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

005502

SEP 15 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Folpet Chronic Rat Feeding, Rabbit Teratology, and Rat Reproduction Studies. EPA ID. No. 239-1763; Accession Nos. 259787-95 (Chronic), 259597 (Teratology), 259585-259596 (Reproduction); Tox. PN #901; Caswell #464.

TO: Henry Jacoby (21)
Registration Division (TS-767C)

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

DS 9-12-86

THRU: Laurence D. Chitlik, DABT
Head, Section V
TOX/HED (TS-769C)
and
Theodore M. Farber, Ph.D.
Chief, Toxicology Branch
TOX/HED (TS-769C)

LDC 9/12/86

TMF 9/12/86

Action Requested

Review the chronic feeding study in rats, the rabbit "pulse-dosing" teratology study, and rat reproduction study.

Reviewer's Note: Signed, final copies of the DERs for the chronic feeding study and rabbit teratology study were forwarded to RD as part of the Folpet Registration Standard. The rat reproduction study was returned to the contractor for corrections, and was not included with the RS, although the conclusions regarding this study are correctly presented in the RS. The corrected final copy of the reproduction study has been returned from the contractor, and all of these studies are being returned to RD together as a complete package in order to complete this action (they were sent to TOX as part of the same RD Data Review Record).

Recommendations/Discussion

1. The chronic feeding study in rats (Project #2107-109) was tentatively classified as Core-Supplementary data, pending submission of additional information. Equivocal findings were

Recommendations/Discussion (con't)

noted in the thyroid and testes, and historical control data for the incidences of C-cell adenoma/carcinoma, and interstitial cell tumors of the testes, are requested. The data should be from the laboratory performing the study for the strain of rats tested (Charles River Sprague-Dawley), and should be tabulated by study for each tumor type. Data from at least the two years preceding the study, and whatever period after the study as is available, is requested. All available data were presented to the Toxicology Branch Peer Review Committee, and it was decided that a final determination was not possible in the absence of the requested historical control data. The Committee also felt that an MTD may not have been reached in this study, however in view of the current classification of folpet as a "B2" carcinogen, additional testing is not required at this time.

Non-oncogenic findings noted in this study included dose-related increases in the incidences of hyperkeratosis/acanthosis and erosion of the stomach. Other potentially treatment-related non-neoplastic findings included "medullary tubule hyperplasia" of the ovaries, and increased "foci of vacuolated hepatocytes" in the liver. Clarification of the lesion observed in the ovary is requested. In addition, a better description of the finding in the liver described as "spongiosis hepatis" is requested, particularly as it relates to findings such as "fatty change (infiltration)" and "foci of vacuolated hepatocytes". The significance of the apparent findings in these two tissues will be further evaluated when the additional descriptions are provided (please refer to DER for a complete discussion of these findings).

The results of diet analyses must also be submitted for this study.

The NOEL for this study is tentatively set as 200 ppm (nominal), and the LEL as 800 ppm (nominal), based on findings in the stomach. When the requested information is submitted, the NOEL/LEL and study classification will be re-evaluated.

2. The "pulse-dosing" rabbit teratology study in the New Zealand White rabbit (Report #303-004) assessed the developmental effects of 60 mg/kg/day administered by gavage in a "pulse dosing" schedule. In this study, a dose (60 mg/kg/day) previously demonstrated to produce hydrocephalus (when administered over the entire gestation period) was administered to different groups of rabbits for three-day periods during gestation. A treatment-related increase in the incidence of hydrocephalus was not produced by this treatment paradigm, however increases in the incidence of "irregularly shaped fontanelles" were observed in rabbits dosed over days 13-15 of gestation. Maternal toxicity in the form of alterations in food consumption and weight gain was also noted in treated does. Since only a single dose was tested, 60 mg/kg/day, a NOEL for developmental toxicity was not established in this study. The study was classified as Core-Minimum

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Recommendations/Discussion (con't)

data when considered with the results of the previous teratology study in rabbits (Argus Report #303-002, see DER in memo Saunders to Jacoby, 11-23-84).

3. The rat reproduction study (#SOCAL 2140) was classified as Core-Supplementary data pending submission of historical control data for male and female rat fertility. The data should be from the laboratory that conducted the study, and should be tabulated as was described for the chronic feeding study in rats. The NOEL for reproductive effects cannot be established until the requested data are submitted. The NOEL for parental toxicity was established as 690 ppm actual (800 ppm nominal), based on decreased weight gain of rats in the 3200 ppm dose group (3600 ppm nominal). When the requested information is submitted, the NOEL/LEL and study classification will be re-evaluated.

DSS:TOX/HED:9-11-86:FILE MEMO901

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Reviewer: D. Stephen Saunders, Ph.D.
Toxicologist, Section V, Toxicology Branch DSS 6/23/86

Secondary Reviewer: Laurence D. Chitlik, DABT
Head, Section V, Toxicology Branch LDC 7/7/86

DATA EVALUATION REPORT

STUDY TYPE: 2-year chronic feeding study in rats. (Guidelines 83-5)

MRID NUMBER: 151560 ACCESSION NUMBER: 259787-95

TEST MATERIAL: Folpet SYNONYMS: Folpan, Phaltan

PROJECT NUMBER: 2107-109 REPORT ISSUED: 9-30-85

SPONSOR: Chevron Environmental Health Center, Inc.
Richmond, CA.

TESTING FACILITY: Hazleton Laboratories America, Inc.
Vienna, VA 22180

TITLE OF REPORT: "Combined Chronic Oral Toxicity/Oncogenicity Study in Rats with Chevron Folpet Technical (SX-1388), Final Report."

AUTHORS: Cox, R.H., Marshall, P.M., Voelker, R.W., Vargas, K.J., Alsaker, R.D., and Dudeck, L.E.

Conclusion: Tentatively classified as positive (in males only) for oncogenicity in the thyroid (C-cell adenoma and carcinoma) and the testes (interstitial cell tumor). Additional historical control data are necessary to fully evaluate these findings (see Discussion).

A clear dose-related increase in the incidences of hyperkeratosis/acanthosis and erosion was noted in the non-glandular stomach of treated males and females. Other possible changes were noted in the liver and ovary, however additional information regarding possible findings in these tissues is requested from the Registrant (see Discussion). Liver and ovary findings will be re-evaluated upon submission of the requested information. The results of diet analyses must also be submitted.

Chronic NOEL = 200 ppm (Nominal LDT)
Chronic LEL = 800 ppm (Nominal MDT) increased incidence of hyperkeratosis, acanthosis, ulceration and/or erosion of the non-glandular stomach.

Classification: Core-Supplementary Additional data requested.

Materials and Methods

A. Materials: (1) Test material- Chevron Folpet Technical, N-(trichloromethylthio)phthalimide; Lot no. SX-1388, 89.5% a.i.

(2) Test animals: Male and female Crl:CD(SD)BR albino rats obtained from Charles River Breeding Laboratories, Kingston, New York. Rats were approximately 6 weeks old at initiation of treatment.

B. Study Design

1) Animal assignment- Sixty rats of each sex were randomly assigned (by means of a computer randomization program) to groups that were fed diets containing 0, 200, 800, or 3200 ppm of folpet for up to 104 weeks. After 52 weeks of treatment, 10 rats/sex/dose were sacrificed and examined for gross and microscopic changes.

Treatment was initiated on October 18, 1982. The study was scheduled for termination on November 2, 1984.

2. Test substance administration- Folpet was administered to rats via the diet. Diets were prepared weekly by adding the appropriate amount of test material to a small amount of diet and blending to form a premix. The premix was then added to the proper amount of basal to form a test diet at the required concentration. After preparation, diets were separated into 3 aliquots and frozen, and offered to rats on days 1, 3, and 5 of each week. The submitted methods stated that diets were "frozen and offered three times weekly because of the relative instability of the test material in the mixed diet" and that "stability and routine analysis samples were collected and sent to the sponsor for analysis".

The results of test diet analyses were not submitted, and are required.

3. Food and Water Administration- Control or test diets and water were offered ad libitum.

4. Statistics- Data were analyzed by first performing Levene's test for homogeneity of variances, and if variances were homogeneous, data were further analyzed with the one-way Analysis of Variance (ANOVA). If variances were heterogeneous, a series of transformations (log10, square, square root, reciprocal, angular, or rank) were performed until the variances were homogeneous. If homogeneity could not be achieved, data were analyzed using the rank transformation by ANOVA. If the ANOVA of transformed or untransformed data was significant ($p<0.05$, one-tailed), data were further analyzed by the Dunnett's T-test. If the ANOVA was not significant, the analysis was terminated.

C. Methods and Results

1. Clinical signs and mortality- Rats were "observed twice daily for "viability and general appearance...Detailed clinical examinations were performed weekly."

Results- Data for the results of routine or detailed clinical examinations were submitted as a summary tabulation. No effect of treatment on the incidence of clinical signs was apparent.

No effect of treatment on survival was apparent. After 18 months of treatment, survival in males (calculated by the reviewer) was 86%, 88%, 96% and 98% in control, low, mid and high dose rats, respectively. For the respective female treatment groups, survival at 18 months was 88%, 92%, 94% and 82%. At termination, survival in the respective male groups was 46%, 74%, 64% and 62%, whereas for females was 62%, 58%, 62% and 60% for control, low, mid and high dose rats, respectively.

2. Body Weight and Food Consumption- "Individual body weights and food consumption values were recorded weekly through Week 14 and biweekly thereafter".

Results- Treatment with the test material did not produce any significant effect on body weights in treated rats (Table 1). Mean body weights were similar at most measured intervals, and total weight gain over the 104 week treatment period was similar in all test groups.

Similarly, no effect of significant effect of treatment on food consumption was apparent.

Average compound intake, calculated by the investigators, was about 9, 35, and 145 mg/kg/day in low, mid and high dose males, respectively, and about 11, 45, and 180 mg/kg/day in the respective female treatment groups.

3. Clinical Pathology- (a) Hematology- Blood was withdrawn from the orbital sinus of 10 rats/sex/dose randomly selected from all animals on test. The following parameters were determined at weeks 27, 53, 79 and 104:

Hemoglobin (HGB)	RBC count
Hematocrit (HCT)	Erythrocyte morphology
Differential leukocyte count	Total leukocyte count
Platelet count	Reticulocyte count (if anemia is observed)

Results- No definitive effects of treatment on hematological paremeters were apparent. A statistically significant increase in hemoglobin concentration was noted in all male treatment groups in week 53, however the change did not appear to be related to dose nor was it apparent at later measurements. No

treatment-related changes in Hct or red cell count were apparent in any of the treatment groups. A slight (6-14%) decrease in platelet count was noted in high dose rats at 52 and 79 weeks for males, and at 52, 79 and 104 weeks for females. Although statistically significant only in males at week 52, the progressive decline in female values over the last year of treatment suggests that this effect may be treatment-related in females. By study termination, no difference in male platelet counts was apparent.

No treatment-related effects on total or differential leukocyte counts were noted.

Table 1. Mean Body Weights and Food Consumption[a]

Group	Week 52	Week 78	Week 104	Weight Gain Weeks 0-104
1M	585.3±53.1 184.6±20.1[b]	583.1±72.0 180.3±37.9	530.0±36.7 190.3±25.7	344.9±32.6
2M	587.1±67.3 177.0±25.2 8.61[c]	591.0±64.4 173.4±24.8 8.38	533.8±68.5 174.0±41.0 9.31	352.3±69.1
3M	581.6±47.9 179.1±21.5 35.19	600.7±49.0 178.8±16.2 34.02	543.4±46.2 183.6±29.0 38.62	364.0±44.7
4M	568.4±56.7 176.4±28.1 141.91	582.0±63.7 184.8±26.3 145.14	540.6±55.5 186.4±18.3 157.65	365.3±54.6
1F	346.9±43.7 143.2±15.5	394.7±52.9 146.5±21.2	385.0±66.2 147.8±45.7	245.1±64.2
2F	346.3±43.7 141.5±16.0 11.68	404.1±46.9 138.3±23.0 9.78	378.9±72.6 144.9±25.1 10.93	240.0±70.7
3F	344.5±40.4 144.6±16.3 47.96	398.6±49.3 149.9±18.2 42.97	416.1±66.5 156.4±32.5 42.97	277.8±64.5
4F	332.8±31.0 147.5±15.0 202.67	384.7±41.2 150.0±16.3 178.31	388.0±58.4 161.2±33.5 189.93	251.4±53.4

[a]data excerpted from submitted study. Values are body weights in grams, mean ± std. dev., calculated by the investigators. M = male, F= female; 1=control, 2=200 ppm. 3=800 ppm, 4=3200 ppm.

[b]mean weekly food consumption in grams, mean ± std. dev.

(b) Clinical chemistry- Serum chemistry measurements were performed at the same times as hematology measurements. The following parameters were determined:

Blood urea nitrogen	Total and direct bilirubin
Cholesterol	Total and differential protein
Blood creatinine	Calcium
Glucose	Sodium
Lactic dehydrogenase	Potassium
Alanine aminotransferase	Chloride
Aspartate aminotransferase	Phosphorus
Alkaline phosphatase	

Results- No treatment-related effects on clinical chemistry parameters were apparent. Although some statistically-significant differences were sporadically noted, these changes were not dose-related and were not observed at later time periods, and are therefore considered spurious.

(c) Urinalysis- Urine was also collected at weeks 27, 53, 79 and 104. The following parameters were determined:

Urine volume	pH
Appearance	Ketones
Specific gravity	Urobilinogen
Protein	Glucose
Bilirubin	Occult blood

Results- No effect of treatment on any of the measured parameters was apparent.

4. Ophthalmoscopic Examinations- Eyes of all rats were examined before initiation of treatment and at weeks 52 and 105. Tropicamide (1.0%) was instilled into the eyes to dilate the pupils, and the examination was performed with an indirect ophthalmoscope.

Results- No treatment-related effects were noted. A common finding (1-5 rats per group) at week 52 without relation to treatment was retinochoroidal degeneration. Additional common observations at week 105 included cataract (1-6/group) and conjunctivitis (1-6/group).

5. Necropsy Data: Necropsies were conducted on all rats sacrificed in a moribund condition and found dead, on the 10 rats/sex/dose randomly selected for the week 52 clinical pathology examinations, and on all animals alive at scheduled termination (week 105). Animals were sacrificed by induction of anesthesia via intravenous sodium pentothal and exsanguination.

Gross examinations included observation of the appearance, consistency, and weight of any tissue masses, as well as examination of the "external surface, orifices, external and cut surface of the brain and spinal cord, cervical tissues and organs, nasal

cavity and paranasal sinuses, cranial, abdominal, pelvic and thoracic cavities and their viscera, and the carcass". Standard necropsy techniques were followed. "All necropsies were performed by appropriately trained personnel under procedures supervised by a board-certified pathologist." Tissues were preserved in 10% neutral buffered formalin (with the exceptions of the eyes and testes with epididymides, which were preserved in Bouin's fixative), and embedded in paraffin (Paraplast) blocks. After sectioning and staining with hematoxylin and eosin, tissues were examined by light microscopy.

The following tissues were weighed (indicated by an asterisk [*]) and/or examined for gross and microscopic changes: Abnormalities, Adrenals, Aorta (thoracic), Blood smear (sacrificed animals only), Bone (sternum + marrow), Brain (fore, mid, hind, brainstem)*, Caecum, Cervix, Colon, Duodenum, Esophagus, Eyes (with Harderian glands), Heart*, Ileum, Jejunum, Kidneys*, Liver (2 lobes)*, Lung, Lymph node (mediastinal, mesenteric), Mammary gland, Ovaries*, Pancreas, Pituitary, Prostate, Rectum, Salivary glands (mandibular), Sciatic nerve, Seminal vesicle, Skeletal muscle (thigh), Skin, Skull, Spleen, Spinal cord (thoracic, cervical), Stomach, Testes (with epididymides)*, Thymus, Thyroid (with parathyroid), Trachea, Urinary bladder, Uterus, Zymbal's gland.

Results: (a) Organ weights- No significant effect of treatment on absolute or relative organ weights was apparent at either the interim or final sacrifice. Organ weight data is presented in Tables 2a and 2b.

6. Necropsy Data: (b) Gross observations- At final sacrifice, potential treatment-related lesions were noted in the stomachs of either sex, and in the liver of males.

"Thickened" stomach (no distinction was made between tissue of the glandular or non-glandular stomach) was noted in 1/23, 5/37, 5/32, and 6/31 control, low, mid and high dose males, respectively, and in 3/31, 0/29, 0/31, and 5/30 of the respective female treatment groups. Similar findings were also noted at the interim sacrifice in 1, 1, 2, and 3 control, low, mid and high dose males (of 10 examined) and in 0, 2, 2, and 3/10 of the respective female treatment groups. A similar effect of treatment on the stomach was not apparent in animals that died on test, as incidences of 8/27 (30%), 3/13 (27%), 3/13 (17%) and 5/19 (26%) were noted in control, low, mid and high dose males, respectively, whereas incidences of 4/19 (21%), 3/21 (14%), 4/19 (21%) and 4/20 (20%) were noted in rats from the respective female treatment groups that died on test.

An apparent increase in the incidence of "dark foci/areas" of the liver was noted in treated males at final sacrifice. The following incidences for control, low, mid and high dose males and females were noted: 2/23, 6/37, 7/32 and 14/31 males; and

8/31, 9/29, 4/31 and 7/30 females. A similar response was not noted at interim sacrifice nor in animals that died on test.

(c) Microscopic observations- (1) Neoplastic Lesions: Apparent increases in the incidences of neoplasia of the thyroid (C-cell adenoma/carcinoma), and interstitial cell tumors of the testes, were noted at final sacrifice in treated males but not females (Table 3).

Although not clearly dose-related, the relatively high incidence of adenoma and carcinoma of the thyroid C-cell in treated animals suggests a compound-related effect that may not be dose-dependent. Similar apparent compound-related increases in the incidence of C-cell hyperplasia were also noted. These data were evaluated by the Toxicology Branch Statistical Support Team (Table 5), who found a positive trend for the carcinoma, but not adenoma. If the incidences of C-cell adenoma and carcinoma are combined, a positive trend is no longer apparent, and pair-wise comparisons yield a significant response only in the low dose group.

An apparent increase in the incidence of interstitial cell tumors and hyperplasia was also noted in treated males. The increase in incidence was most apparent at final sacrifice, although a possible slight increase was noted in rats that died on test. These findings were also evaluated by the Toxicology Branch Statistical Support Team. A positive trend for these tumors was also noted ($p=0.02$), however pair-wise comparisons did not yield a significant result.

Neoplastic lesions of the stomach or intestines, as were noted in the mouse, were not noted in this study. Other neoplastic lesions appeared to be randomly distributed, and were not related to treatment with the test compound.

Table 2a. Absolute and Relative Organ Weights- Interim Sacrifice[a]

Tissue	Control	200 ppm	800 ppm	3200 ppm
		MALES		
Brain	2.14±0.15[b]	2.18±0.12	2.11±0.10	2.13±0.11
	0.41±0.03[c]	0.38±0.04	0.39±0.03	0.39±0.03
Kidney	3.70±0.55	3.87±0.59	3.65±0.45	3.60±0.56
	0.71±0.10	0.68±0.08	0.67±0.07	0.66±0.07
Heart	1.56±0.23	1.54±0.17	1.46±0.13	1.48±0.18
	0.30±0.06	0.27±0.02	0.27±0.02	0.27±0.04
Liver	15.95±2.90	16.38±2.16	14.80±2.09	15.00±1.81
	3.08±0.64	2.86±0.26	2.71±0.29	2.73±0.16
Testes	5.01±0.45	5.17±0.44	4.86±0.39	4.66±0.86
	0.97±0.11	0.91±0.10	0.90±0.11	0.86±0.16
		FEMALES		
Brain	1.95±0.10	1.94±0.12	1.95±0.09	1.94±0.08
	0.62±0.07	0.59±0.11	0.65±0.05	0.64±0.06
Kidneys	2.23±0.30	2.41±0.33	2.14±0.33	2.13±0.18
	0.70±0.07	0.72±0.09	0.71±0.11	0.70±0.05
Heart	1.06±0.13	1.04±0.13	1.00±0.08	0.97±0.11
	0.33±0.02	0.31±0.05	0.33±0.04	0.32±0.03
Liver	8.38±1.30	9.00±1.47	8.28±0.39	7.78±0.85
	2.62±0.32	2.68±0.39	2.75±0.20	2.56±0.14
Ovaries	0.11±0.03	0.11±0.03	0.11±0.06	0.12±0.05
	0.03±0.01	0.03±0.01	0.04±0.02	0.04±0.02

[a]Data excerpted from submitted study.
[b]Absolute organ weights are in grams, mean ± std. dev.
[c]Relative organ weights as percent of body weight.

Table 2b. Absolute and Relative Organ Weights- Final Sacrifice[a]

Tissue	Control	200 ppm	800 ppm	3200 ppm
		MALES		
Brain	2.28±0.10[b]	2.28±0.12	2.24±0.11	2.26±0.11
	0.46±0.04[c]	0.46±0.06	0.45±0.05	0.45±0.05
Kidney	4.05±0.64	4.49±1.24	4.50±0.99	4.35±0.88
	0.82±0.15	0.90±0.24	0.90±0.13	0.86±0.19
Heart	1.79±0.23	1.76±0.26	1.79±0.27	1.68±0.20
	0.36±0.05	0.36±0.06	0.36±0.07	0.33±0.04
Liver	14.34±1.48	14.91±2.90	15.92±3.16	15.84±3.23
	2.90±0.35	2.99±0.54	3.16±0.70	3.10±0.53
Testes	4.84±0.76	4.90±1.13	4.66±0.70	5.42±1.69
	0.98±0.15	0.98±0.22	0.92±0.13	1.07±0.36
		FEMALES		
Brain	2.02±0.10	2.04±0.10	2.05±0.10	2.01±0.10
	0.59±0.11	0.61±0.13	0.54±0.09	0.58±0.10
Kidneys	2.78±0.37	2.80±0.44	2.95±0.69	2.77±0.54
	0.82±0.20	0.83±0.20	0.78±0.29	0.79±0.16
Heart	1.24±0.16	1.27±0.15	1.32±0.15	1.26±0.16
	0.36±0.06	0.38±0.08	0.35±0.07	0.36±0.06
Liver	10.10±1.99	10.36±1.70	10.90±1.90	10.40±2.45
	2.95±0.79	3.02±0.57	2.83±0.38	2.92±0.57
Ovaries	0.14±0.08	0.15±0.08	0.17±0.12	0.17±0.12
	0.04±0.02	0.04±0.02	0.05±0.03	0.05±0.03

[a]Data excerpted from submitted study.
[b]Absolute organ weights in grams, mean ± std. dev.
[c]Relative organ weights as percent of body weight.

Table 4. Selected Non-Neoplastic Findings[a]

Tissue/ Lesion	Sacrifice	DOSE GROUPS (PPM) MALES 0	200	800	3200	FEMALES 0	200	800	3200
STOMACH									
Hyperkeratosis	1yr Int.	0/10	0/10	1/10	1/10	0/10	1/10	1/10	2/10
/Acanthosis	DOT/MS	6/27	0/13	6/18	12/19	3/19	4/21	7/19	15/20
	Final	2/23	3/37	4/32	22/31	4/31	1/29	3/31	22/30
	TOTAL	8/60	9/60	15/60	35/60	7/60	6/60	11/60	39/60
Ulceration/	1yr Int.	0/10	0/10	1/10	3/10	0/10	0/10	1/10	0/10
Erosion	DOT/MS	4/27	0/13	2/18	3/19	1/19	1/21	1/19	3/20
Non-glandular	Final	0/23	0/37	3/32	4/31	1/31	1/29	2/31	5/30
Stomach	TOTAL	4/60	0/60	6/60	10/60	2/60	2/60	4/60	8/60
Submucosal	1yr Int.	0/10	0/10	1/10	0/10	0/10	1/10	1/10	0/10
Edema	DOT/MS	5/27	1/13	5/18	4/19	0/19	3/21	0/19	4/20
	Final	1/23	1/37	3/32	6/31	3/31	1/29	3/31	4/30
	TOTAL	6/60	2/60	9/60	14/60	3/60	5/60	4/60	8/60
Submucosal	1yr Int.	0/10	1/10	1/10	1/10	0/10	1/10	1/10	1/10
Inflammation	DOT/MS	5/27	0/13	4/18	6/19	2/19	4/21	1/19	5/20
	Final	2/23	1/37	3/32	7/31	4/19	1/21	1/19	7/20
	TOTAL	7/60	2/60	8/60	14/60	6/60	6/60	3/60	13/60

[a]data excerpted from submitted study. 1yr Int = 1 year interim sacrifice; DOT/MS = Died on test/Moribund sacrifice; Final = terminal sacrifice.

Table 3. Selected Neoplastic Findings[a]

Lesion	Sacrifice	DOSE GROUPS (PPM) MALES 0	200	800	3200	FEMALES 0	200	800	3200
THYROID									
C-cell	1yr Int.	0/10	0/10	0/10	0/10	1/10	1/10	0/10	1/10
Hyperplasia	DOT/MS	0/27	0/13	1/18	2/19	4/19	2/21	0/19	2/20
	Final	3/23	6/37	3/32	6/31	9/31	9/29	8/31	3/30
	TOTAL	3/60	6/60	4/60	8/60	14/60	12/60	8/60	6/60
C-cell	1yr Int.	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
Adenoma	DOT/MS	0/27	1/13	0/18	1/19	2/19	0/21	1/19	1/20
	Final	0/23	7/37	2/32	1/31	2/31	4/29	2/31	1/30
	TOTAL	0/60	8/60	2/60	2/60	4/60	4/60	3/60	2/60
C-cell	1yr Int.	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
Carcinoma	DOT/MS	1/27	0/13	0/18	1/19	0/19	0/21	2/19	0/20
	Final	0/23	1/37	2/32	3/31	1/31	1/29	1/31	0/30
	TOTAL	1/60	1/60	2/60	4/60	1/60	1/60	3/60	0/60
Adenoma + Carcinoma	TOTAL	1/60	9/60	4/60	6/60	3/60	5/60	3/60	1/60
TESTES									
Interstitial	1yr Int.	0/10	0/10	2/10	1/10				
Cell	DOT/MS	0/27	0/12	1/17	1/19				
Hyperplasia	Final	2/23	10/37	8/32	7/31				
	TOTAL	2/60	10/60	11/60	9/60				
Interstitial	1yr Int.	0/10	0/10	0/10	0/10				
Cell Tumor	DOT/MS	0/27	0/12	1/17	2/19				
	Final	1/23	5/37	3/32	6/31				
	TOTAL	1/60	5/60	4/60	8/60				

[a]data excerpted from submitted study. 1yr Int = 1 year interim sacrifice; DOT/MS = Died on test/Moribund sacrifice; Final = terminal sacrifice.

Table 4. Selected Non-Neoplastic Findings (con't)[a]

Tissue/ Lesion	Sacrifice	DOSE GROUPS (PPM) MALES 0	200	800	3200	FEMALES 0	200	800	3200
LIVER									
Foci of	1yr Int.	1/10	2/10	0/10	1/10	0/10	2/10	2/10	3/10
Vacuolated	DOT/MS	3/27	1/13	6/18	6/19	2/19	4/21	2/19	0/20
Hepatocytes	Final	2/23	11/37	9/32	9/31	13/19	9/21	8/19	13/20
	TOTAL	6/60	14/60	15/60	16/60	15/60	15/60	12/60	16/60
Spongiosis	1yr Int.	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
Hepatis	DOT/MS	3/27	0/13	0/18	2/19	0/19	1/21	0/19	0/20
	Final	4/23	7/37	8/32	8/31	1/31	0/29	0/31	1/30
	TOTAL	7/60	7/60	8/60	10/60	1/60	1/60	0/60	1/60
Focal	1yr Int.	2/10	3/10	2/10	3/10	1/10	0/10	1/10	0/10
Necrosis	DOT/MS	6/27	2/13	0/18	5/19	2/19	3/21	2/19	1/20
	Final	0/23	5/37	5/32	3/31	1/31	1/29	4/31	0/30
	TOTAL	8/60	10/60	7/60	11/60	5/60	4/60	7/60	1/60
OVARY									
Medullary	1yr Int.					0/10	0/10	0/10	0/10
Tubule	DOT/MS					2/18	4/20	3/19	3/20
Hyperplasia	Final					7/31	9/27	10/31	13/30
	TOTAL					9/59	13/57	13/60	16/60

[a]data excerpted from submitted study. 1yr Int = 1 year interim sacrifice; DOT/MS = Died on test/Moribund sacrifice; Final = terminal sacrifice.

(2) Non-neoplastic Lesions- The most significant effect of treatment on the incidence of chronic, non-neoplastic lesions occurred in the stomach (Table 4). A large increase in the incidence of hyperkeratosis/acanthosis was noted in high dose males and females at final sacrifice, and appeared to be associated with an increase in the incidence of erosion/ulceration of the non-glandular portion of the stomach, and submucosal edema/ inflammation in mid and high dose rats. A similar pattern of response was noted in rats at the 1 yr interim sacrifice, however only the incidence of hyperkeratosis/acanthosis of the stomach appeared to be clearly increased in rats that died on test.

Other lesions that were observed with increased incidence at final sacrifice included acinar atrophy of the pancreas, which was observed in increased incidence in high dose males and females, and medullary tubule hyperplasia of the ovaries. However, when the incidences of these findings for animals that died on test and rats sacrificed at one year are included, no effect of treatment on the pancreas is apparent. The incidence of "medullary tubule hyperplasia" appeared to be increased in a dose-related manner even after the addition of findings in rats that died on test and from the interim sacrifice. However, this finding is unusual in the experience of Toxicology Branch, and further description of these microscopic findings is requested.

Other changes possibly related to treatment were noted in the liver, however Toxicology Branch is unfamiliar with the term "Spongiosis Hepatis", and how this lesion relates to other findings reported in the liver. Clarification of this finding is requested from the Registrant, and possible findings in the liver will be re-evaluated at that time.

The decrease in the incidence of microcalculi of the kidney, reported for high dose males and females, is without toxicological significance.

Other lesions noted were not related to treatment, and were considered usual for the age and strain of rats used.

(d) Correlation of gross and microscopic observations- Individual animal findings tabulated gross findings with microscopic observations. Most gross findings relevant to a specific organ or tissue appeared to have been examined microscopically and diagnosed.

Discussion

The highest dose tested in this study, 3200 ppm in the diet, produced no effect on growth or food consumption in treated rats. Body weights and total weight gain were comparable in all treatment groups at study termination.

No toxicologically significant effect of treatment on hematology, clinical chemistry, or urinalysis was noted.

Ophthalmoscopic examinations did not reveal any treatment-related effects.

At necropsy, no effect of treatment on absolute or relative organ weights was apparent.

Upon gross and microscopic examinations, treatment-related non-neoplastic effects were noted in the stomachs of mid and high dose male and female rats. An increased incidence of hyperkeratosis/acanthosis was noted in mid and high dose males and females (approximately 60% in high dose and 18-25% in mid dose rats compared to about 13% in controls). This finding was related to an increased incidence of ulceration and/or erosion of the non-glandular portion of the stomach in mid and high dose rats.

Other potentially treatment-related non-neoplastic findings included "medullary tubule hyperplasia" of the ovaries, and increased "foci of vacuolated hepatocytes" in the liver. Clarification of the lesion observed in the ovary is requested. In addition, a better description of the finding in the liver described as "spongiosis hepatis" is requested, particularly as it relates to findings such as "fatty change (infiltration)" and "foci of vacuolated hepatocytes". The significance of the apparent findings in these two tissues will be further evaluated when the additional descriptions are provided.

Apparent increases in the incidences of C-cell adenoma/carcinoma of the thyroid and interstitial cell tumor of the testis were noted in treated males, however no effect of treatment on the incidence of any neoplastic lesion was noted in females. Although not strictly dose-related, a higher incidence of these tumors was noted in treated males as compared to control rats. Increases in the incidences of hyperplasia of these tissues were also noted that appeared to be compound-related but not strictly dose-related. Statistical evaluation of these findings revealed a positive trend, however pair-wise comparisons revealed a significant result only for the combined incidence of C-cell adenoma and carcinoma in the low dose group.

Interpretation of these findings in complicated by the fact that there is little apparent evidence that the MTD was reached in this study. No effect on body weight gain, food consumption, clinical signs, clinical pathology, ophthalmology, or organ weights was noted. The only treatment related effects noted

(other than possible neoplasia in the thyroid and testes) were in the stomach. However, the findings in the stomach were not of sufficient severity as to affect feeding behavior or body weight gain, and one must question whether these effects were of sufficient severity as to constitute the MTD. Further, a previously-reviewed 90-day feeding study in the Sprague-Dawley rat found a NOEL of 3000 ppm and an LEL of 10000 ppm, as compared to the HDT in this study of 3200 ppm.

In summary, equivocal evidence of oncogenicity in the thyroid and testis of the male rat are presented in this study. This interpretation is reinforced by an increased incidence of hyperplasia in these tissues, evidence of mutagenicity in a number of different test systems, and demonstrated oncogenicity in the mouse in two other studies. This interpretation is complicated by a lack of a clear dose-effect relationship for these findings, and the possibility that the MTD was not reached in this study.

However, in order to fully interpret these findings, historical control data for the incidences of these neoplastic lesions are required. These data should be tabulated by study for a least two years prior to the present study, and for whatever period after as may be available. In addition to incidence data, the Toxicology Branch Statistical Support Team requests that these data include information as to survival in each study, presented for each month on test. When these requested data are submitted, all relevant information will be presented to the Toxicology Branch Ad Hoc Oncogenicity Committee for a determination of the proper Weight-of-the-Evidence for this study.

> Oncogenicity: Tentatively classified as positive (in the male rat only) based on an increase in the incidence of C-cell adenoma and carcinoma of the thyroid, and interstitial cell tumors of the testes.
>
> Chronic NOEL = 200 ppm (LDT).
> Chronic LEL = 800 ppm (MDT) Hyperkeratosis/acanthosis and ulceration/erosion of the non-glandular stomach in males and females.
>
> Classification: Core-Supplementary Historical control data requested; additional clarification of liver and ovary lesions requested, results of diet analyses must be submitted

DSS:TOX/HED/TS-769C:6/17/86:file RAT464

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

JUN 25 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Chevron Folpet Technical (SX-1388) - Qualitative Analysis of Male Rat Crl:CD(SD)BR Oncogenicity Study.

Caswell #464

FROM: Richard Levy, Statistician
Scientific Mission Support Staff
Toxicology Branch/HED (TS-769)

6/25/86

TO: Stephen D. Saunders, Pharmacologist
Section V, Toxicology Branch/HED (TS-769)

THRU: Bertram Litt, Leader, Statistical Team
Scientific Mission Support Staff
Toxicology Branch/HED (TS-769)

THRU: Reto Engler, Chief
Scientific Mission Support Staff
Toxicology Branch/HED (TS-769)

Survival and time to tumor analyses were done for a 2-year Folpet feeding regimen in Crl:CD(SD)BR male rats. Nonparameteric statistics - testing for homogeneity and linear trend, while adjusting for the time to event - are summarized in the attached table.

Attachment

#12 6/24/86 sb

CHEVRON FOLPET TECHNICAL (SX-1388)
MALE RAT Crl:CD (SD) BR

	Dose Group				P-Values Generalized K/W (Gehan-Breslow)[1]	
	0	200 ppm	800	3000	Homogeneity (Exact Inverse)	Trend (one sided)
DEATH ON STUDY	27	13	18	19	0.0304[2]	0.1426
TESTES						
Interstitial Cell Tumor	1	5	4	8	0.20	0.02
THYROID						
C-Cell Adenoma	0	8	2	2	0.02	0.20
C-Cell Carcinoma	1	1	2	4	0.42	0.05
C-Cell Adenoma & or Carcinoma	1	9*	4	6	0.22	0.34
Animals in Study[3]	60	60	60	60		

1 = Thomas, D. G., Breslow, N. and Gart, J. J. Trend and Homogeneity Analyses of Proportions and Life Table Data. Computers and Biomedical Research 10, 373-381 (1977), Version 9/26/84.

Adjusted Analysis are accomplished by accounting for time to event. The generalized K/W (Gehan-Breslow) uses a scoring procedure which gives more weight to early deaths.

2 = Since there is a significant lack of homogeneity after adjusting for early deaths, all the tumor analyses must be adjusted similarly.

3 = All animals were examined.

* = The pairwise comparison, control vs. low dose, was borderline significant at 0.05.

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DATA EVALUATION RECORD

Reviewer: D. Stephen Saunders, Ph.D. DSS 8/07/86
Toxicologist, Section V

Secondary Reviewer: Laurence D. Chitlik, DABT Laurence Chitlik for LDC 8/7/86
Head, Section V

STUDY TYPE: Rabbit teratology study- pulse dosing (Guidelines 83-3).

ACCESSION NUMBER: 259597 MRID NUMBER: 151490

TEST MATERIAL: Folpet

SYNONYMS: Folpan, phaltan

REPORT NUMBER: 303-004

SPONSOR: Chevron Chemical Company
Richmond, CA.

TESTING FACILITY: Argus Research Labs., Inc.
Horsham, PA. 19044

TITLE OF REPORT: "Teratology Study in Rabbits with Folpet Technical Using A 'Pulse-dosing' Regimen."

AUTHORS: Feussner, E.L., Hoberman, A.M., Johnson, E.M., Christian, M.S.

REPORT ISSUED: 8-8-85

Conclusion: A clearly treatment-related effect on the incidence of major malformations was not apparent. A previous study (Argus #303-002) in which rabbits were treated with doses up to 60 mg/kg/day over days 6-28 of gestation, demonstrated a statistically significant increase in the incidence of hydrocephalus (5.5% of fetuses, 25% of litters). This finding was not reproduced in this study which tested 60 mg/kg/day over three day intervals, although the two observed incidences in the present study (out of 309 fetuses and 44 litters) were higher than reported overall historical control incidences. An increased incidence of irregularly-shaped fontanelles was noted in rabbits dosed over days 13-15 of gestation, and possible increases in the incidence of angulated alae of the hyoid were noted in rabbits dosed over gestation days 7-9 or 10-12. As the purpose of this pulse-dose protocol was to determine the critical period of treatment for previously observed teratogenic response, NOELs for developmental or maternal toxicity were not established. The NOEL for developmental toxicity was established as 10 mg/kg/day in the previous study.

Classification: Core-Minimum when considered with the data from Argus Study #303-002.

A. Materials

(1) Test material: Technical Folpet, batch #SX-1388, "an off-white, fine powder with a pungent, slightly disagreeable odor", 89.5% a.i.

(2) Test animals: Hazleton Dutchland New Zealand White rabbits (Dla Hra:[NZW]SPF), obtained from Hazleton Dutchland Labs., Inc., Denver, PA.

B. Study Design

After acclimation, 100 female rabbits, previously determined to be in good health, were assigned to five treatment groups, 20/group. Each rabbit was administered 20 USP units/kg of human chorionic gonadotropin (HCG) by intravenous injection. Three hours later, each rabbit was artificially inseminated with 0.25 ml of semen, which had been diluted with normal saline to a concentration of 6 X 106 sperm/0.25 ml. Four proven male breeders were the source of semen for all treatment groups. Insemination of rabbits was staggered so that 4 rabbits from each treatment group were inseminated on each of 5 consecutive days. The day of insemination was designated as day 0 of gestation.

Treatment groups were dosed with either the vehicle (Group I, control) or 60 mg/kg/day of technical folpet (Groups II-V). Control rabbits were treated over days 7-18 of gestation; rabbits treated with folpet were treated for short periods according to the "pulse-dosing" scheme below:

Treatment Group	Dose (mg/kg/day)	Gestation Days of Treatment
I	0	7-18
II	60	7-9
III	60	10-12
IV	60	13-15
V	60	16-18

Test dosages were prepared by suspending an appropriate amount of technical folpet in 0.5% Tween 80 and 0.7% carboxymethylcellulose (CMC), w/w. Dose "calculations were not adjusted for purity." Test doses were prepared daily; three samples were saved from each dose preparation for analysis. The concentration of test solutions was calculated to provide an administration volume of 5 ml/kg. All doses were administered by gavage.

All rabbits were sacrificed on day 29 of presumed gestation by intravenous administration of "T-61 Euthanasia Solution".

C. Methods and Results

1. Physical Observations- Rabbits were observed "several times each day" during the treatment period for toxic signs, viability, and evidence of abortion or delivery. Rabbits were observed twice daily after the period of treatment for these signs.

Results- Only one mortality was recorded in the study, and was noted in a rabbit from Group II. This rabbit was treated over days 7-9 of gestation, and was found dead on day 25. Prior to its death, this rabbit aborted a single fetus, which appeared normal and was alive at the time of delivery. No clinical signs were recorded for this animal prior to death, and weight gain and food consumption appeared to be similar to that of other treated animals. Necropsy did not reveal any lesions, and the cause of death was not established, although the investigators speculated that the death was treatment-related. Three dead fetuses and 3 resorptions were present in the uterus of this animal.

One other doe, from Group III (treated over days 10-12), aborted on day 18 of gestation. No clinical signs of toxicity were reported for this animal prior to the abortion, although this doe lost 163 grams of body weight over the treatment period, which was the greatest loss of any doe in Group III, and was higher than the average loss of 40 grams/doe. Feed consumption was somewhat reduced in this rabbit during the treatment period, however this parameter was similarly affected in other does of Group III. As two placentas were found in the litter pan, it was assumed that this rabbit cannibalized two aborted fetuses. Necropsy data for this animal were not provided.

Other physical signs noted in treated does included "soft or liquid feces", which was noted with increased frequency and of greater duration in treated does compared to control. However, the investigators stated that this finding "was not considered to be an effect of the test substance" as its occurence did not appear to be related to the period of treatment. Alopecia was noted in all test groups, and "was considered attributable to expected nesting activity of the animals". One other physical observation, "red exudate in pan", was noted in single does from Groups IV and V, and was related to complete resorption of litters in these animals.

2. Body Weights and Feed Consumption- Body weights were recorded on day 0 of presumed gestation, and daily on days 7-28. Day 29 body weights were corrected by subtraction of gravid uterus weights.

Feed consumption was determined daily, by measuring the amount of the 180 gram daily offering that remained in the individual feed cups.

Results- Group mean maternal body weights tended to decline in treated rabbits over the period of treatment, and then tended to rebound after treatment was completed (Table 1.) Although this trend was apparent in all treatment groups, the effect was not statistically significant. Calculated body weight changes were statistically different from control, and followed the same pattern- a decrease in weight gain during the treatment period, and then an increase in weight gain after treatment was completed (Table 6, photocopied from the study report). When calculated over days 7-29 (corrected or uncorrected for uterus weights) or over days 0-29, no statistically significant differences were apparent.

Feed consumption was altered in a pattern similar to the effects on body weight. During treatment, feed consumption was significantly lower in treated does compared to control, however after treatment was ended, food consumption recovered to be no different from average control consumption.

TABLE 6 (PAGE 1): MATERNAL BODY WEIGHT CHANGES - SUMMARY

Dosage Group (mg/kg/day):		I 0(Vehicle)	II 60	III 60	IV 60	V 60
Days of Administration:[a]		7-18	7-9	10-12	13-15	16-18
ANIMALS - TESTED		20	20	20	20	20
PREGNANT	N(%)	18(90.0)	15(75.0)	16(80.0)	16(80.0)	16(80.0)
MATERNAL BODY WEIGHT CHANGE						
DAYS 0- 7	MEAN±S.D.	+0.18 ± 0.07	+0.20 ± 0.08	+0.18 ± 0.09	+0.19 ± 0.07	+0.19 ± 0.08
DAYS 7-10	MEAN±S.D.	+0.02 ± 0.04	-0.08 ± 0.08**	+0.04 ± 0.04	+0.02 ± 0.03	+0.06 ± 0.13
DAYS 10-13	MEAN±S.D.	+0.07 ± 0.05	+0.17 ± 0.05** [12]	-0.04 ± 0.08** [12]	+0.05 ± 0.06	+0.05 ± 0.15 [13]
DAYS 13-16	MEAN±S.D.	+0.06 ± 0.06	+0.07 ± 0.06 [12]	+0.15 ± 0.09** [12]	-0.11 ± 0.10**	+0.04 ± 0.11 [13]
DAYS 16-19	MEAN±S.D.	+0.00 ± 0.08	+0.02 ± 0.06	+0.00 ± 0.04 [15]	+0.05 ± 0.10	-0.17 ± 0.13**
DAYS 19-22	MEAN±S.D.	+0.02 ± 0.08	+0.02 ± 0.04	+0.04 ± 0.07 [15]	+0.06 ± 0.08	+0.06 ± 0.12
DAYS 7-19	MEAN±S.D.	+0.16 ± 0.09	+0.16 ± 0.06	+0.14 ± 0.09 [15]	+0.00 ± 0.17**	-0.01 ± 0.14**
DAYS 7-29	MEAN±S.D.	+0.30 ± 0.22	+0.23 ± 0.22 [14]	+0.23 ± 0.17 [15]	+0.09 ± 0.23	+0.08 ± 0.39
DAYS 0-29	MEAN±S.D.	+0.37 ± 0.24	+0.43 ± 0.25 [14]	+0.40 ± 0.19 [15]	+0.28 ± 0.23	+0.27 ± 0.41
DAYS 7-29C[b]	MEAN±S.D.	-0.21 ± 0.19	-0.14 ± 0.31 [14]	-0.26 ± 0.18 [15]	-0.30 ± 0.30	-0.23 ± 0.26

This table is restricted to pregnant animals.
All weights values are in kg.
[ ] = Number of values averaged.
a. "Days" refers to days of presumed gestation.
b. "Corrected" day 29 maternal body weight (day 29 body weight of doe minus of gravid uterus).
** Significantly different from control value, at P≤0.01

Table 1. Group Mean Maternal Body Weights[a]

Day	Control (7-18)[b]	Group II (7-9)	Group III (10-12)	Group IV (13-15)	Group V (16-18)
0	4.03±0.41	4.00±0.26	3.97±0.30	3.97±0.30	3.94±0.38
7	4.20±0.43	4.20±0.26	4.14±0.33	4.17±0.33	4.13±0.38
10	4.22±0.42	4.11±0.28	4.18±0.31	4.19±0.33	4.18±0.37
13	4.30±0.43	4.24±0.32	4.10±0.34	4.24±0.36	4.27±0.43
16	4.35±0.47	4.34±0.30	4.28±0.32	4.12±0.36	4.29±0.39
19	4.36±0.45	4.36±0.29	4.28±0.32	4.17±0.37	4.12±0.45
29	4.40±0.54	4.40±0.41	4.36±0.26	4.26±0.36	4.21±0.57
29[c]	4.00±0.50	4.04±0.45	3.88±0.40	3.86±0.40	3.89±0.52

[a]data excerpted from submitted study. Values are mean body weights in kilograms, mean ± standard deviation, calculated by the investigators.
[b]days of treatment.
[c]corrected body weights, by subtraction of gravid uterus weights.

3. Necropsy Data- (a) Reproductive parameters- At sacrifice, "the abdomen of each rabbit was opened, corpora lutea were counted, and the uterus was examined for pregnancy and number and placement of implantations, fetuses and early and late resorptions." Early resorptions were defined as implants in which organogenesis was incomplete, whereas late resorptions were defined as implants in which organogenesis was apparent. The viability of fetuses was determined by the response to "mechanical stimulation".

Results- No statistically significant alterations in maternal reproductive parameters were apparent (Table 10, photocopied from the study report). An apparent increase in the number of early resorptions was noted in group II does (treated days 7-9), however individual animal data revealed that this apparent increase was due to a single doe, #9229, with 9 early resorptions and 2 viable female fetuses. The number of does in this group with any resorptions (5) was the same as control, which further indicates that this finding is spurious and not related to treatment. An apparent increase in the number of late resorptions was also noted in group III does (treated days 10-12). Although suggestive of a possible treatment-related effect, this group also had a significantly higher number of implantations ($p<0.05$), and non-significant increases in litter size and the number of live fetuses. Further, these late resorptions were noted only in does with 8 or more implantations. Historical control data revealed a single study (out of 22) in which a similar incidence of late resorptions was noted, 5/11 or 0.45/litter. Therefore, this change cannot be definitively attributed to treatment with the test material.

3.(b). Fetal data- Each fetus was weighed and examined for gross external bnormalities. Live fetuses were killed by intraperitoneal injection with T-61 olution. Fetuses were examined to determine sex, and organs were examined sing "a variation of the Staples technique". Tissues considered abnormal were etained in neutral buffered 10% formalin. All fetuses obtained after 27 days f gestation were examined for external malformations, eviscerated, and stained ith Alizarin red-S for skeletal evaluations. Late resorptions were similarly rocessed where possible.

Results- No statistically significant effects on litter size, fetal iability, fetal body weight, or sex ratio were apparent (Table 12, photocopied rom the submitted study report).

No effect of treatment on the incidence of externally visible fetal nomalies was noted. A single control fetus was observed to have hemorrhagic reas of the head and white areas of the cornea, and a single fetus from Group / was observed to have "moderately small" body size. All other fetuses ppeared grossly normal at necropsy.

Upon visceral examination, single incidences of internal hydrocephalus were oted in one fetus each from Group III and Group V (Table 13). This finding was ot noted in any control fetuses. If it is assumed that the critical period for nis developmental defect extended from days 10-18 (the treatment period for roups III-V), an overall incidence of 2/201 (1%) fetuses and 2/29 (6.9%) itters is observed. These values are higher than the reported historical alues of 3/2160 (0.1%) fetuses and 3/285 (1.0%) litters, but are much lower nan the fetal and litter incidences of 5.5% and 25%, respectively, observed in ne previous study.

Agenesis of the left ovary and oviduct was noted in a single fetus from roup II, and "very small" gall bladder was reported for a single fetus from roup IV. A subcapsular hemorrhage of the left kidney (normal otherwise) was eported for a single control fetus. All other fetuses were reported to be ormal, without apparent soft tissue variations.

A statistically significant increase ($p<0.01$) in the fetal incidence of regularly shaped fontanelle was noted in Group IV fetuses, 13/107 (12.1%) ompared to a control incidence of 5/112 (4.5%). The litter incidence of this ariation was 3/15 (20%) Group IV litters, compared to 2/18 (11.1%) control itters. This variation was noted in a single Group III fetus, and no fetuses om Groups II or V were observed to have this variation. The fetal and litter cidences of this finding in the previous study were 6.8% and 25%, espectively. Angulated alae of the hyoid were noted in 6/76 (7.9%) Group II tuses and 6/113 (5.4%) Group III fetuses, and the litter incidences of this riation were 4/14 (28.6%) in Group II and 4/15 (26.7%) in Group III. Although ot statistically significant, these incidences were substantially greater than ne control fetal or litter incidences of this finding, 3/112 (2.7%) and 3/18 6.7%), respectively. The fetal and litter incidences of this finding in roups IV and V were similar to control. Other skeletal findings did not appear be affected by treatment.

PROTOCOL 303-004: TERATOLOGY STUDY IN RABBITS WITH FOLPET TECHNICAL USING A "PULSE-DOSING" REGIMEN

TABLE 10 (PAGE 1): CAESAREAN DELIVERY DATA - SUMMARY

Dosage Group (mg/kg/day):		I 0(Vehicle)	II 60	III 60	IV 60	V 60
Days of Administration:[a]		7-18	7-9	10-12	13-15	16-18
ANIMALS - TREATED		20	20	20	20	20
PREGNANT	N(%)	18(90.0)	15(75.0)	16(80.0)	16(80.0)	16(80.0)
ABORTED	N	0	1[b]	1	0	0
DIED	N	0	1[b]	0	0	0
DELIVERED NATURALLY	N	0	0	0	0	1
ANIMALS PREGNANT AND DELIVERED BY CAESAREAN-SECTIONING ON DAY 29	N	18	14	15	16	15
CORPORA LUTEA	MEAN±S.D.	10.8 ± 2.4	10.6 ± 1.6	11.8 ± 2.1	10.2 ± 1.9	9.9 ± 3.1
IMPLANTATIONS	MEAN±S.D.	6.5 ± 2.1	6.6 ± 3.1	8.3 ± 2.5*	7.1 ± 2.5	6.1 ± 2.2
LITTER SIZE	MEAN±S.D.	6.2 ± 1.9	5.4 ± 2.7	7.5 ± 2.3	6.8 ± 2.8	5.5 ± 2.5
LIVE FETUSES	N	1[1]	76	112	108	82
	MEAN±S.D.	6.2 ± 1.9	5.4 ± 2.7	7.5 ± 2.3	6.8 ± 2.8	5.5 ± 2.5
DEAD FETUSES	N	0	0	1	0	0
	MEAN±S.D.	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.2	0.0 ± 0.0	0.0 ± 0.0
RESORPTIONS	MEAN±S.D.	0.3 ± 0.6	1.2 ± 2.5	0.8 ± 0.8	0.4 ± 0.7	0.7 ± 1.0
EARLY RESORPTIONS	N	5	13	5	5	5
	MEAN±S.D.	0.3 ± 0.5	0.9 ± 2.4	0.3 ± 0.6	0.3 ± 0.7	0.3 ± 0.7
LATE RESORPTIONS	N	1	4	7	1	5
	MEAN±S.D.	0.0 ± 0.2	0.3 ± 1.1	0.5 ± 0.6	0.1 ± 0.2	0.3 ± 0.8
DOES WITH ANY RESORPTIONS	N(%)	5(27.8)	5(35.7)	9(60.0)	4(25.0)	6(40.0)
DOES WITH ALL IMPLANTATIONS RESORBING	N(%)	0	0	0	1(6.2)	1(6.7)
DOES WITH VIABLE FETUSES	N(%)	18(100.0)	14(100.0)	15(100.0)	15(93.8)	14(93.3)

a. "Days" refers to days of presumed gestation.
b. This rabbit died following abortion.
* Significantly different from control value, at $P \leq 0.05$.

PROTOCOL 303-004: TERATOLOGY STUDY IN RABBITS WITH FOLPET TECHNICAL USING A "PULSE-DOSING" REGIMEN

TABLE 12(PAGE 1): LITTER DATA - SUMMARY

Dosage Group (mg/kg/day):		I 0(Vehicle)	II 60	III 60	IV 60	V 60
Days of Administration:[a]		7-18	7-9	10-12	13-15	16-18
LITTERS EXAMINED DAY 29	N	18	14	15	15	14
IMPLANTATIONS	MEAN+S.D.	6.5 + 2.1	6.6 + 3.1	8.3 + 2.5	7.5 + 2.1	6.4 + 1.9
LIVE FETUSES	MEAN+S.D.	6.2 + 1.9	5.4 + 3.7	7.5 + 3.3	7.2 + 3.2	5.8 + 2.1
LITTERS WITH ONE OR MORE LIVE FETUSES	N	18	14	15	15	14
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN+S.D.	45.13 + 5.57	46.55 + 6.53	46.14 + 6.70	42.81 + 6.83	45.60 + 7.62
MALE FETUSES	MEAN+S.D.	45.75 + 6.37	48.02 + 8.72 [13][b]	47.21 + 6.77	43.76 + 6.95	45.31 + 7.45 [13][b]
FEMALE FETUSES	MEAN+S.D.	44.66 + 5.67	44.90 + 5.02 [12][c]	44.11 + 5.47 [14][c]	41.88 + 6.82	45.38 + 8.27 [13][c]
% DEAD OR RESORBED CONCEPTUSES/LITTER	MEAN+S.D.	4.4 + 7.5	13.5 + 25.1	9.5 + 9.2	3.6 + 8.2	8.8 + 15.0
LIVE FETUSES	N	111	76	112	108	82
LIVE MALE FETUSES	N	47	32	55	55	36
% LIVE MALE FETUSES/LITTER	MEAN+S.D.	43.1 + 17.1	46.8 + 28.1	51.5 + 19.0	52.0 + 16.6	44.9 + 22.4

NOTE: - Animals with all implants resorbing excluded from this table.
[ ] = Number of values averaged

a. "Days" refers to days of presumed gestation.
b. One (9229) Group II litter and one (9296) Group V litter had no male fetuses.
c. Two (9226, 9233) Group II litters, one (9246) Group III litter and one (9298) Group V litter had no female fetuses.

Table 13. Selected Fetal Variations[a]

	Group I Control	Group II days 7-9	Group III days 10-12	Group IV days 13-15	Group V days 16-18
No. litters examined	18	14	15	15	14
No. fetuses examined	112	76	113	108	88
Hydrocephalus	0	0	1/1[b] (6.7/0.9)[c]	0	1/1 (7.1/1.2)
Irregularly-shaped fontanelle	2/5 (11.1/4.5)	0	1/1 (6.7/0.9)	3/13** (20.0/12.1)	0
Angulated alae of the hyoid	3/3 (16.7/2.7)	4/6 (28.6/7.9)	4/6 (26.7/5.4)	3/3 (20.0/2.8)	2/3 (14.3/3.6)

[a] data excerpted from submitted study.
[b] litter/fetal incidences.
[c] litter/fetal percentages.
**$p<0.01$

Discussion

This study utilized a "pulse-dosing" regimen in which a dose of 60 mg/kg/day was administered for 3 consecutive days at various stages of gestation. The purpose of this study was to determine the critical period of exposure for a dose that had previously been demonstrated to cause hydrocephalus in rabbits treated over days 6-28 of gestation.

Evidence of maternal toxicity was noted in the form of disruption of feeding behavior and decreased body weight gain. The NOEL for these effects was established in the previous study (Argus #303-002) as 10 mg/kg/day.

No effect of treatment on the number of early or late resorptions, litter size, fetal body weight, or fetal sex ratio was noted.

A clearly treatment-related increase in the incidence of hydrocephalus, the major finding of the previous study, was not apparent in the present study. Although the two observed incidences of hydrocephalus resulted in a higher overall incidence than historical control, the incidences were not statistically significant when compared to concurrent control, and were about five-fold lower than the incidences observed in the previous study.

An increased incidence of irregularly-shaped fontanelles was noted in Group IV fetuses, and possible treatment-related increases in the incidence of angulated alae of the hyoid were noted in Groups III and IV. The incidence of irregularly-shaped fontanelle was similar to the finding in the previous study, however angulated hyoid was not a significant finding in the previous study. As only a single dose was tested, a NOEL for this finding was not established in this study. As these findings were also noted in the previous study, the NOEL for skeletal variations has been established as 10 mg/kg/day.

Therefore, a clear effect of treatment on the incidence of the teratogenic finding of hydrocephalus, as was demonstrated in a previous study with dosing over days 6-28 of gestation, was not reproduced in the present study using a "pulse-dosing" schedule with 3-day treatment periods. However, irregularly-shaped fontanelle, also demonstrated in the previous study, was noted in the present study in rabbits dosed over days 13-15 of gestation.

Classification: Core-Minimum when considered with the data from Study #303-002.

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EPA: 68-02-4225
DYNAMAC No. 228-A
September 8, 1986

DATA EVALUATION RECORD

FOLPET

Two-Generation Reproduction Study in Rats

STUDY IDENTIFICATION: Hardy, L. H. and Richter, W. R. Two generation (two litter) reproduction study in rats with Chevron folpet technical. (Unpublished study No. SOCAL 2140 by Chevron Environmental Health Center, Inc., for Chevron Chemical Company, Richmond, CA; dated September 19, 1985.) Accession Nos. 259585-259596.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Department Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 9-9-86

005502

1. CHEMICAL: Chevron folpet; N-(trichloromethylthio)phthalimide ($C_9H_4Cl_3NO_2S$); Phaltan.

2. TEST MATERIAL: Chevron folpet technical was described as a fine, off-white powder, with a pungent, slightly disagreeable odor and a purity of 89.5%.

3. STUDY/ACTION TYPE: Two-generation reproduction study in rats.

4. STUDY IDENTIFICATION: Hardy, L. M. and Richter, W. R. Two generation (two litter) reproduction study in rats with Chevron folpet technical. (Unpublished study No. SOCAL 2140 by Chevron Environmental Health Center, Inc., for Chevron Chemical Company, Richmond, CA; dated September 19, 1985.) Accession Nos. 259585-259596.

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7. CONCLUSIONS:

A. We assess the NOEL and LOEL for parental toxicity at 690 and 3200 ppm (the approximate concentrations of the mid-dose and high-dose), respectively based on significant reductions in parental body weight, body weight gain and food consumption reported at 3200 ppm. Although our assessment of the body weight data for F_0 parents was confounded by the fact that F_0 males and females were significantly lighter than controls from the onset of the study, we concluded that the reductions reported for F_1 parents were compound-related.

We tentatively assess the LOEL for reproductive/developmental toxicity at 150 ppm (the approximate concentration at the low-dose level), based on apparent decreases in F_1 parental reproductive indices at all dose levels (see Item 8 below) and on significant reductions in pup body weights during the latter part of the lactation periods of F_1 and F_2 pups at 3200 ppm. The NOEL for reproductive/developmental toxicity could not be assessed.

B. This study is classified Core Supplementary.

8. RECOMMENDATIONS:

We request that the study sponsor submit historical control data on male and female fertility. These data are necessary to completely evaluate the results of this study.

Items 9 and 10--see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods: (See Appendix A.)

1. Test Material: Chevron folpet technical, N-(trichloromethylthio)phthalimide, Phaltan, from lot/batch No. SX-1388, was described as a fine off-white powder with a pungent, slightly disagreeable odor and a reported purity of 89.5%. Animals in this study were continuously fed diets containing 0 (control, Purina Certified Rodent Laboratory Chow #5002), 200, 800, or 3600 ppm of the test material. Test diets were prepared at least once weekly and stored frozen (-20°C). Analyses for diet homogeneity were conducted prior to study initiation. The concentration of test material in the diets was analyzed by Chevron from weekly samples obtained for the first 4 weeks and monthly thereafter. The stability of the test material was analyzed by Chevron from samples obtained every 6 months during the study and at study termination.

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[1] Only items appropriate to this DER have been included.

2. Test System: CrL:COBS/CD(SD) male and female rats were obtained from Charles River Breeding Laboratory, Portage, MI, at 44-45 days of age. After an acclimatization ("equilibrium") period of 8 days, 30 animals of each sex were randomly assigned to each of four study groups to become F_0 parents. Animals were housed individually (except during mating) in temperature- and humidity-controlled rooms. Water and diets were available ad libitum.

   Following an exposure to the test material for a period of 62 days, males and females from the same dose group were paired on a 1:1 basis. Mating was confirmed by the presence of copulatory plugs or sperm in vaginal smears; the day of mating was considered gestational day (GD) 0. The resulting F_{1a} pups were sacrificed by CO_2 inhalation at weaning (21-23 days postpartum). After a rest period of approximately 2 weeks, F_0 parents were mated again (different pairs) to produce F_{1b} pups. At weaning, 30 F_{1b} pups per sex per group were selected to be parents of the F_2 litters. The F_{1b} rats were mated after a 12-week dosing period to produce the F_{2a} pups; after a rest period of at least 1 week following the weaning of the F_{2a} pups, F_{1b} rats were mated again to produce the F_{2b} litters. F_{2b} litters were sacrificed at weaning.

3. Parameters Examined: Animals were observed twice daily for mortality and overt changes in appearance and behavior. Body weights of F_0 and F_1 animals were measured on the second day of feeding and weekly thereafter. Females that mated were weighed on GD 0, 7, 14, and 21 and on days 0, 7, 14, and 21 of lactation. Premating food consumption was measured three times per week for the first month and then during a 2-day interval once weekly. Food consumption was not measured during the mating period. Food consumption during gestation and lactation was measured at 2-day intervals for the F_{1b} parental females only.

   Pups were evaluated for abnormalities shortly after birth and were weighed on lactation days 0, 4, 7, 14, and 21. Litters were evaluated for size, pup sex, number of stillborn, number of live births, survival, and pup observations.

   All animals were subjected to a gross necropsy. Selected tissues from reproductive organs of parental animals from the control and high-dose groups were examined histologically. Abnormal tissues from animals in all groups were examined microscopically.

4. Statistical Methods: Body weights, body weight changes, and food consumption were evaluated using one-way analysis of variance (ANOVA). Significant differences were further evaluated using Dunnett's test. Reproductive parameters, such as mating index, pregnancy rate, and fertility index, were assessed using Chi-square analysis.

B. Protocol: A protocol was presented in the study report (see Appendix B).

12. REPORTED RESULTS:

A. Diet Analyses: The study authors reported that the test material contained approximately 90% active ingredient and that the test material was stable in the diet mixtures. Results from concentration analyses indicate that diet mixtures contained approximately 143-175 ppm, 670-710 ppm, and 3210-3260 ppm for nominal 200, 800, and 3600 ppm levels, respectively.

B. Adult Animal Effects: A total of 1, 2, and 1 F_0 parental males in the groups exposed to 200, 800, and 3600 ppm, respectively, were found dead or were sacrificed prior to termination. The only mortality reported for F_{1b} parents was one female that was exposed to 3600 ppm. These deaths were considered incidental since clinical observations, necropsy, and histopathological findings did not suggest compound-related effects. Clinical observations for F_0 and F_1 adults were comparable for all groups.

At study initiation, body weights of male and female animals selected to be F_0 parents in the control and 200- and 800-ppm groups were comparable; however, the study authors stated that due to randomization procedures, the body weights of male and female animals assigned to the 3600 ppm (highest level tested) group were significantly less ($p < 0.01$ and $p < 0.05$, respectively) than those of controls at study initiation (Tables 1 and 2). Significantly lower body weights were reported for F_0 and F_1 males and females dosed with 3600 ppm during most study periods (premating, mating, gestation, lactation; see Tables 1-8). Body weights of adult F_0 and F_1 males and females dosed with 200 and 800 ppm were generally comparable to the controls at all times (Tables 1-8).

No compound-related effects were noted for maternal body weight changes during the two gestation and the two lactation periods of F_0 females (Tables 3 and 4). Similarly, no compound-related effects in maternal body weight changes were reported for the gestation and lactation periods of F_1 females (Tables 7 and 8).

The food intake of F_0 and F_1 males and females dosed with 3600 ppm was significantly reduced at several times during the premating periods when compared with controls. The food consumption in the other dose groups was generally comparable to controls during these periods, except for sporadic reductions reported for F_0 males dosed with 800 ppm, F_1 males dosed with 200 and 800 ppm, and F_1 females dosed with 800 ppm when compared with controls (Tables 9-12).

TABLE 1. Effects of Folpet on Body Weight of F_0 Male Rats

Study Period	Study Day	Dose Level (ppm) 0	200	800	3600
Premating	1	275.7±13.4[a]	277.1±13.1	275.6±12.8	261.7±11.3**
	8	305.3±15.0	310.9±15.5	303.4±14.7	303.2±17.5
	36	408.5±23.3	414.0±24.8	404.1±29.4	401.6±26.7
Mating (1a)	64	455.7±27.3	461.3±29.3	447.4±31.5	444.7±33.1
Rest	92	496.1±34.8	498.2±34.8	484.0±33.5	471.3±40.0*
	120	531.5±40.7	524.5±38.9	521.8±39.2	509.6±38.3
Mating (1b)	134	536.5±41.5	524.4±39.5	523.6±42.7	507.8±41.3*
	141	548.4±43.7	533.9±41.7	533.8±43.6	519.7±40.2*
	148	553.2±43.3	535.2±43.2	539.2±47.1	525.3±39.9*
	155	561.4±44.2	539.3±48.4	547.6±46.8	531.4±41.4*

[a]Values represent mean (g) ±S.D. Calculations are based on approximately 30 animals per group.

*Significantly different from control value ($p \leq 0.05$).

**Significantly different from control value ($p \leq 0.01$).

TABLE 2. Effects of Folpet on Body Weight of F_0 Female Rats During Premating and Rest Periods

Study Period	Study Day	Dose Level (ppm) 0	200	800	3600
Premating	1	177.9±12.3[a]	179.1±12.6	175.8±12.0	169.7±11.4*
	8	190.7±13.9	189.6±13.7	188.1±14.6	188.1±14.5
	22	216.7±19.0	218.1±14.6	215.3±17.8	213.8±17.0
	36	236.0±20.1	234.9±19.5	232.5±21.6	228.1±17.1
	50	247.4±21.1	247.0±19.6	246.0±22.6	242.1±19.2
Rest	113	281.3±21.9	276.3±15.7	279.9±30.6	276.4±17.4
	127	294.5±22.1	295.2±20.7	291.3±28.0	288.3±20.6

[a]Values represent mean (g) ± S.D. Calculations are based on approximately 30 animals per group.

*Significantly different from control value ($p \leq 0.05$).

TABLE 3. Effects of Folpet on Body Weight of F_0 Female Rats During Gestation and Lactation of F_{1a} Litters

	Dose Level (ppm)			
	0	200	800	3600
No. pregnant	24	26	22	26
Gestation				
Day 0	255±24[a]	259±20	252±18	252±18
Day 7	280±25	284±22	280±19	281±20
Day 14	307±28	312±24	306±20	307±19
Day 21	375±42	380±30	373±21	363±26
Gestation Weight Change				
Days 0- 7	25± 7	25± 6	28± 5	30± 8*
Days 7-14	27± 7	28± 5	26± 6	26± 4
Days 14-21	67±16	68±15	67±11	56±14*
Days 0-21	119±23	122±19	121±12	112±19
No. delivering	24	26	22	26
Lactation				
Day 0	288±23	293±23	281±23	284±22
Day 7	308±29	315±24	306±19	304±21
Day 14	324±29	329±20	324±19	322±19
Day 21	315±26	317±17	318±23	320±18
Lactation Weight Change				
Days 0- 7	16±14	22±14	25±13	21±12
Days 7-14	16±16	14±11	18± 7	18± 9
Days 14-21	-9±12	-12±11	-5±12	-2± 9
Days 0-21	25±11	24±15	37±19*	37±16*

[a]Values represent mean (g) ± S.D.

*Significantly different from control value ($p \leq 0.05$).

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TABLE 4. Effects of Folpet on Body Weight of F_0 Female Rats During Gestation and Lactation of F_{1b} Litters

	Dose Level (ppm)			
	0	200	800	3600
o. pregnant	22	25	25	28
estation				
Day 0	297±25[a]	297±20	290±24	285±20
Day 7	320±27	321±22	315±27	313±24
Day 14	345±33	345±25	344±26	339±25
Day 21	413±42	421±23	400±35	401±35
estation Weight Change				
Days 0- 7	23± 6	25± 7	26± 8	26±10
Days 7-14	26± 8	23± 6	29± 7	27± 5
Days 14-21	67±15	76±11	56±21	61±16
Days 0-21	115±21	124±15	111±24	113±21
o. delivering	22	25	25	28
actation				
Day 0	322±28	325±28	306±26	312±28
Day 7	345±29	353±25	340±29	341±26
Day 14	354±26	364±20	352±28	349±25
Day 21	339±24	344±17	336±23	340±23
actation Weight Change				
Days 0- 7	23±22	28± 8	33±16	29±13
Days 7-14	9±17	10±11	11± 8	8±14
Days 14-21	-15±13	-19± 9	-16±14	-8±14
Days 0-21	17±20	18±17	29±18	29±18

alues represent mean (g) ± S.D.

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TABLE 5. Effects of Folpet on Body Weight of F_1 Male Rats

udy riod	Study Day	Dose Level (ppm) 0	200	800	3600
ɛmating	1	71.6±10.7[a]	69.7± 7.8	65.6± 8.8	57.5±13.6**
	8	114.9±23.0	117.9±12.1	112.0±13.2	96.2±21.7**
	36	321.6±41.3	320.6±34.7	307.6±33.5	277.8±35.5**
	64	436.5±47.0	427.4±36.1	420.8±37.0	385.5±41.4**
	92	492.7±50.0	484.5±40.1	474.2±38.3	444.3±44.3**
	106	508.7±49.7	502.2±46.2	490.0±38.4	464.0±40.3**
ːing (2a)	120	514.9±49.2	508.6±41.5	498.2±35.9	473.8±37.7**
ːt	148	553.3±56.3	538.4±47.4	531.5±39.6	505.0±39.2**
	176	571.5±59.0	546.4±51.7	544.5±43.0	517.4±42.2**
ːing (2b)	197	571.0±53.9	553.2±48.7	548.7±42.1	522.2±45.0**
ːmating Body ːght Change ːys 1 to 106)		439.8±46.6	432.0±41.9	423.8±36.1	406.8±36.8**

ːues represent mean (g) ± S.D. Calculations based on approximately 30 animals ˙ group.

ːnificantly different from control value ($p \leq 0.01$).

TABLE 6. Effects of Folpet on Body Weight of F_1 Female Rats During Premating and Rest Periods

Study Period	Study Day	Dose Level (ppm) 0	200	800	3600
Premating	1	64.3±10.4[a]	63.5± 9.9	60.0± 8.2	52.7±10.8**
	8	99.7±15.2	103.0±12.5	97.1±10.6	87.2±16.0**
	36	199.7±17.7	198.1±22.9	192.2±17.5	185.1±20.4*
	64	247.4±23.2	245.1±26.1	238.5±21.2	230.8±23.0*
	92	275.9±29.8	272.4±28.3	267.1±23.4	257.6±24.6*
	106	283.2±31.8	283.8±29.0	275.0±25.6	268.8±26.0
Rest	162	298.6±44.6	296.8±32.7	283.5±24.9	288.0±31.5
	176	312.5±41.3	309.6±36.7	297.8±25.7	295.5±30.1
Premating Body Weight Change (Days 1 to 106)		219.0±33.7	220.2±25.1	215.3±24.0	216.6±22.1

[a]Values represent mean (g) ± S.D. Calculations based on approximately 30 animals per group.

*Significantly different from control value ($p \leq 0.05$).

**Significantly different from control value ($p \leq 0.01$).

TABLE 7. Effects of Folpet on Body Weight of F_1 Female Rats During Gestation and Lactation of F_{2a} Litters

	Dose Level (ppm)			
	0	200	800	3600
No. pregnant	21	22	20	19
Gestation				
Day 0	285±26[a]	271±27	276±24	256±25**
Day 7	304±29	300±29	302±24	286±24
Day 14	330±27	323±28	328±27	308±25*
Day 21	379±39	382±33	386±39	359±32
Gestation Weight Change				
Days 0- 7	19±11	29±18*	26± 6	30± 8*
Days 7-14	26±10	23± 4	26± 6	22± 4
Days 14-21	48±32	60±16	58±20	51±20
Days 0-21	93±32	111±25	110±23	104±24
No. delivering	23	22	20	18
Lactation				
Day 0	306±36	301±25	297±28	286±27
Day 7	318±25	317±24	309±34	298±24
Day 14	326±24	325±23	317±26	308±24*
Day 21	318±25	319±25	311±23	307±26
Lactation Weight Change				
Days 0- 7	12±21	17±12	12±20	12±16
Days 7-14	8±11	8±14	6±19	9±10
Days 14-21	-9±11	-6±13	-5±12	-3±14
Days 0-21	11±27	18±12	14±14	19±26

[a]Values represent mean (g) ± S.D.

*Significantly different from control value ($p \leq 0.05$).

**Significantly different from control value ($p \leq 0.01$).

TABLE 8. Effects of Folpet on Body Weight of F_1 Female Rats During Gestation and Lactation of F_{2b} Litters

	Dose Level (ppm)			
	0	200	800	3600
No. pregnant	20	19	19	16
Gestation				
Day 0	318±47[a]	299±28	303±26	290±28*
Day 7	341±48	324±31	330±25	319±27
Day 14	368±49	348±31	350±31	343±29
Day 21	435±52	419±36	411±38	405±31
Gestation Weight Change				
Days 0- 7	23± 7	25± 9	25± 8	29± 9*
Days 7-14	27± 6	24±11	22±14	24± 7
Days 14-21	65±18	70±17	64±19	62±18
Days 0-21	115±22	119±18	112±30	115±24
No. delivering	20	20	20	17
Lactation				
Day 0	346±53	320±35[b]	328±34[c]	319±30
Day 7	358±44	344±27	338±31	336±23
Day 14	369±38	357±26	347±27	339±21**
Day 21	353±41	346±28	343±23	337±23
Lactation Weight Change				
Days 0- 7	13±15	22±18	14±24	16±21
Days 7-14	11±15	14±13	9±11	3±13
Days 14-21	-11±10	-12±10	-5±12	-8±13
Days 0-21	12±21	25±25	15±26	10±26

[a]Values represent mean (g) ± S.D.

[b]The body weight of 2 females was not available due to technical error.

[c]The body weight of 1 females was not available due to technical error.

*Significantly different from control value ($p \leq 0.05$).

**Significantly different from control value ($p \leq 0.01$).

TABLE 9. Effects of Folpet on Food Consumption of F_0 Male Rats

Study Period	Study Days	Dose Level (ppm) 0	200	800	3600
Premating	0 to 2	24±1[a]	25±2	24±2	18±2**
	2 to 5	25±1	25±2	24±1	24±2
	7 to 9	25±5	26±2	26±2	25±2
	14 to 16	26±3	26±2	26±2	25±2
	16 to 19	26±2	26±2	26±2	25±2*
	19 to 21	28±2	26±2	26±1*	26±2**
	21 to 23	25±2	26±2	26±1	25±2
	28 to 30	27±2	27±2	26±2	25±2**
	35 to 37	26±2	26±2	25±3	25±2
	42 to 44	26±2	26±2	26±2	25±2
	49 to 51	27±5	27±2	26±2	26±2
	56 to 58	26±2	26±2	25±2	25±2*
Rest	84 to 86	26±2	26±3	25±2	24±4**
	91 to 93	26±2	25±2	24±1	23±6**
	98 to 100	26±2	25±4	25±3	25±2
	105 to 107	25±2	24±3	24±2	24±3
	112 to 114	27±2	26±5	26±3	25±2
	119 to 121	25±2	26±2	25±3	24±2*
	126 to 128	26±2	25±2	25±2	25±2*

[a]Values represent mean ± S.D. food consumption (g/animal/day). Calculations are based on approximately 30 animals per group.

*Significantly different from control value ($p \leq 0.05$).

**Significantly different from control value ($p \leq 0.01$).

TABLE 10. Effects of Folpet on Food Consumption of F_0 Female Rats During Premating and Rest Periods

Study Period	Study Days	Dose Level (ppm) 0	200	800	3600
Premating	0 to 2	18±2[a]	18±2	18±2	14±1**
	2 to 5	17±1	18±2	17±2	18±2
	7 to 9	18±2	18±2	18±2	18±2
	14 to 16	19±2	19±2	19±2	17±2**
	16 to 19	19±2	19±2	19±2	18±2
	19 to 21	20±2	19±2	20±2	18±2**
	21 to 23	18±4	19±2	19±2	18±2
	26 to 28	20±2	19±2	19±3	18±2**
	28 to 30	19±2	20±2	19±2	18±2
	35 to 37	19±2	18±2	18±2	18±2
	42 to 44	19±2	18±2	19±2	18±2*
	49 to 51	19±2	20±4	20±3	19±2
	56 to 58	18±2	19±2	19±2	18±2
Rest	112 to 114	23±3	24±3	23±3	23±5
	126 to 128	21±3	21±3	20±3	20±2

[a]Values represent mean ± S.D. food consumption (g/animal/day). Calculations are based on approximately 30 animals per group.

*Significantly different from control value ($p \leq 0.50$).

**Significantly different from control value ($p \leq 0.01$).

TABLE 11. Effects of Folpet on Food Consumption of F_1 Male Rats

Study Period	Study Days	Dose Level (ppm) 0	200	800	3600
Premating	0 to 2	13±1[a]	12±2	11±2**	10±2**
	7 to 9	18±3	18±2	18±2	15±3**
	14 to 16	22±3	22±3	21±2	19±3**
	21 to 23	25±3	24±3	23±2	22±2**
	35 to 37	28±3	26±2*	27±3	25±2**
	49 to 51	27±3	26±2	27±2	24±3**
	63 to 65	27±3	26±2	26±2	25±3**
	77 to 79	26±2	25±2	26±2	25±3*
	91 to 93	27±3	26±2	25±2*	25±2
	105 to 107	25±2	25±2	24±2	25±2
Rest	133 to 135	27±3	26±2	25±2	22±3**
	147 to 149	27±3	24±3**	25±2	25±3*
	175 to 177	25±3	25±3	24±4	25±2

[a]Values represent mean ± S.D. food consumption (g/animal/day). Calculations are based on approximately 30 animals per group.

*Significantly different from control value ($p \leq 0.05$).

**Significantly different from control value ($p \leq 0.01$).

TABLE 12. Effects of Folpet on Food Consumption of F_1 Female Rats During Premating and Rest Periods

Study Period	Study Days	Dose Level (ppm) 0	200	800	3600
Premating	0 to 2	12±1[a]	12±2	10±1	9±3**
	2 to 5	14±1	14±2	13±2*	12±1**
	5 to 7	15±2	15±2	14±2*	13±2**
	7 to 9	16±2	16±2	15±2	14±2**
	14 to 16	17±1	17±2	17±2	16±2**
	19 to 21	18±2	17±1	17±2*	16±1**
	21 to 23	18±2	18±2	17±2	17±1**
	42 to 44	20±2	19±2	19±3	18±2
	63 to 65	19±2	19±2	18±2*	18±2*
	91 to 93	19±2	19±2	18±2	19±2
	105 to 107	18±2	18±2	18±3	18±2
Rest	175 to 177	21±3	21±3	21±4	20±3

[a]Values represent mean ± S.D. food consumption (g/animal/day). Calculations are based on approximately 30 animals per group.

*Significantly different from control value ($p \leq 0.05$).

**Significantly different from control value ($p \leq 0.01$).

Food consumption values during the two gestation and lactation periods of F_1 females were generally comparable for all groups at all times with the exception of significant increases reported during days 4-6 of the first gestation period and days 0-2 of the second lactation period for the 3600-ppm groups when compared with controls (Tables 13 and 14).

No compound-related adverse effects were reported for the mating, fertility, and pregnancy rates of F_0 animals during the F_{1a} or F_{1b} intervals (Table 15); however, reductions in reproductive parameters were reported for F_1 parents in the dose groups during the F_{2a} and F_{2b} intervals (Table 16). The fertility (male) and pregnancy (female) rates were reduced at 800 and 3600 ppm when compared with controls during the F_{2a} interval. The fertility index was reduced at 800 and 3600 ppm, and the pregnancy rate was reduced at 3600 ppm when compared with controls during the F_{2b} interval (Table 16). However, the authors reported that none of the above differences were statistically significant.

No compound-related findings were noted for F_0 or F_1 adults at necropsy; no effects on histopathologic observations were reported.

C. Offspring Effects: During lactation, pup body weights at 200 and 800 ppm were generally comparable to controls for all litter intervals (F_{1a}, F_{1b}, F_{2a}, and F_{2b}); however, significant reductions in the weights of pups exposed to 3600 ppm were reported for all litter intervals at the end of lactation (Table 17).

No compound-related adverse effects were reported for litter size or pup survival during the lactation periods of any generation in this study (Table 18).

No compound-related changes were noted in the necropsy or histopathologic data presented.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The study authors concluded that the test material produced decreases in adult and pup body weights at 3600 ppm and that 800 ppm was the NOEL for parental and pup parameters.

B. A quality assurance statement was signed and dated September 19, 1985.

TABLE 13. Effects of Folpet on F_1 Maternal Food Consumption During the Gestation and Lactation Periods of F_{2a} Rat Litters

	Dose Level (ppm)			
	0	200	800	3600
No. Pregnant[a]	21	22	20	19
Gestational Days				
0 - 2	20.6±7.8[b]	18.2±2.1	17.8±2.0	17.8±3.9
2 - 4	21.3±2.8	21.1±5.9	21.1±4.2	22.6±8.2
4 - 6	19.1±5.0	21.6±3.0	21.7±3.0	24.6±7.0**
6 - 8	21.3±2.3	21.5±2.9	21.8±2.3	21.6±1.4
8 - 10	21.5±2.7	22.3±3.0	23.1±2.5	22.1±2.1
10 - 12	23.6±2.8	23.0±3.0	23.7±2.5	22.8±2.2
12 - 14	22.7±4.2	20.9±5.0	22.4±2.7	21.7±1.9
14 - 16	17.6±3.7	16.6±1.4	16.8±3.1	17.1±3.2
16 - 18	21.4±3.1	19.7±2.9	20.0±2.8	19.9±3.8
18 - 20	19.3±5.3	19.6±3.5	18.7±5.0	20.0±2.4
No. Delivering	23	22	20	18
Lactational Days				
0 - 2	16.7± 3.6	20.1± 4.4	18.5±5.6	19.2± 4.1
2 - 4	27.7± 6.3	32.5± 7.6*	29.3±5.5	28.1± 6.5
4 - 6	33.4± 8.3	37.7± 6.6	35.8±9.1	35.1± 9.1
6 - 8	36.8±11.5	43.6± 7.6	39.4±9.8	39.6±10.4
8 - 10	42.5±13.3	46.8±11.8	46.8±9.6	42.1±12.2
10 - 12	46.2±13.9	49.1±13.0	52.3±9.7	45.8±12.7
12 - 14	49.5±15.5	53.9±12.9	54.3±9.1	48.9±14.0

[a]No. of pregnant animals as presented in Table 28 of the study report. No. of pregnant animals reported in Table 30 are 23, 22, 20, and 19 for the 0-, 200-, 800-, and 3600-ppm groups, respectively.

[b]Values represent group means (g/animal/day)±SD.

**Significantly different from control value ($p \leq 0.01$).

TABLE 14. Effects of Folpet on F_1 Maternal Food Consumption During the Gestation and Lactation Periods of F_{2b} Rat Litters

	Dose Level (ppm)			
	0	200	800	3600
No. Pregnant[a]	20	19	19	16
Gestational Days				
0 - 2	20.8±2.3[b]	20.8±4.3	21.2±1.8	21.6±2.9
2 - 4	23.4±2.4	22.1±4.6	23.1±2.4	22.9±3.3
4 - 6	24.0±1.9	23.7±3.1	23.5±3.0	25.5±8.4
6 - 8	23.9±2.0	22.9±3.8	23.2±2.8	24.3±3.1
8 - 10	24.3±2.9	23.1±3.8	22.0±5.6	23.6±2.4
10 - 12	24.6±3.0	22.9±3.2	22.7±5.0	23.9±3.1
12 - 14	23.8±2.5	22.1±2.1	22.0±3.6	23.0±2.6
14 - 16	20.2±2.8	16.4±5.1	17.4±5.6	21.1±7.2
16 - 18	20.3±3.8	19.2±3.9	19.3±6.0	21.7±3.2
18 - 20	19.3±4.9	18.9±4.7	18.4±4.8	21.2±2.6
No. Delivering	20	20	20	17
Lactational Days				
0 - 2	20.1± 4.9	23.3±5.7	20.4± 5.3	25.7± 7.9*
2 - 4	30.8± 5.7	34.4±5.8	31.1± 4.4	31.3± 6.4
4 - 6	39.5± 7.4	44.7±7.0	40.9± 8.6	38.4± 7.9
6 - 8	44.0±11.3	50.4±9.4	46.7±10.1	44.7±11.1
8 - 10	52.3±12.1	57.0±9.2	53.6±11.1	48.1±10.8
10 - 12	57.0±14.5	63.0±9.7	58.9±12.6	52.6±11.0
12 - 14	60.5±14.5	66.7±11.3	61.5±11.4	53.2±11.0

[a]No. of pregnant animals as presented in Table 34 of the study report. No. of pregnant animals reported in Table 36 are 20, 20, 20, and 17 for the 0-, 200-, 800-, and 3600-ppm groups, respectively.

[b]Values represent group means (g/animal/day)±SD.

*Significantly different from control value ($p \leq 0.05$).

TABLE 15. Effects of Folpet on Mating, Fertility, and Pregnancy Rates of the F_0 Rats

Dose Level (ppm)	F_0 Males					F_0 Females				
	No. Cohabited	Mated		Fertile		No. Cohabited	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	92.3	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

[a] Based on reviewer's calculations from available individual animal data; the study authors reported 26 mated (86.7%).

[b] Based on reviewer's calculations from available individual animal data; the study authors reported 28 fertile (96.6%).

TABLE 16. Effects of Folpet on Mating, Fertility, and Pregnancy Rates of the F_1 Rats

Dose Level (ppm)	F_1 Males: No. Cohabited	Mated: No.	Mated: %	Fertile: No.	Fertile: %	F_1 Females: No. Cohabited	Mated: No.	Mated: %	Pregnant: No.	Pregnant: %
				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.

[f]Female 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.

TABLE 17. Effects of Folpet on Rat Pup Weights During Lactation

Dose Level (ppm)	No. of Litters		Lactation Day			
	Birth	Day 21	0	4	14	21
			F_{1a} Litters			
0	24	24	5.9±0.5[a]	8.3±1.7	23.5±3.5	36.5±5.3
200	26	26	5.8±0.5	8.6±1.1	24.5±2.3	37.4±4.0
800	22	22	5.8±0.3	8.4±0.9	23.6±2.4	35.5±4.4
3600	26	26	5.7±0.4	8.1±1.0	22.2±2.5	31.8±4.1**
			F_{1b} Litters			
0	22	22	5.9±0.6	9.0±1.4	25.3±3.3	40.0±6.0
200	25	25	5.8±0.4	8.6±1.0	24.5±3.0	37.8±5.0
800	25	25	5.9±0.5	8.9±1.2	24.4±2.8	37.2±5.0
3600	28	28	5.8±0.5	8.7±1.3	23.3±3.0	33.1±4.4**
			F_{2a} Litters			
0	23	20	5.9±0.9	9.0±1.8	25.4±3.6	37.2±5.1
200	22	21	6.3±0.7	8.4±1.5	24.7±3.2	38.3±4.3
800	20	20	5.7±0.6	8.0±1.4	23.0±3.6	34.3±5.2
3600	18	16	6.0±0.9	8.2±1.3	21.8±2.5**	31.2±4.2**
			F_{2b} Litters			
0	20	19	5.9±0.6	9.0±1.2	25.9±2.4	39.5±5.3
200	20	20	5.9±0.6	8.8±1.6	24.4±4.5	37.6±7.9
800	20	20	5.8±0.6	8.8±1.5	24.4±4.6	37.2±6.6
3600	17	17	5.7±0.4	8.6±1.2	22.8±3.4*	32.0±5.3**

Values represent mean (g) ± S.D.

*Significantly different from control value ($p \leq 0.05$).

*Significantly different from control value ($p \leq 0.01$).

TABLE 18. Effects of Folpet on Litter Size and Pup Survival During Lactation in Rats

	Dose Level (ppm)			
	0	200	800	3600
		F_{1a} Litter Interval		
litters with live pups				
At day 0	24	26	22	26
At day 21	24	26	22	26
er size				
Total at day 0	12.1±3.2[a]	12.7±2.6	13.0±1.4	11.8±2.9
Live at day 0	12.1±3.2	12.5±2.6	12.9±1.6	11.8±2.8
Live at day 21	11.3±3.3	12.0±2.7	12.2±1.9	11.1±3.0
urvival days 0-21	93.1%	95.7%	94.7%	94.4%
		F_{1b} Litter Interval		
litters with live pups				
At day 0	22	25	25	28
At day 21	22	25	25	28
er size				
Total at day 0	11.9±3.0[a]	13.5±2.0	12.8±3.1	12.5±2.8
Live at day 0	11.8±3.0	13.5±2.0	12.6±3.2	12.3±2.8
Live at day 21	11.2±2.9	13.0±2.2	12.4±3.1	12.0±2.9
urvival days 0-21	94.6%	96.1%	98.4%*	98.3%*

(Continued)

represent group mean ± S.D.

icantly different from control value ($p \leq 0.05$).

TABLE 18. Effects of Folpet on Litter Size and Pup Survival During Lactation in Rats (Continued)

	Dose Level (ppm)			
	0	200	800	3600
		F_{2a} Litter Interval		
No. litters with live pups				
At day 0	23	22	20	18
At day 21	20	21	20	16
Litter size				
Total at day 0	9.5±4.5[a]	11.1±3.3	12.3±3.3	10.4±4.2
Live at day 0	8.9±4.8	11.0±3.3	12.0±2.9*	10.2±4.2
Live at day 21	8.4±4.9[b]	10.0±2.7	10.8±2.9	9.4±4.1[c]
Pup survival days 0-21	94.1%	87.1%*	90.0%	92.4%
		F_{2b} Litter Interval		
No. litters with live pups				
At day 0	20	20	20	17
At day 21	19	20	20	17
Litter size				
Total at day 0	11.8±3.6[a]	13.6±2.5	11.9±3.9	12.1±3.6
Live at day 0	11.4±3.6	13.4±2.6	11.8±3.9	11.7±3.6
Live at day 21	11.3±3.5	12.4±2.2	11.3±3.6	11.2±3.4
Pup survival days 0-21	93.9%	92.9%	96.2%	96.0%

(Concluded)

[a]Values represent group mean ± S.D.

[b]Value presented in the study rports is 9.6±3.9 which resulted from the study authors' exclusion of litters 1615, 1616, and 1622 due to the death of all pups.

[c]Value presented in the study report is 10.6±2.5 which resulted from the study authors' exclusion of litters 4618 and 4627 due to the death of all pups.

*Significantly different from control value ($p \leq 0.05$).

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. Diet Analyses: Results presented in Addendum 1, Volume XI, of the study report indicate that the actual concentrations of folpet in fresh and frozen diet mixtures were:

	Average Concentration (ppm) of Folpet			
Dose Level	Fresh Sample	2 Days in Feeders	2 Days Frozen/ 3 Days in Feeders	5 Days Frozen/ 2 Days in Feeders
200 ppm	175±6.7%	152±8.8%	143±5.2%	146±7.3%
800 ppm	710±3.9%	670±4.9%	669±3.4%	683±3.5%
3600 ppm	3230±4.2%	3210±5.9%	3210±2.9%	3260±2.9%

These data indicate that the actual average concentrations of folpet in the test diets were at times 28%, 16%, and 11% lower than the 200-, 800-, and 3600-ppm nominal levels, respectively; it is also apparent from the above data that the concentration of the test material in the diet mixtures decreased after 2 days.

B. Effects on Parents and Pups: At study initiation, the body weights of male and female F_0 rats assigned to the control and 200- and 800-ppm groups were comparable; however, the group mean body weights of animals of both sexes assigned to the 3600-ppm groups were approximately 5% lower than their corresponding controls; our analyses using ANOVA and Dunnett's test agree with the study authors' results, which showed that these differences were statistically significant (Tables 19 and 20). Following initiation, the body weights of F_0 males and females were generally comparable for all groups. Body weight changes for F_0 males and females were also comparable for all groups, except for the significantly higher weight gains noted for females in the 800- and 3600-ppm groups during the first lactation period when compared with controls (Table 20); the biological significance of these body weight gains is not clear.

Food consumption data indicates that F_0 rats in the 3600-ppm groups consumed significantly less than controls during several intervals of the premating period. At the end of the premating period the food consumption of males was slightly (but significantly) less in the 3600-ppm group when compared with controls; food consumption was comparable for all female groups at the end of the premating period (Table 21).

TABLE 19. Effects of Folpet on F_0 Male Rat Body Weights and Weight Changes

	Dose Level (ppm)			
	0	200	800	3600
	Mean Body Weight (g) ±SD			
Study initiation (Day 1)	275.7±13.5	277.1±13.2	275.6±12.7	261.7±11.3*(5%)
End of premating (Day 57)	454.8±26.3	460.2±30.5	446.5±31.5	443.7±31.6
	Mean Body Weight Change (g) ±SD			
Premating period (Days 1-57)	179.1±20.8	183.1±22.7	170.9±29.5	182.0±25.3

* Significantly different from control value ($p \leq 0.05$) according to reviewers calculation using ANOVA and Dunnett's test; indicated percentage represents difference from control value.

TABLE 20. Effects of Folpet on F_0 Female Rat Body Weights and Weight Changes

	Dose Level (ppm)			
	0	200	800	3600
	Mean Body Weight (g) ±SD			
Study initiation (Day 1)	178.0±12.3	179.0±12.5	176.0±11.9	169.8±11.4*(-5%)
End of premating (Day 57)	250.4±22.2	252.7±19.8	249.5±24.3	246.8±18.1
Start of 1st gestation	255.5±24.5	258.6±19.7	252.1±18.0	251.7±18.5
End of 1st gestation	374.5±41.5	380.2±29.6	372.6±20.5	363.2±26.3
Start of 1st lactation	288.2±22.6	293.2±23.2	281.1±23.0	283.7±22.6
End of 1st lactation	315.6±26.1	316.7±17.5	317.9±23.5	320.6±17.7
Start of 2nd gestation	297.4±24.8	297.6±16.0	289.7±23.8	285.6±20.1
End of 2nd gestation	412.5±42.1	421.0±22.9	400.3±34.8	401.1±34.8
Start of 2nd lactation	322.0±27.7	325.3±28.3	306.3±26.3	312.3±28.0
End of 2nd lactation	339.1±23.5	343.7±17.2	335.7±23.0	339.8±23.2
	Mean Body Weight Change (g) ±SD			
Premating	72.4±14.5	73.6±13.8	73.5±18.7	77.1±12.4
1st gestation	118.7±22.6	121.6±18.8	120.5±11.8	111.5±18.6
1st lactation	24.7±10.9	27.5±19.4	36.8±18.9*(49%)	36.9±15.7*(49%)
2nd gestation	115.4±20.8	128.3±22.9	110.6±23.7	112.8±21.2
2nd lactation	17.2±20.1	18.4±17.5	28.7±18.4	29.1±17.9

* Significantly different from control value ($p \leq 0.05$); indicated percentage represent difference from control value.

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TABLE 21. Effects of Folpet on Food Consumption of F_0 Rats During the Premating Period

	Dose Level (ppm)			
	0	200	800	3600
			F_0 Males	
Days 0-2	24.5±1.4[a]	24.6±1.6	23.6±1.7	17.5±2.0*(-29%)[b]
Days 56-58	26.1±1.5	26.0±1.9	25.1±1.9	25.0±1.7*(-4%)
			F_0 Females	
Days 0-2	17.7±2.0	18.1±1.9	17.7±1.9	14.2±1.5*(-20%)
Days 56-58	18.3±2.1	19.0±2.2	18.5±2.3	18.3±2.0

[a]Values represent group means (g/animal/day)±SD.
[b]Values in parentheses represent changes from control values.
*Significantly different from control value ($p \leq 0.05$).

The reproductive indices of F_0 parents were comparable for all groups during both litter (F_{1a} and F_{1b}) intervals. No compound-related effects were noted in F_0 parental clinical signs, mortality, necropsy findings, or histopathological observations.

At birth the body weights and number of pups in F_{1a} and F_{1b} litters were comparable for all groups (Tables 17 and 18). However, at the end of lactation, pup body weights at 3600 ppm were significantly reduced when compared with controls for the F_{1a} (13% reduction) and F_{1b} (17% reduction) litters, suggesting a compound effect. There were no adverse compound-related effects noted in pup survival during either lactation period. Body weights of F_{1b} animals selected to be parents of the F_2 litters were signifi- cantly less in the 3600-ppm group when compared with controls at the initiation of the premating period; these differences were approximately 19% and 16% for males and females, respectively (Tables 22 and 23). At the end of the premating period, the body weight gains of F_{1b} males in the 3600-ppm group were significantly reduced (8% when compared with controls), but the gains of females were comparable to controls. The body weight gains of F_{1b} females were comparable for all groups during both gestation and both lactation periods (Table 23).

The food consumption of F_{1b} males was significantly reduced at the initiation of the premating period at 800 and 3600 ppm (14% and 26% less than controls, respectively; Table 24). Female food consumption at the initiation of the premating period was significantly reduced only at 3600 ppm (20% when compared with controls; Table 23). Maternal food consumption was generally comparable for all groups during both gestation and both lactation periods except for significant increases reported at 200 ppm at the end of the first lactation period and at 3600 ppm at the start of the second lactation period when compared with controls (Table 24); these changes do not appear to be compound-related.

The fertility indices of F_1 males were reduced in a significant dose-related pattern during the F_{2a} litter interval, and the index at 3600 ppm was significantly different from control (Table 16). Female fertility during this interval was less than control value at 800 and 3600 ppm, but these differences were not significant. During the F_{2b} litter interval, males and females had reductions in fertility indices similar to those noted during the F_{2a} interval; however, the differences in the F_{2b} interval were not statistically significant (Table 16).

No compound-related effects were noted in F_1 parental clinical signs, mortality, necropsy, or histopathologic findings.

TABLE 22. Effects of Folpet on F_{1b} Male Rat Body Weight and Body Weight Change During the Premating Period

	Dose Level (ppm)			
	0	200	800	3600
	Mean Body Weight (g) ± S.D.			
Study initiation (Day 1)	71.5±10.8	69.8± 7.8	65.7± 8.8	57.6±13.7*(19%)[a]
End of premating (Day 106)	508.8±49.7	502.3±46.2	490.7±38.3	464.1±40.3*(9%)
	Mean Body Weight Change (g) ± S.D.			
Premating (Days 1-106)	439.9±46.6	432.0±41.9	423.7±36.0	406.0±36.9*(8%)

[a]Values in parentheses represent changes from control values.

*Significantly different from control value ($p \leq 0.05$).

TABLE 23. Effects of Folpet on F_{1b} Female Rat Body Weights and Weight Changes

	Dose Level (ppm)			
	0	200	800	3600
	Mean Body Weight (g) ±SD			
Study initiation (Day 1)	64.4±10.4	63.6±10.0	60.1± 8.1	53.8± 9.3*(16%)[a]
End of premating (Day 106)	283.3±31.9	283.9±29.1	275.0±25.6	268.3±26.0
Start of 1st gestation	285.1±26.2	271.1±27.0	275.6±24.5	255.7±25.4*(10%)
End of 1st gestation	378.6±38.6	382.5±33.2	385.8±38.7	359.3±32.2
Start of 1st lactation	306.3±35.8	300.6±25.3	297.1±28.2	286.6±27.2
End of 1st lactation	317.7±24.9	319.0±24.5	310.9±22.6	307.1±25.8
Start of 2nd gestation	318.2±47.3	299.2±27.9	302.8±26.5	290.1±27.8
End of 2nd gestation	435.1±51.8	407.5±41.2	411.3±37.5	404.7±31.0
Start of 2nd lactation	345.7±53.4	320.3±34.6	328.2±34.5	319.6±30.1
End of 2nd lactation	358.1±41.2	345.5±27.8	342.6±23.3	337.5±22.8
	Mean Body Weight Change (g) ±SD			
Premating	219.0±33.9	220.2±25.2	215.2±24.0	216.5±22.1
1st gestation	93.5±31.9	111.4±25.5	110.1±22.5	103.7±24.0
1st lactation	11.4±27.4	18.3±11.7	13.8±13.9	19.4±26.1
2nd gestation	115.2±21.6	107.9±43.0	111.9±29.9	114.6±23.7
2nd lactation	12.4±20.8	24.9±25.3	15.4±25.5	17.9±26.3

[a]Values in parentheses represent changes from control values.

*Significantly different from control value ($p \leq 0.05$).

TABLE 24. Effects of Folpet on Food Consumption of F_{1b} Parents in Rats

	Dose Level (ppm)			
	0	200	800	3600
			Males	
nitiation	13.0± 1.2	12.2± 1.9	11.2± 1.7*(14%)[a]	9.6± 2.0*(26%)
nd of premating	25.1± 2.2	24.8± 2.4	24.4± 2.0	24.9± 2.3
			Females	
nitiation	11.6± 1.2	11.6± 2.5	10.5± 1.5	9.3± 2.0*(-20%)
nd of premating	17.7± 1.9	17.7± 1.9	17.7± 2.5	18.3± 1.8
tart of 1st gestation	20.6± 7.8	18.2± 2.1	17.8± 2.0	17.8± 3.9
nd of 1st gestation	19.3± 5.3	19.6± 3.5	18.7± 5.0	20.0± 2.4
tart of 1st lactation	16.7± 3.6	20.2± 4.5	18.5± 5.6	19.2± 4.2
nd of 1st lactation	53.8±17.0	65.2±10.4*(21%)	57.5±12.7	54.0±14.8
tart 2nd gestation	20.8± 2.3	20.8± 4.3	21.2± 1.8	21.6± 2.9
nd of 2nd gestation	19.3± 4.9	18.9± 4.7	18.5± 4.8	21.2± 2.6
tart of 2nd lactation	20.1± 4.9	23.4±5.7	20.5± 5.3	25.7± 8.1*(28%)
nd of 2nd lactation	68.0±16.2	75.4±12.5	70.8±15.1	61.2±12.4

Values in parentheses represent changes form control values.

Significantly different from control value ($p \leq 0.05$).

The body weights and numbers of F_1 and F_2 pups at birth were comparable for all groups; however, significant reductions in pup weight were noted at the end of lactation during all litter intervals at 3600 ppm when compared with controls (Table 17). No compound-related effects were noted in pup survival during lactation (Table 18).

C. The following are differences between conclusions reported by the study authors and those of the reviewers:

1. Results from chemical analyses suggest that the exposure levels were approximately 0, 150, 690, and 3200 ppm rather than the nominal values of 0, 200, 800, and 3600 ppm; therefore, our assessment of effect levels was based on the analytical levels and not on the reported nominal concentrations.

2. The study authors concluded that there were no compound-related changes in reproductive parameters at any dose level in this study. In contrast, we assess that the F_1 male and female fertility indices were adversely affected during both litter intervals (Table 16). Decreases in fertility were noted in all dosed groups; furthermore, a significant dose-related trend in male fertility was observed during the F_{2a} litter interval, and the value at 3600 ppm was significantly different from control.

D. The following deficiencies in study design and reporting of data have adversely affected the scientific validity of the study:

1. The study authors reported that F_0 males and females assigned to the high-dose (3600 ppm) groups were significantly lower in weight than controls at study initiation; these differences resulted (according to the study authors) from the randomization program used in the study. This deficiency confounded our assessment of potential compound-related effects since the parental toxicity reported at this dose level was based primarily on reductions in body weights.

2. Several discrepancies were noted in the study report. We were not able to explain or justify some of these discrepancies because the necessary data were not always available. The following are examples of noted discrepancies as presented in tables of this review:

- Table 13: The number of pregnant animals during gestation were reported as 21, 22, 20, and 19 for the 0-, 200-, 800-, and 3600-ppm groups, respectively; however, after deliveries there were 23, 22, 20, and 18 litters, respectively.

- Table 14: Similar to data in Table 13, the number of pregnant animals during gestation were 20, 19, 19, and 16, respectively; the number of litters were reportedly 20, 20, 20, and 17, respectively.

- Tables 15 and 16: Several discrepancies noted by the reviewers are presented at the end of these table.

- Table 18: The mean numbers of F_{2a} pups in the control group were reportedly 8.9 at lactation day 0 and 9.6 at lactation day 21. In the high dose group the mean number of pups were 10.2 and 10.6 for these lactation days, respectively. These apparent increases resulted from the exclusion of litters with no surviving pups. These exclusions should have been more clearly indicated by the authors.

Item 15--see footnote 1.

16. CBI APPENDIX: Materials and Methods (Appendix A); Protocol (Appendix B).

APPENDIX A

Materials and Methods

Folpet toxicology review

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