD-1(ICR)BR] Charles River Laboratory Mobay Corporation Corporate Toxicology Deopartment

Study Number	MALE		FEMALE	
	Liver hemangiosarcoma			
80-271-02*	3/50(6)	M	1/50(2)	M
83-271-03	0/50(0)		1/50(2)	M
85-271-01	1/50(2)	M	1/50(2)	M
Totals	4/150(2.7)	M	3/150(2)	M
	Lung alveolar/branchiolar adenoma			
80-271-02	14/50(28)	B	7/50(14)	B
83-271-03	3/50(6)	B	0/50(0)	
85-271-01	12/50(24)	B	4/50(8)	B
Totals	29/150(19.3)	B	11/150(7.3)	B
	Small intestine adenocarcinoma			
80-271-02	0/50(0)		0/50(0)	
83-271-03	0/50(0)		0/50(0)	
85-271-01	0/50(0)		0/50(0)	
Totals	0/150(0)		0/150(0)	

M = malignant
B = benign
* First number is the year the study started (80 = 1980)

E. Additional Toxicology Data on Tribufos:

1. Metabolism

No metabolism studies were available; however, it is generally accepted that n-Butylmercaptan can be released from tribufos by hydrolysis (this release then deactivates the tribufos cholinesterase activity). It was speculated that n-Butylmercaptan could be released in the liver and small intestine and gassed-off in the lungs, and may be the proximate tumorigenic agent at these three sites.

2. Mutagenicity

Three acceptable studies are available; results were negative in all three.

a. Unscheduled DNA synthesis in rat primary hepatocytes. The test compound was negative at concentrations of 0.0001 to 0.006 ul/ml. Higher concentrations were toxic.

b. Salmonella typhimurium plate incorporation assay. "Test systems used were the histidine auxotrophs TA98, TA1000, TA1537 and TA1538 as described by Ames et al. (1975)." The test compound was negative with and without microsomal activation at concentrations up to 10,000 ug/plate.

c. Chromosomal aberrations in Chinese hamster ovary (CHO) cells. The test compound was negative with (at concentrations up to 0.1 ul/ml) and without (at concentrations up to 0.05 ul/ml) microsomal activation.

3. Developmental and Reproductive Effects

Guideline studies in the rat (28 mg/kg/day) and rabbit (9 mg/kg/day) showed no developmental toxicity.

No reproductive toxicity studies were available.

4. Structure-Activity Correlations

No data were available on structurally related analogs.

F. Weight of Evidence Considerations:

The Committee considered the following facts regarding the toxicology data on Tribufos to be of importance in a weight-of-the-evidence determination of carcinogenic potential.

Tribufos administered in the diet to CD-1 mice was associated with increased tumor incidences at three sites:

Liver: In male mice only, there was a statistically significant increase in hemangiosarcoma at 250 ppm (HDT).

Lung: In female mice only, there was a statistically significant increase in alveolar/bronchiolar adenoma at 250 ppm (HDT).

Small Intestine: There were increases in adenocarcinoma in both sexes at 250 ppm which were statistically significant in male mice only. This tumor type is considered to be rare in this strain of mice with a reported incidence of 0/150 in either sex (3 studies).

The dosing in the mouse study was adequate for assessing the carcinogenic potential for Tribufos.

Tumors caused by Tribufos in the mouse were for the most part late occurring.

Tribufos was negative for developmental effects in the rat and rabbit and was negative in 3 acceptable mutagenicity studies.

No data was available for reproductive effects or on structure activity relationships.

A carcinogenicity study of Tribufos in the rat is in progress; preliminary data indicate treated rats suffered blindness at 320 ppm (HDT). (No such effect was reported in the eyes of mice.)

n-Butylmercaptan, a possible metabolite of Tribufos, may be implicated in the carcinogenic process.

G. Classification of Carcinogenic Potential:

Criteria contained in the EPA Guidelines [FR51: 33992-34003, 1986] for classifying a carcinogen were considered.

The Committee classified Tribufos as a Group C (possible) human carcinogen, based on the findings of tumors in both sexes at multiple sites in the mouse study. Although the tumors were late-occurring, they were malignant in the male liver and in the male and female small intestine (a rare type, with a background occurrence of 0/150 in both sexes at the testing facility).

Ancillary evidence from mutagenicity studies did not indicate much concern; SAR was unavailable. However, based on the multiple and rare tumor types in 2 sexes and their malignancy, the consensus of the Committee was that a low dose extrapolation model applied to the experimental animal tumor data should be used for quantification of human risk (Q_1^*) for Tribufos.

> This is an interim classification, pending completion and HED review of an acceptable carcinogenicity study in the rat.

It was also recommended that n-butylmercaptan be tested for mutagenicity. (Metabolism studies with the parent compound are in progress.)