A. Cosme 88

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

NOV 3 1988

MEMORANDUM:

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Re-evaluation of Trifluralin Kidney Effects in a Short-term Rat Feeding Study (Acc# 261912); [TOX CHEM NO. 889].

TO: Reto Engler, Ph.D. 11/3/88
Chief
Science Analysis and Coordination Branch (TS-769)

FROM: R. Bruce Jaeger, Chief 10/28/88
Special Analysis and Outreach Section (TS-769)

Relevant previous reviews include the following:

1. Tox Document # 005521

   a. 2-week Rat Feeding Study, Acc# 261912, B. Dementi, 9/9/86

   b. 3-month Special Urinalysis Study in the Rat, Acc# 261912, B. Dementi, 9/9/86

   c. Memo to R. Mountfort, B. Dementi, 9/26/86

2. Tox Document # 005945

   a. Subchronic Urinalysis Study in Fischer 344 Male Rats, Acc# 261912, B. Jaeger, 6/16/87

   b. Memo to C. Gray, B. Jaeger, 6/17/87

The conclusion in the Jaeger, 6/17/87 memo stated that a NOAEL had been demonstrated at 50 ppm. However, this more recent conclusion differed from an earlier conclusion by Dementi, 9/26/86, wherein he stated a NOAEL had not been demonstrated due to increases in urinary protein excretion at all dose levels.

50

1

I re-examined the original data from Acc# 261912 with regard to total protein, alpha 1, alpha 2, beta and gamma globulin. This re-examination supported the previous conclusion by Jaeger, 6/17/87, that a NOAEL of 50 ppm had been demonstrated for these parameters. The attached tables have been extracted from these data. It is important to consider (1) the pre-test values for all groups, as well as (2) the fluctuations in control values with time. These two factors negate the concern for "positive trend" referred to by Dementi, 9/26/86. The NOAELs for each parameter are summarized below:

Total Protein (mg), all animals	=	200 ppm
Total Protein (mg), subset of animals	=	50 - 200 ppm
Alpha 1 (mg)	=	200 ppm
Alpha 2 (mg)	=	200 ppm
Beta Globulin (mg)	=	200 - 800 ppm
Gamma Globulin (mg)	=	50 ppm

This issue needs to be discussed with the RfD Work Group since their latest evaluation does not include the review by Jaeger, 6/17/87, nor the re-examination included herein. The RfD should reflect a NOAEL = 50 ppm (2.5 mg/kg bw) for non-neoplastic kidney effects. However, the 4 month rat study is not necessarily an adequate reflection of long-term exposure to trifluralin. Only if it can be determined that the short-term effects on urinary protein excretion can be adequately assessed after 4 months exposure then a 100X UF is appropriate. Thus, based on the data available at this time the 4-month rat study should only be regarded as a subchronic assay and a 1000X UF should be used; i.e. the RfD previously established is not changed at this time:

RfD = 2.5/ 1000 = 0.0025 mg/kg bw

[rounded to 0.003 mg/kg bw]

TABLE 1 Total Protein (mg) all animals

DOSE (ppm)	DAY -4 to 0	28-29	58-59	91-94
0	3.52 (0.86) N=14	2.75 (0.83) N=15	4.12 (1.35) N=15	2.63 (0.78) N=27
50	3.73 (0.99) N=12	2.89 (0.75) N=15	3.60 (0.75) N=14	2.69 (0.77) N=29
200	3.26 (1.08) N=8	3.07 (1.33) N=10	4.35 (1.25) N=10	3.27 (1.02) N=20
800	4.14 (1.35) N=5	4.76* (2.10) N=10	4.92 (1.27) N=10	3.72 (1.35) N=19
3200	3.27 (1.07) N=8	5.67* (2.73) N=10	7.83* (1.52) N=10	6.62* (2.25) N=20
6400	2.98 (1.18) N=7	7.11* (2.26) N=10	8.76* (1.57) N=9	9.26* (2.75) N=20

N = number of animals examined
() = STD
* = $p < 0.05$

NOAEL = 200 ppm

TABLE 2 Total Protein (mg) - subset of animals with larger urine volumes needed to perform protein electrophoresis assays

DOSE (ppm)	-4 to 0	DAY 28-29	DAY 58-59	DAY 91-94	Normalized to Urine Vol
0		2.61 (0.83) N=10	4.23 (1.36) N=10	2.76 (0.81) N=10	1.20
50		3.11 (0.60) N=9	3.66 (0.94) N=5	3.43 (0.62) N=5	1.24
200		3.72 (1.44) N=5	4.84 (1.48) N=5	3.99 (0.88) N=5	1.46
800		4.21 (0.92) N=5	5.08 (1.37) N=5	4.50 (1.41) N=5	1.21
3200		5.81* (1.47) N=5	7.67* (1.51) N=5	6.12* (2.44) N=5	1.41
6400		7.11* (2.26) N=10	9.15* (1.61) N=5	8.97* (2.58) N=5	2.49

N = number of animals (NOTE: also different animals were examined at each time interval)

() = STD

* = $p < 0.05$

NOAEL = 50 - 200 ppm

TABLE 3 Urine Electrophoresis - Subset (same # of animals as in Table 2)

Alpha 1 Globulin

DOSE (ppm)	-4 to 0	DAY 28-29	DAY 58-59	DAY 91-94	Normalized to Urine Vol
0		0.228 (0.08)	0.411 (0.15)	0.30 (0.13)	.130
50		0.324 (0.10)	0.376 (0.06)	0.495 (0.28)	.179
200		0.351 (0.15)	0.473 (0.12)	0.510 (0.12)	.186
800		0.380 (0.09)	0.590 (0.197)	0.635 (0.179)	.171
3200		0.542* (0.21)	0.927* (0.28)	0.596 (0.15)	.137
6400		0.707* (0.34)	0.972* (0.36)	1.308* (0.65)	.361

Calculated as a %:

0	9.13	-	10.78
50	10.48	-	13.88
200	9.24	-	12.78
800	9.00	-	14.24
3200	9.22	-	10.96

() = STD
* = $p < 0.05$

NOAEL = 200 ppm

TABLE 4 Urine Electrophoresis - Subset (same 3 of animals as Table 2)

Alpha 2 Globulin (mg)

DOSE (ppm)	-4 to 0	DAY 28-29	DAY 58-59	DAY 91-94	Normalized to Urine Vol
0		1.627 (0.63)	2.62 (0.97)	1.74 (0.47)	.76
50		1.941 (0.41)	2.22 (0.85)	2.08 (0.36)	.75
200		2.413 (0.90)	2.97 (1.11)	2.40 (0.46)	.88
800		2.748 (0.85)	3.22 (0.99)	2.58 (0.99)	.70
3200		4.141* (1.06)	5.12* (0.95)	4.20* (1.91)	1.00
6400		5.243* (1.77)	6.78* (1.19)	6.32* (1.97)	1.80

Calculated as a %:

0	61.31	-	63.67
50	62.43	-	61.56
200	65.52	-	60.44
800	64.42	-	57.14
3200	71.28*	-	65.74

() = STD
* = $p < 0.05$

NOAEL = 200 ppm

TABLE 5 Urine Electrophoresis - Subset (same # of animals as in Table 2)

Beta Globulin (mg)

DOSE (ppm)	-4 to 0	DAY 28-29	DAY 58-59	DAY 91-94	Normalized to Urine Vol
0		0.257 (0.08)	0.395 (0.12)	0.253 (0.10)	.110
50		0.301 (0.09)	0.347 (0.09)	0.306 (0.09)	.111
200		0.345 (0.13)	0.464 (0.11)	0.373 (0.16)	.136
800		0.351 (0.06)	0.459 (0.107)	0.421 (0.14)	.113
3200		0.409 (0.13)	0.564* (0.11)	0.506* (0.15)	.116
6400		0.512 (0.15)	0.596 (0.08)	0.578 (0.16)	.161

Calculated as a %:

0	10.06	-	8.90
50	9.62	-	8.86
200	9.46	-	9.06
800	8.58	-	9.30
3200	7.00*	-	9.14

() = STD
* = $p < 0.05$

NOAEL = 200 - 800 ppm

TABLE 6 Urine Electrophoresis - Subset (same # of animals as in Table 2)

Gamma Globulin (mg)

DOSE (ppm)	-4 to 0	DAY 28-29	DAY 58-59	DAY 91-94	Normalized to Urine Vol
0		0.296 (0.12)	0.436 (0.20)	0.209 (0.14)	.091
50		0.290 (0.15)	0.388 (0.10)	0.269 (0.14)	0.97
200		0.296 (0.32)	0.589 (0.21)	0.378 (0.15)	.138
800		0.449 (0.25)	0.390 (0.20)	0.438 (0.26)	.118
3200		0.259 (0.18)	0.597 (0.41)	0.501 (0.48)	.115
6400		0.385 (0.22)	0.511 (0.23)	0.450 (0.29)	.125

Calculated as a %:

0	11.84	-	7.33
50	9.16	-	7.52
200	7.34	-	9.50
800	11.24	-	9.64
3200	5.10	-	9.32

() = STD
* = $p < 0.05$

NOAEL = 50 ppm