UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

MAY 22 1997

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Carcinogenicity Peer Review (2nd) of Tribufos (DEF™)

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and
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The Health Effects Division Carcinogenicity Peer Review Committee (CPRC) met on November 20, 1996 and January 8, 1997, to discuss and evaluate the weight-of-the-evidence on Tribufos, with particular reference to its carcinogenic potential.

In accordance with the EPA proposed Guidelines for Carcinogen Risk Assessment (April 23, 1996), Tribufos was characterized as "likely" at high doses and "unlikely" at low doses, based on increases in multiple tumor types in both sexes of the CD-1 mouse only at the highest dose, which were accompanied by severe toxicity caused by cholinesterase inhibition at all doses.

A low dose linear extrapolation risk assessment based on the tumors was not recommended, because of the severe accompanying toxicity, typical of many organo-phosphate chemicals, which occurred at all doses in the mouse. Therefore a non-linear approach (Margin of Exposure or MOE) using the most sensitive toxic endpoint considering all species tested was recommended for the purpose of risk characterization. It was determined that the most sensitive endpoint for chronic toxicity was plasma cholinesterase inhibition seen in the 1 year dog study with Tribufos.

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SUMMARY

At the first peer review, Tribufos was given an interim classification of Group C and for the quantification of human risk, a low dose extrapolation method was recommended (Q_1^*), based on the findings of tumors in both sexes at multiple sites in the mouse study (Memo, Oct. 2, 1990). This classification was interim, pending completion of an acceptable study in the rat.

The rat study has now been completed and reviewed and found to be acceptable at the present meeting.

Tribufos was administered in the diet to Fischer 344 rats at 0, 4, 40 or 320 ppm (equivalent to 0.0, 0.2, 1.8 or 16.8 mg/kg/day in males and, 0.0, 0.2, 2.3 or 21.1 mg/kg/day in females). There was no apparent increase in tumors and the dosing was considered adequate for assessing the carcinogenicity potential of Tribufos in rats.

At this meeting the mouse study was also revisited; both the tumor profile and accompanying toxicity were reviewed.

Tribufos was administered in the diet to groups of male and female CD-1 mice at 0 (control), 10, 50 or 250 ppm (equivalent to 0, 1.64, 8.28 or 48.02 mg/kg/day in males, 0, 2.08, 11.14 or 630.4 mg/kg/day in females) for 90 weeks. In the livers of male mice only, there was an increase in hemangiosarcoma at the mid-dose (50 ppm) and a statistically significant increase in hemangiosarcoma at the highest dose (250 ppm). In the lungs of female mice only, there was a statistically significant increase in alveolar/bronchiolar adenoma at 250 ppm. In the small intestine of both sexes, there were increases in adenocarcinoma 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). The CPRC noted that the tumors, which occurred only at the highest dose, were accompanied by severe toxicity, with cholinesterase inhibition at all doses.

There was no apparent concern for mutagenicity and no structural analogs of concern were identified.

Since there were no doses in the mouse study at which there was not also severe toxicity, a non-linear approach (ie: MOE) using the most sensitive toxic endpoint considering all species tested was recommended for the purpose of risk characterization. It was determined that the most sensitive endpoint for chronic toxicity was plasma cholinesterase inhibition in the 1 year dog study, for which the NOEL was 0.1 mg/kg (4 ppm).

A. Individuals in Attendance at one or both meetings:

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

Stephanie Irene

William Burnam

Karl Baetcke

Marion Copley

Kerry Dearfield

Elizabeth Doyle

Yiannakis Ioannou

Esther Rinde

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

Robert Zendzian[1] 4/18/97

Lori Brunsman

Lucas Brennecke[2] SEE 3a
(PAI/ORNL)

[1]Also a member of the PRC for this chemical; signature indicates concurrence with the peer review unless otherwise stated.

[2]Signature indicates concurrence with pathology report.

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B. Material Reviewed

The material available for review by the CPRC consisted of DER's, one-liners, data from the literature and other data summaries prepared and/or supplied by Dr. Zendzian. The material reviewed is in the Carcinogenicity Peer Review File.

C. Background

At the first peer review (Memo, Oct. 2, 1990), Tribufos was given an interim classification of Group C and for the quantification of human risk, a low dose extrapolation method was recommended (Q_1^*), based on the findings of tumors in both sexes at multiple sites in the mouse study. This classification was interim, pending completion of an acceptable study in the rat.

The rat study has now been completed and was available for evaluation by the CPRC at the present meeting.

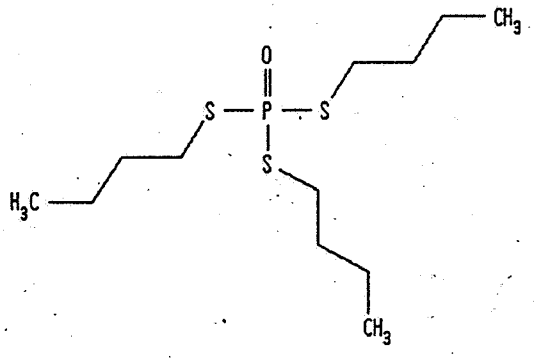

Figure 1 Tribufos (DEF)

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.

a. Experimental Design

Tribufos was administered in the diet to groups of 50 male and 50 female mice at 0, 10, 50 or 250 ppm for 90 weeks (males: 0, 1.64, 8.28 or 48.02 mg/kg/day, females: 0, 2.08, 11.14 or 630.4 mg/kg/day).

b. Discussion of Tumor Data

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 with a reported incidence of 0/50 in each of three studies at the Registrant's facility (1980-1985).

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.

c. Non-neoplastic Lesions

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.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential of Tribufos

Dosing was considered adequate for assessing the carcinogenic potential of Tribufos in the mouse.

Table 1. Tumor incidence by organ. Carcinogenicity study of tribufos in Crl:CD-1(ICR)BR Mice.

Organ & Disease	MALES Dose (ppm)				FEMALES Dose (ppm)			
	Cont	10	50	250	Cont	10	50	250
Liver	50	50	50	50	50	50	50	50
Hemangiosarcoma	1/50 M	1/50 M	4/50 M	7/50* M	2/50 M	2/50 M	2/50 M	1/50 M
Lung	50	50	50	50	50	50	50	50
Alveolar/bronchiolar adenoma	11/50 B	9/50 B	5/50 B	9/50 B	5/50 B	5/50 B	2/50 B	15/50* B
Mesenteric Lymph	48	50	48	46	49	50	50	50
Small Intestine	50	50	50	50	50	50	50	50
Adenocarcinoma, NOS	0/50	0/50	0/50	9/50* M	0/50	1/50 M	0/50	4/50 M

observed/# examined; mean of severity codes(1-5); B = Benign; M = Malignant; NOS = Not Otherwise Specified; *P<0.05

Table 2. Historical control data.

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

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 in which the study started (80 = 1980)

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2. A Combined Chronic/Oncogenicity Study in the Fisher 344 rat.

Reference Technical grade tribufos (DEF™): A chronic feeding study in the Fischer 344 rat, W.R. Christenson, Miles Inc. Study No. 88271-AA, Report #102675, May 1, 1992, MRID 423351-01.

a. Experimental Design

Tribufos was administered in the diet at doses of 0, 4, 40 or 320 ppm (males: 0.0, 0.2, 1.8 or 16.8 mg/kg/day, females: 0.0, 0.2, 2.3 or 21.1 mg/kg/day) according to the following experimental design:

Number of rats per dose group and observation/sacrifice regimen:

Dose (ppm)	Onco 24	Chronic 24	Neurotoxic 12	Neurotoxic 24 (month of sacrifice)
0	50/50	20/20	10/10	10/10
4	50/50	10/10	10/10	10/10
40	50/50	10/10	10/10	10/10
320	50/50	20/20	10/10	10/10

males/females

b. Discussion of Tumor Data

There was no apparent increase in tumors.

c. Non-neoplastic Lesions

Because of the variety of non-oncogenic compound related effects observed, they are listed in order below at the lowest dose at which they were observed: (Males. Female 12 months.)

4ppm
decreased plasma cholinesterase M&F

40ppm
decreased weight gain M
decreased RBC count, Hemoglobin, hematocrit. M&F
decreased cholesterol, calcium M
decreased RBC cholinesterase M&F

320ppm
decreased weight gain F
increased food consumption M&F
terminal ophthalmological exam; cataract, lens opacity, corneal opacity, corneal neovascularization, iritis/uveitis M&F
terminal ERG - unrecordable M&F

decreased Totprotein, globulin, cholesterol, calcium M&F
increased BUN M&F
decreased brain cholinesterase M&F
Adrenals; vacuolar degeneration 12m M&F
Eyes; retinal atrophy 12m M&F
Small intestine; autolysis, vacuolar degeneration 12m M&F
Eyes; retinal atrophy, uveitis, cataract, neovascularization 24m M&F
Optic nerves; atrophy 24m M&F
Small intestine; autolysis, vacuolar degeneration, hyperplasia 24m M&F

Adequacy of Dosing for Assessment of Carcinogenic Potential

Dosing was considered adequate for assessing the carcinogenic potential of Tribufos in the rat.

E. Additional Toxicity Data on Tribufos:

There was no apparent concern for mutagenicity and no structural analogs of concern were identified.

F. Weight of the 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 its carcinogenic potential.

1. Tribufos was administered in the diet to groups of 50 male and 50 female CD-1 (Crl:BR) mice at 0, 10, 50 or 250 ppm for 90 weeks (males: 0, 1.64, 8.28 or 48.02 mg/kg/day, females: 0, 2.08, 11.14 or 63.4 mg/kg/day). Increased tumor incidence was observed as follows:

> Liver: In male mice only there was an increase in hemangiosarcoma at the mid-dose (50 ppm) and a statistically significant increase in hemangiosarcoma at the highest dose (250 ppm).
>
> Lung: In female mice only, there was a statistically significant increase in alveolar/bronchiolar adenoma at 250 ppm.
>
> Small Intestine: There were increases in adenocarcinoma in both sexes at 250 ppm that was statistically significant in males only. This tumor type is considered to be rare in this strain of mice (0/150 in both male and female controls in three studies).

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

2. Tribufos was administered in the diet at doses of 0, 4, 40 or 320 ppm to 50 male and 50 female Fischer 344 rats for two years (males: 0.0, 0.2, 1.8 or 16.8 mg/kg/day, females: 0.0. 0.2, 2.3 or 21.1 mg/kg/day).

> There was no apparent increase in tumors.

The dosing in the rat study was considered adequate for assessing the carcinogenic potential of Tribufos.

3. Tribufos was negative in three mutagenicity studies.

4. n-Butylmercaptan, a possible metabolite of Tribufos, may be implicated in the carcinogenic process. Butanol the oxygen analog of this compound is a severe irritant.

G. Classification of Carcinogenic Potential:

The Peer Review Committee considered the *EPA proposed Guidelines for Carcinogen Risk Assessment (April 23, 1996)* for classifying the weight of evidence for Tribufos. The CPRC concluded that the overall evidence in animals for Tribufos should be characterized as "likely" at high doses, based on increases in tumors in both sexes of the CD-1 mouse; the liver of male mice, in the lung of female mice, and in the small intestine (rare tumors) in both sexes of mice. There was no increase in tumors reported in an adequate chronic study in Fischer 344 rats. There is no human data for Tribufos.

There was no apparent concern for mutagenicity and no structural analogs of concern were identified.

No mechanistic or mode of action data were presented. The CPRC also concluded that the evidence for Tribufos at low doses, would be characterized as "unlikely" since all the tumor increases occurred only at the highest dose (250 ppm, equivalent to 48.02 mg/kg/day in male mice and 630.4 mg/kg/day in females) and were accompanied by severe toxicity. It was felt that human exposure would not approach this dose. A low dose linear extrapolation risk assessment based on the tumors was not recommended, because of the severe accompanying toxicity, typical of organo-phosphate chemicals, which occurred at all doses in the mouse. Therefore a non-linear approach (ie: MOE) utilizing the most sensitive toxic endpoint, considering all species tested, was recommended for the purpose of risk characterization. It was determined that the most sensitive endpoint for chronic toxicity was plasma cholinesterase inhibition in the 1 year dog study, for which the NOEL was 0.1 mg/kg (4 ppm).