6-7-84

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

003847

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Terbufos, EPA Reg. No. 241-241. Response of American Cyanamid to the Review of the Rat Chronic Feeding Study by Bio/dynamics Inc. (Project #71R-725, 7/31/74).

CASWELL#131A

TO: William Miller, PM#16
Registration Division (TS-767)

FROM: Amal Mahfouz, Ph.D.
Toxicologist, Section V
Toxicology Branch/HED (TS-769)

Amal Mahfouz 6/7/84

THRU: Laurence D. Chitlik, DABT
Section Head, Toxicology Branch
Hazard Evaluation Division (TS-769)

A/M for LDC 6/8/84

THRU: William L. Burnam, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

Action Requested:

In a letter dated 3/13/84, the registrant asked the Agency to concur with Cyanamid's conclusion that there is a demonstrated chronic NOEL for mortality, and RBC and plasma cholinesterase activity in the 2-year chronic feeding/oncogenic study by Bio/dynamics, Project #71R-725, 7/31/74. This request was based on Cyanamid's statistical analysis of the low dose and the control data.

Recommendation and Discussion:

At the present time the Agency cannot establish a NOEL for chronic effects in the rat based on the 2-year chronic feeding/oncogenic study by Bio/dynamics (Project #71R-725, 7/31/74) due to the following reasons:

188

003847

- As discussed with Cyanamid's representatives in the 3/8/84 meeting, although Dr. Sinah's statistical analysis demonstrated that the red blood cell cholinesterase inhibitions were not statistically significacant at the lowest dose tested, 0.25 ppm (see the attached letter by Cyanamid dated 3/7/84), the study still did not demonstrate a NOEL for cholinesterase inhibition because of other biological considerations:

  - A 7% brain cholinesterase inhibition in the low dose female group which increased in a dose-related fashion at the mid and high dosage levels ,see table below.

  - A biologically significant RBC inhibition at the lowest dosage tested which increased in a dose-ralated fashion at the higher levels in this study as reflected in the table below.

Cholinesterase Inhibition (% I)

		BChE			
	Dosage	pH		% I	
Group	(ppm)	Male	Female	Male	Female
I & II	0.00	1.448	1.537	00	00
III	0.25	1.495	1.435	00	7
IV	1.00	1.415	1.353**	2	12
V	4.00	-----	0.645**	--	58
	8.00	0.547**	-----	62	--

		RBCChE			
	Dosage	pH		% I	
Group	(ppm)	Male	Female	Male	Female
I & II	0.00	0.407	0.435	00	00
III	0.25	0.357	0.368*	12	15
IV	1.00	0.273**	0.248**	33	43
V	4.00	-----	0.153**	--	65
	8.00	0.155**	-----	62	--

		PChE			
	Dosage	pH		% I	
Group	(ppm)	Male	Female	Male	Female
I & II	0.00	0.642	1.037	00	00
III	0.25	0.655	1.243	00	00
IV	1.00	0.627	1.102	2	00
V	4.00	-----	0.703**	--	32
	8.00	0.508	-----	21	--

*p < 0.05 **p < 0.01

2

- The Agency agrees with the registrant that there is no statistical significance in male mortality at the low dose level when this value is compared to the value of the combined control data I & II. However, the percentage of mortality is higher in this group when compared to control I alone, see the table below.

Group	Dosage (ppm)	No. Died/No. Initiated (less interim sacrifice) 0-24 Months Males No.	(%)	Females No.	(%)
I	0.00	18/55	32.7	16/55	29.1
II	0.00	24/55	43.6	20/55	36.4
I and II	0.00	42/110	38.0	36/110	32.7
III	0.25	24/50	48.0	13/50	26.0
IV	1.00	28/49*	57.1	17/50	33.3
V	8.0(M)&4.0(F)	31/50**	62.0	30.50**	60.00

*p < 0.05 **p < 0.01

- Another effect noted in this study is of concern to this reviewer, i.e. increased incidences of exophthalmos in all dosage groups from week 14 to week 42, see table below.

% of female rats affected with exophthalmos

	11	12	13	14	16	19	26	32	42 WK
Control	0.0	0.0	0.0	0.9	0.0	1.8	9.1	10.9	9.1
0.25ppm	0.0	0.0	0.0	6.0	22.0	4.0	26.0	14.0	18.0
1.0 ppm	0.0	0.0	0.0	2.0	64.7	19.6	58.8	25.5	10.2
4-8-4ppm*	0.0	16.7	66.0	91.7	82.6	26.1	20.5	34.1	23.3

*Dose increased to 8 ppm on day 77, but reduced back to 4 ppm on day 105 due to severe toxicity.

Hence, it is recommended that a one year study be performed in the same strain of rats to verify the extend of the above mentioned effects, and to establish a NOEL for chronic toxicity in this animal species. Adequate necropsy and histopathological examination should be performed on these animals at the end of the study period.

3

American Cyanamid Company
Agricultural Research Division
P.O. Box 400
Princeton, NJ 08540
(609) 799-0400

003847

March 7, 1984

Mr. William Miller
Product Manager (16)
Registration Division (TS-767)
U.S. Environmental Protection Agency
Crystal Mall, Building #2
1921 Jefferson Davis Highway
Arlington, VA 22202

Re: Your letter to W. A. Steller of January 27, 1984
24-Month Chronic Toxicity and Carcinogenicity Study of
Terbufos in Rats

Dear Mr. Miller:

Attached are three (3) copies of a statistical report by Dr. Agam N. Sinha to compare the mortality and cholinesterase activity of a control group of rats and those fed with a low dose (0.25 ppm) of AC 92,100 (terbufos). The study shows that: (1) There was no statistical difference between the AC 92,100 treated and untreated control groups with respect to mortality at the end of 24 months nor was there a significant trend over this same time period; and (2) The growth patterns of cholinesterase levels either in RBC or plasma, for both the control and 0.25 ppm treated groups, were not significantly different. We conclude that the NOEL (no observable effect level) has been established for terbufos at the 0.25 ppm dietary level and that the data gap has been satisfied for the chronic study in rats.

We look forward to your early review of the attached report.

Very truly yours,

Kenneth A. Sund

Kenneth A. Sund, Ph.D.
Registrations Coordinator
Plant Industry Registrations

KAS:sd
Enc.

Rec'd EPA
3/8/84

Terbufos toxicology reviews

Page _____ is not included in this copy.

Pages 5 through 8 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

X FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.