



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

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MAR 4 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Historical Control Data For Chevron Reproduction
Study in Rats With Folpet. Caswell #464;
EPA I.D. No. 239-1763; Tox. PN #7-0440.

TO: Richard Mountfort (23)
Registration Division (TS-767C)

FROM: D. Stephen Saunders, Ph.D.
Toxicologist, Section V
TOX/HED (TS-769C)

DS 3/3/87

THRU: Quang Bui, Ph.D., DABT
Acting Head, Section V
and
Theodore M. Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Quang Bui 3/4/87

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Action Requested

Review the submitted historical control data requested by the Agency for the Chevron reproduction study in rats with folpet (SOCAL #2140).

Recommendations

It is recommended that the Chevron folpet reproduction study in rats (SOCAL #2140) be upgraded to Core-Guideline status, as the submitted historical data resolve questions regarding this study. The NOEL for this study is now 800 ppm (690 ppm analytical), on the basis of decreased body weight gain and decreased fertility in rats fed diets containing 3600 ppm.

We are still requesting historical data for mouse pup survival, in either reproduction studies or in somatic cell mutation assays. A potential treatment-related finding was noted in our review of the folpet mouse somatic cell mutation assay (memo Saunders to Jacoby, 8-18-86); a NOEL for pup mortality was not apparent in that study at the lowest dose tested of 10.9 ng/kg/day. If this issue cannot be resolved, a

BB-1448
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005756

Folpet Rat Historical Control Data Page 2

full two-generation reproduction study in the mouse will be necessary.

Since the rat reproduction study was previously the basis for the ADI, a new Tolerance Reassessment is required for the folpet registration standard. The new ADI will likely be based on the 1-year chronic feeding study in dogs, which is currently under review. The NOEL in that study is tentatively established as 10 mg/kg/day, based on decreases in body weight gain and changes in clinical chemistry parameters at 60 mg/kg/day. When the DER for this study has been completed, the new ADI will be presented to the Toxicology Branch ADI Committee for verification, and a new Tolerance Reassessment will be prepared.

Discussion

The original review of the folpet rat reproduction study (memo Saunders to Jacoby, 9-15-86), suggested a possible effect of treatment on male fertility at the F2 mating. The relevant tables from the DER are appended.

The historical control data for male fertility were limited to only one completed study, a study in progress, and a pilot study (data table is appended). Data were provided for 4 F1a matings and for single F1b, F2a and F2b matings. These data indicate that the range for male fertility overall was 68-87%, with a mean fertility rate of 77.1%. If only F2 matings are considered, the historical rate (2 matings) was 72%.

The fertility rates in males at the F2a mating of the folpet study were 88%, 80%, 69% and 64.3% for control, low (200 ppm), mid (800 ppm) and high dose (3600 ppm) males, respectively. The rates in the F2b mating were 78.3%, 69.2%, 62.5% and 65.2% in the respective dose groups. Therefore, although an apparent dose-related decrease in fertility was noted in F2a high dose males that is below the historical control values, a similar dose-related change was not noted at the F2b mating. The fertility rates for mid and high dose male rats were below the historical control values, however the effect did not appear to be related to dose, and is therefore of questionable toxicological significance. However, in view of the limited historical data available for F2 matings, a conservative interpretation of the data would place the LEL for male fertility in the folpet study at 3600 ppm, with the NOEL for this effect at 800 ppm on the basis of the potential dose-related findings noted in the F2a mating.

2

005756

CHEVRON ENVIRONMENTAL HEALTH CENTER

HISTORICAL DATA 1985 - 1986

MATING INDICES, MALE FERTILITY AND PREGNANCY RATES

	Mating Indices				Pregnant Rate ^c		Male Fertility ^d	
	Female ^a		Male ^b		N	%	N	%
	N	%	N	%				
F _{1a} control diet	27/30	90.0	25/30	83.3	20/27	74.1	19/25	76.0
vehicle								
F _{1a} control(p.o.)	27/29	93.1	23/30	76.7	25/27	92.6	20/23	87.0
F _{1a} control diet	29/30	96.7	25/29	86.2	22/29	75.9	21/25	84.0
F _{1b} control diet	28/30	93.3	25/29	86.2	18/28	64.3	17/25	68.0
F _{2a} control diet	28/30	93.3	25/30	83.3	21/28	75.0	18/25	72.0
F _{2b} control diet	29/29	100.0	25/30	83.3	21/29	72.4	18/25	72.0
F _{1a} control diet	27/28	96.4	27/29	93.1	22/27	81.5	22/27	81.5
Grand totals								
"A" Litters	138/147	93.9	125/148	84.5	110/138	79.7	100/125	80.0
"B" Litters	57/59	96.6	50/59	84.8	39/57	68.4	35/50	70.0
"A + B" Litters	195/206	94.7	175/207	84.5	149/195	76.4	135/175	77.1

^aNumber of females with plug and/or sperm or produced a litter/total number mated

^bNumber of males for which evidence of mating was detected in at least one female/total number mated

^cNumber pregnant/number with positive signs of mating

^dNumber males mated with at least one female which produced a litter/number with positive signs of mating

C. I. TELLONE
12/18/86

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005756

TABLE 15. Effects of Folpet on Mating, Fertility, and Pregnancy Rates of the F₀ Rats

Dose Level (ppm)	No. Cohabited	F ₀ Males				F ₀ Females				
		Mated		Fertile		Mated		Pregnant		
		No.	%	No.	%	No.	%	No.	%	
F _{1a} Litter Interval										
0	30	28	93.3	24	85.7	30	28	93.3	24	85.7
200	30	30	100.0	26	86.7	30	30	100.0	26	86.7
800	30	28	93.3	22	78.6	30	28	93.3	22	78.6
3600	30	29 ^a	96.7 ^a	26	86.7	30	29	96.7	26	89.7
F _{1b} Litter Interval										
0	30	29	96.7	22	75.9	30	30	100.0	22	73.3
200	29	26	89.7	24	82.3	30	29	96.7	25	86.2
800	29	27	93.1	23	85.2	30	30	100.0	25	83.3
3600	29	29	100.0	27 ^b	93.1 ^b	30	30	100.0	28	93.3

^aBased on reviewer's calculations from available individual animal data; the study authors reported 26 mated (86.7%).

^bBased on reviewer's calculations from available individual animal data; the study authors reported 23 fertile (96.6%).

005756

TABLE 16. Effects of Folpet on Mating, Fertility, and Pregnancy Rates of the F₁ Rats

Dose Level (ppm)	No. Cohabited	F ₁ Males				F ₁ Females				
		Mated		Fertile		No. Cohabited	Mated		Pregnant	
		No.	%	No.	%		No.	%	No.	%
F _{2a} Litter Interval										
0	30	25	83.3	22	88.0	30	29	96.7	23	79.3
200	30	25	83.3	20	80.0	30	27	90.0	22	81.5
800	30	29	96.7	20	69.0	30	30	100.0	20	66.7
3600	30	28	93.3	18	64.3*	30	29	96.7	19 ^f	65.5
F _{2b} Litter Interval										
0	30	23	76.7	18 ^c	78.3 ^c	30	28	93.3	20	71.4
200	30	26 ^a	86.7 ^a	18	69.2 ^d	30	30	100.0	20	66.7
800	30	24 ^b	80.0 ^b	15	62.5 ^e	30	29	96.7	20	69.0
3600	30	23 ^b	80.0 ^b	15	65.2 ^e	29	27	93.1	17	63.0

NOTE: Values a, b, c, d, and e are based on reviewers' calculations of available individual animal data. The reported values are slightly different.

^fFemale No. 4623 died on G.D. 18; this animal was pregnant and was included in the calculation of pregnancy rates.

* Significantly different from control value ($p \leq 0.05$) according to reviewers' calculations using Fisher's exact test; also, significant dose-related trend ($p \leq 0.05$) by Cochran-Armitage trend test.