12/15/1998

CGA 184927 CHRONIC/CARCINOGENICITY STUDY (85-3)

Original Reviewer: Brenda MacDonald, Toxicological Evaluation Division, PMRA, CANADA
EPA Reviewer: Sanjivani B. Diwan, Ph.D. S. Diwan, Date 12/15/98
Toxicology Branch I/HED (7509C)

013787

DATA EVALUATION RECORD

STUDY TYPE: Combined chronic oncogenicity Study [Feeding]-[Rat]; OPPTS 870.4300 (rodent) [§83-5]

DP BARCODE: D244310 SUBMISSION #: S539279
P.C. CODE: 125203 TOX. CHEM. NO.: [New Chemical]

TEST MATERIAL (PURITY): CGA 184927 technical (93.7%, batch no. P 612003)

SYNONYMS: Clodinafop-propargyl; TOPAK

CITATION: Fankhauser, H. (1992). 24-Month Carcinogenicity and Chronic Toxicity Study in Rats. Novartis Crop Protection, Inc. (formerly Ciba-Geigy Crop Protection, Stein, Switzerland), Greensboro, NC 27419. Report No. 861139; October, 21, 1992. MRID NUMBER: 44399147 (Unpublished)

EXECUTIVE SUMMARY: In a combined chronic/carcinogenicity study (MRID# 44399147), CGA 184927 (93.7% a.i.) was administered in diet to male and female Tif: RAIf (SPF) albino rats (80/sex/group) for a period of 24 months. The test diets contained technical CGA 184927 at dietary concentrations of 0, 1, 10, 300 or 750 ppm (0, 0.031, 0.32, 10.18, 26.28 mg/kg/day for males; and 0, 0.034, 0.36, 11.31 and 29.48 mg/kg/day for females, respectively). At interim sacrifice, during week 53, 10 rats/sex/dose were sacrificed.

An increase in liver enzyme levels was noted in both sexes at ≥300 ppm. At interim and final sacrifices, absolute and/or relative liver and kidney weights increased in one or both sexes at ≥300 ppm. Necropsy revealed increased incidence of enlarged, or mottled liver in males at ≥300 ppm and in females at 750 ppm. In addition, there was dose-related increase in the incidence of microscopic changes in the liver including hepatocytic hypertrophy in males at ≥10 ppm as well as focal or nodular hyperplasia and fibrosis in one or both sexes at ≥300 ppm. Thyroid hypertrophy of follicular epithelium was noted in females at 750 ppm. Kidney changes noted in both sexes consisted of increased incidence of chronic progressive nephropathy and tubular

pigmentation at ≥10 ppm. Increased incidence of ovarian medullary tubular hyperplasia was noted at ≥300 ppm.

Under the conditions of this study, treatment with CGA 184927 increased the incidence of prostate and ovarian tumors in rats at 750 ppm. For males, an increased incidence of prostate adenoma was seen in the high-dose group, i.e., incidence rates were 8/80 (10.0%), 9/80 (11.25%), 12/80 (15.0%), 13/80 (16.25%) and 19/80 (23.75%) in the 0, 1, 10, 300 and 750 ppm groups, respectively. At 750 ppm, one of 80 males developed hepatocarcinoma.

For females, an increased incidence of tubular adenomas of the ovary was noted in the high-dose group, i.e., incidence rates of 2/80 (2.5%), 1/80 (1.25%), 1/80 (1.25%), 1/80 (1.25%) and 9/80 (11.25%) for the 0, 1, 10, 300 and 750 ppm groups, respectively. The chemical was administered at a dose sufficient to test its carcinogenic potential.

The EPA reviewer does not concur with the NOAEL/LOAEL established by the Canadian and determines that the LOAEL for systemic toxicity is 10 ppm (0.32 and 0.36 mg/kg/day in males and females, respectively) based on hepatocytic hypertrophy, chronic progressive nephropathy and tubular pigmentation. The systemic NOAEL is 1 ppm (0.031 and 0.034 mg/kg/day in males and females, respectively) .

This combined chronic/carcinogenicity study is classified acceptable/guideline, and satisfies the guideline requirement for a chronic/carcinogenicity study (85-3) in rats.

COMPLIANCE: Signed and dated GLP, Quality assurance, Data Confidentiality, and Flagging statements were provided.

CARCINOGENICITY AND CHRONIC TOXICITY STUDY IN RATS

Test no. 861139, conducted by Sisseln facility, Ciba-Geigy Ltd., Switzerland, for Ciba-Geigy Ltd., Plant Protection Division, Switzerland, dated October 21, 1992.

Study Director: Dr. H. Fankhauser

Study Conducted: February 13, 1989 to February 25, 1991.

Test Material: CGA 184927 technical, purity 93.7%, beige powder, Batch no. P 612003.

Dose Levels: 0, 1, 10, 300 or 750 ppm, 80 rats per sex per group.

Dose levels were chosen based on the results of 4 previously conducted, short-term studies, i.e.,
i) Exploratory acute oral toxicity study in the rat, project no. 861363;
ii) 28-day oral cumulative toxicity study in rats (gavage), project no. 861134;
iii) 28-day range finding study in rats (administration in food), project no. 861133; and,
iv) 3-month oral toxicity study in rats (administration in food), project no. 861135.

Test diets were not corrected for purity of the test material; however, the calculated average doses of CGA 184927 in mg/kg bw/day were corrected for the actual amount of CGA 184927 (determined by chemical analysis).

Test Animals: Tif: RAIf (SPF) albino rats, hybrids of RII/1 x RII/2, 4 to 5 weeks of age upon receipt, and weights ranging from 88.9 to 120.9 g for males, and 71.3 to 121.0 g for females. Animals were randomly assigned to study groups by means of computer-generated random numbers, and were then acclimatized for 10 days prior to study initiation. Animals were housed 5 per cage (same sex) in macrolon cages type 4. Powdered, certified standard diet (Nafag No. 890 Tox) and water were available ad libitum.

Diet Preparation: The appropriate amount of CGA 184927 technical was homogeneously mixed with the pulverized food. Diets were freshly prepared every 4 weeks, and stored at -20°C until used. Further details on diet preparation were not provided.

Stability of test material in diet was analyzed prior to study initiation, for diets containing 1, 15 and 150 ppm CGA 184927, after
storage for 5 weeks at room temperature or deep frozen.

The actual test material concentration was determined for samples of test diets, at all dose levels, taken at least once every 2 to 3 months throughout the study period, i.e., a total of 14 different batches prepared for each dose level were analyzed.

In the concurrent long-term mouse study, homogeneity of the test material in pulverized food, at dietary levels of 1, 10, 100 and 250 ppm, was analyzed and found to be adequate, i.e., refer to test no. 861138, pages 39/40. Hence, it was concluded that test diets were also homogeneous in the current study, since the same diet and diet preparation methods were used in both studies.

Study Method, Observations and Measurements: Rats were fed test diet at the appropriate concentration of CGA 184927 for a period of up to 24 months. An interim sacrifice was conducted on 10 randomly chosen rats/sex/group during week 53. Animals were sacrificed by exsanguination while under ether anesthesia.

Animals were observed daily for mortality, morbidity and overt clinical signs of intoxication.

An ophthalmological examination was conducted on all animals in the control and high-dose groups just prior to study initiation (study day -3), and on study days 170, 359, 534 and 723. An eye examination was also conducted on all rats in the 300 and 750 ppm groups on study days 725/726.

Bodyweights and food consumption were measured on a weekly basis for the first three months of the study, then every month for the remainder of the study. From these data, the food consumption ratios (g food/kg bw/day) and the test article intake (mg test article/kg bw/day) were calculated. Water consumption was measured on a monthly basis throughout the study period.

Individual urine samples were collected at weeks 13, 26, 53, 78 and 105 from 10 randomly chosen rats per sex per group. Animals were placed in individual metabolism cages and urine samples were collected overnight, during which time the rats were food and water fasted. Urinalysis included color, volume, relative density, pH, protein, glucose, ketones,

99

4

bilirubin, blood and urobilinogen. Microscopic examination of urine sediment was not conducted.

After the fasting period, blood samples were collected from the orbital sinus of each of these rats, while under ether anesthesia. [Note: At the same time, blood samples were collected from an additional 10 randomly chosen, food fasted rats/sex/group, for hematological assessment only].
Hematological parameters measured were Hgb, HCT, MCV, MCH, RBC count and morphology, reticulocyte count, platelet count, prothrombin time, and WBC count and differential.
Clinical chemistry parameters measured were glucose, urea, creatinine, total bilirubin, total protein, albumin, globulins, A/G ratio, cholesterol, triglycerides, phospholipids, sodium, potassium, calcium, chloride, inorganic phosphorus, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), alkaline phosphatase (Alp) and gamma-glutamyl transpeptidase (GGT).
All animals found dead, moribund or surviving to scheduled sacrifice underwent a gross post mortem examination.

At necropsy, the exsanguinated body, brain, liver, kidneys, adrenals, testes/ovaries and spleen were weighed. At this time, a complete tissue inventory was collected from each animal for routine histopathological evaluation. Tissues were preserved in 4% buffered formalin, and then processed for routine histopathological examination (hematoxylin and eosin). In addition, samples of abdominal fat were taken from all animals at interim sacrifice (53 weeks), and from 10 rats/sex/group at terminal sacrifice (week 105) for residue analysis (refer to "Special Examinations", Test no. 861139, Report nos. 803/91 and 810/91, pages 59, 60). Individual fat portions were pooled per group and sex, then stored deep frozen until analyzed.

The appropriate and currently acceptable statistical analyses were conducted on the data generated in this study.

STUDY RESULTS

Dietary Analyses:

NOTE: Deviations from protocol: a) During study weeks 13, 14 and 15, animals in the 1 ppm group received diet containing 10 ppm CGA 184927.
b) During study weeks 73 to 76, animals in the 750 ppm group received diet containing about 760 ppm. These minor deviations were not considered likely to have altered the outcome of this study.

i) Stability: (measured in diets prior to study initiation, at concentrations of 1, 15 and 150 ppm). The actual concentration of CGA 184927 in the test diets were as follows: a) after storage at room temperature (i.e., 22°C ± 2°C) for 5 weeks: 125%, 81% and 84% of the nominal concentrations for the 1, 15 and 150 ppm diets, respectively, and b) after 5 weeks stored deep frozen: 128%, 92% and 96% of the nominal concentrations for the 1, 15 and 150 ppm diets, respectively. Based on these results, it was decided to store freshly prepared diets deep frozen until used.

ii) Homogeneity: It was concluded that homogeneity of the test material in pulverized feed was adequate for the purposes of this study, based on homogeneity analyses of test diets in the concurrent long-term mouse study (study no. 861138, pages 39/40).

iii) Actual Test Material Concentrations (with the exception of the above-mentioned deviations from protocol concentrations):
For 0 ppm: < 0.14 ppm of CGA 184927 was detected in 11 of the 14 control diets sampled. In the remaining 3 samples of control diet, < 0.23 ppm of CGA 184927 was detected.

For 1 ppm: range 0.71 ppm to 1.15 ppm, mean 0.90 ppm, or, 71% to 115% of the nominal concentration, mean 90%.
For 10 ppm: range 8.30 ppm to 10.9 ppm, mean 9.65 ppm, or, 83% to 109% of the nominal concentration, mean 96.5%.
For 300 ppm: range 258 ppm to 324 ppm, mean 295 ppm, or, 86% to 108% of the nominal concentration, mean 98.3%.
For 750 ppm: range 681 ppm to 812 ppm, mean 746 ppm, or, 90.8% to 108.3% of the nominal concentration, mean 99.5%.

Based on these results, the actual test material concentrations, when compared to the target concentrations, were considered to be satisfactory for the purposes of this study.
Mortality: There was no effect of treatment with CGA 184927 on mortality during the entire study period.

Mortality rates (excluding accidental deaths) were as follows: i) for males, 34.3%, 34.3%, 46.4%, 30.0% and 28.6% for the 0, 1, 10, 300 and 750 ppm groups, respectively; ii) for females, 55.9%, 42.6%, 35.7%, 30.4% and 33.8% for the 0, 1, 10, 300 and 750 ppm groups, respectively.

101

6

[Accidental death rates were 0/80, 0/80, 1/80, 0/80 and 0/80 for males, and 2/80, 2/80, 0/80, 1/80 and 2/80 for females, in the 0, 1, 10, 300 and 750 ppm groups, respectively.]

Clinical Observations: There were no overt clinical signs of treatment-related toxicity.

Ophthalmological Examination: There did not appear to be any treatment-related ocular effects.

Bodyweight and Bodyweight Gain: i) Males: The mean final bodyweight and overall mean bodyweight gain for males in the 750 ppm group were significantly lower than in the control group, i.e., 94.0% and 93.2% of the control group values, respectively. This was primarily due to lower mean bodyweight gain seen during the first week of the study. Mean bodyweight and bodyweight gain values were comparable among the 0, 1, 10 and 300 ppm groups.

ii) Females: The mean final bodyweight of females in the 750 ppm group was significantly lower than that of the control group, i.e., 94.3% of the control group value. This was due to lower mean bodyweight gains occurring sporadically between study weeks 42 and 91. Overall mean bodyweight gain in the high-dose group was 92.4% of the control group value.

Mean bodyweight and bodyweight gains were comparable among the 0, 1, 100 and 300 ppm groups.

Food Consumption: Mean food intake was significantly lower for males in the 750 ppm group during the first week of the study, i.e., 70.6% of the control group value. There were no other findings which were considered to be treatment-related.

Total mean food intake values for all treatment groups, both sexes, were comparable to the control group values, i.e., for males: 101.1%, 101.0%, 101.2% and 98.5% of the control group value for the 1, 10, 300 and 750 ppm groups, respectively, and, ii) for females: 99.5%, 97.4%, 99.6% and 100.8% of the control group value for the 1, 10, 300 and 750 ppm groups, respectively.

Food Consumption Ratios: The mean food consumption ratio for the first study week was slightly lower for males in the 750 ppm group, i.e., 83.1% of the control group value. This reflects the associated decreases in mean food intake and mean bodyweight gain seen during study week 1 for males in the high-dose group.

Total mean food consumption ratios for the study period were comparable between the control and all treatment groups, both sexes.

Test Article Intake: The mean actual test article intake values for the study period, corrected for the actual amount of CGA 184927 (determined by chemical analysis) were as follows:

For males:	For females:
1 ppm, 0.031 mg/kg bw/day	1 ppm, 0.034 mg/kg bw/day
10 ppm, 0.324 mg/kg bw/day	10 ppm, 0.366 mg/kg bw/day
300 ppm, 10.18 mg/kg bw/day	300 ppm, 11.31 mg/kg bw/day
750 ppm, 26.28 mg/kg bw/day	750 ppm, 29.48 mg/kg bw/day.

Water Consumption: For males, all dose levels, mean water consumption was slightly increased throughout most of the study period, resulting in higher mean total water consumption values, i.e., 111.3%, 107.7%, 112.7% and 110.1% of the control group value for the 1, 10, 300 and 750 ppm groups, respectively. This was not considered to be an adverse health effect.

For females, there was no treatment-related effect on total mean water consumption.

Hematology: Refer to Table 1. Findings considered to be treatment-related were decreased RBC count, HCT and Hgb, seen in the 300 and 750 ppm groups, at most time intervals, both sexes. However, the values for these parameters fell at the lower limit of the normal range of values expected to be seen, and although findings were suggestive of a marginal treatment-related effect, they were not considered to be toxicologically significant.

Table 1 - Selected Hematological Findings, Group Means, with the Interquartile Range

Parameter		Dose (ppm)	Males	Females
1. RBC (T/l)	13 weeks	0	8.60±0.44	8.09±0.54
		1	8.73±0.84	8.12±0.45
		10	8.89±0.46	8.18±0.52
		300	8.32±0.73*	8.00±0.72
		750	8.02±0.54*	7.97±0.55
	26 weeks	0	8.06±0.33	7.42±0.67
		1	7.95±0.68	7.41±0.41
		10	8.17±0.37	7.46±0.25
		300	7.57±0.42*	7.23±0.53
		750	7.53±0.38*	7.14±0.51
	53 weeks	0	8.18±0.30	7.54±0.58
		1	8.21±0.65	7.43±0.30
		10	8.31±0.47	7.59±0.26
		300	7.85±0.60	7.49±0.39
		750	7.51±0.64*	7.34±0.59
	78 weeks	0	8.37±0.43	7.75±0.41
		1	8.33±0.70	7.63±0.51
		10	8.33±0.57	7.75±0.42
		300	7.79±0.81*	7.52±0.46
		750	7.80±0.65*	7.58±0.26
	105 weeks	0	7.82±0.81	7.07±0.92
		1	7.60±0.53	7.12±0.93
		10	7.71±0.78	7.28±0.64
		300	7.05±0.68*	6.97±0.69
		750	6.89±1.05*	6.88±0.83
2. Hgb (mmol/l)	13 weeks	0	9.71±0.48	9.33±0.45
		1	9.66±0.41	9.28±0.34
		10	9.72±0.56	9.22±0.50
		300	9.32±0.42*	9.00±0.49*
		750	8.97±0.38*	8.89±0.72*
	26 weeks	0	9.30±0.32	8.94±0.48
		1	9.08±0.27	8.99±0.55
		10	9.24±0.49	9.07±0.39
		300	8.75±0.45*	8.69±0.21
		750	8.78±0.43*	8.53±0.36*
	53 weeks	0	8.98±0.89	8.72±0.36
		1	8.98±0.36	8.62±0.48
		10	8.99±0.45	8.70±0.23
		300	8.67±0.45*	8.55±0.40
		750	8.32±0.39*	8.28±0.36*

104

9

	78 weeks	0	9.77±0.36	9.51±0.22
		1	9.74±0.51	9.40±0.63
		10	9.65±0.36	9.48±0.46
		300	9.15±0.60*	9.07±0.54*
		750	9.14±0.43*	9.01±0.38*
	105 weeks	0	9.46±0.73	8.90±1.06
		1	9.34±0.70	9.04±0.91
		10	9.39±1.16	9.17±0.88
		300	8.69±0.96	8.66±0.83
		750	8.33±0.91*	8.56±0.79
3. HCT (1)	13 weeks	0	0.469±0.015	0.445±0.026
		1	0.473±0.025	0.448±0.029
		10	0.478±0.024	0.449±0.026
		300	0.456±0.018	0.433±0.028
		750	0.435±0.014*	0.428±0.027*
	26 weeks	0	0.447±0.018	0.408±0.032
		1	0.438±0.024	0.408±0.020
		10	0.442±0.024	0.410±0.018
		300	0.421±0.021*	0.392±0.014*
		750	0.416±0.023*	0.387±0.022*
	53 weeks	0	0.451±0.013	0.427±0.020
		1	0.452±0.026	0.425±0.022
		10	0.453±0.020	0.432±0.017
		300	0.435±0.026*	0.420±0.026
		750	0.415±0.023*	0.407±0.032*
	78 weeks	0	0.468±0.017	0.447±0.012
		1	0.466±0.022	0.444±0.032
		10	0.463±0.033	0.448±0.023
		300	0.435±0.038*	0.428±0.22*
		750	0.434±0.027*	0.426±0.016*
	105 weeks	0	0.424±0.034	0.396±0.050
		1	0.419±0.036	0.403±0.050
		10	0.423±0.051	0.423±0.040
		300	0.386±0.043*	0.390±0.050
		750	0.374±0.047*	0.384±0.034

* - significantly different from control, $p < 0.01$
Interquartile Range - the difference between the 75th and the 25th percentile.

Clinical Chemistry: Refer to Table 2. Findings considered to be treatment-related were an increase in alkaline phosphatase (Alp) levels seen for males in the 300 and 750 ppm groups, at all time intervals; increased cholesterol (Chol) for females in the 750 ppm group at 53, 78 and 105 weeks; and increased triglycerides (Triglyc) and phospholipids (Phoslip) for females in the 750 ppm group at 78 and 105 weeks.

Findings suggestive of a marginal, treatment-related effect were slightly increased serum ASAT levels for females in the 750 ppm group at all time intervals; slight increases in serum alanine aminotransferase (ALAT) and/or aspartate aminotransferase (ASAT) levels for males in the 300 and 750 ppm groups at 26, 53 and 78 weeks; slightly increased cholesterol for females in the 300 and 750 ppm groups at 53, 78 and 105 weeks; and slightly increased triglycerides and/or phospholipids for females in the 300 and 750 ppm groups at 78 and 105 weeks.

Table 2 - Selected Clinical Chemistry Findings, Group Means, with the Interquartile Range

Parameter		Dose (ppm)	Males	Females
1. Alp	13 weeks	0	110.6±24.9	65.5±12.7 (U/l)
		1	109.0±21.7	72.8±19.0
		10	106.5±6.90	71.9±25.2
		300	131.8±15.7	71.9±8.8
		750	177.4±16.7*	78.2±22.1
	26 weeks	0	86.4±9.20	51.5±14.7
		1	89.0±13.	56.3±15.9
		10	97.71±14.	57.3±25.5
		300	153.5±66.0	57.2±17.7
		750	217.8±57.9	64.8±19.2
	53 weeks	0	112.4±45.7	43.2±11.9
		1	104.9±24.7	53.4±15.0
		10	130.9±27.5	51.0±14.8
		300	235.4±124.8*	52.5±21.8
		750	378.1±144.7*	64.2±16.1
	78 weeks	0	108.9±28.8	42.8±16.2
		1	111.4±42.7	45.0±20.2
		10	96.3±29.2	48.9±18.4
		300	231.2±118.7	56.3±20.2
		750	379.0±289.4*	69.6±13.4*
	105 weeks	0	75.4±73.7	37.8±17.3
		1	99.4±82.3	45.16±23.4
		10	73.5±80.0	45.5±31.9
		300	160.1±116.3	56.2±9.4
		750	297.5±148.7*	79.7±48.7*
2. Chol (mmol/l)	53 weeks	0		2.23±0.51
		1		3.22±0.94
		10		2.47±0.56
		300		3.90±1.93

		750		4.79±3.12*
	78 weeks	0		2.27±0.75
		1		2.73±1.02
		10		2.59±0.94
		300		3.62±1.17
		750		5.57±3.26*
	105 weeks	0		2.66±0.48
		1		3.16±0.92
		10		2.74±0.86
		300		3.78±1.31
		750		5.26±3.40*
3. Triglyc (mmol/l)	78 weeks	0		1.39±0.48
		1		1.77±1.59
		10		1.92±0.61
		300		2.89±2.22
		750		3.60±4.18*
	105 weeks	0		1.84±1.89
		1		2.29±1.03
		10		1.81±1.25
		300		1.78±1.79
		750		3.61±4.45
4. Phoslip (mmol/l)	78 weeks	0		2.12±0.48
		1		2.60±0.82
		10		2.47±0.70
		300		3.35±1.32
		750		4.56±2.56*
	105 weeks	0		2.60±0.26
		1		2.97±0.73
		10		2.65±0.76
		300		3.40±0.36*
		750		4.55±2.35*
5. ASAT (U/l)	26 weeks	0	63.6±10.8	87.8±32.3
		1	67.0±14.4	68.4±19.7
		10	80.9±11.3	73.9±11.9
		300	105.7±29.9*	75.3±20.9
		750	90.3±12.6*	86.6±19.1
	53 weeks	0	70.3±18.8	81.6±33.9
		1	79.1±33.9	97.3±7.9
		10	85.9±20.6	66.2±17.5
		300	115.9±30.3*	92.1±23.1
		750	148.7±62.4*	179.4±135.5

~~107~~

12

	78 weeks	0	72.5±21.8	68.2±27.9
		1	70.3±23.1	89.1±36.1
		10	64.7±7.9	80.8±27.3
		300	104.3±44.3	76.6±21.8
		750	109.8±59.4	130.4±105.6
	105 weeks	0	64.6±20.0	64.5±22.4
		1	139.5±66.1	96.0±67.8
		10	78.6±21.8	67.9±25.5
		300	83.4±47.9	100.0±51.5
		750	91.8±40.0	117.2±88.5
6. ALAT (U/l)	26 weeks	0	48.0±16.7	
		1	45.9±12.7	
		10	48.9±11.9	
		300	70.6±21.4	
		750	65.7±29.4*	
	53 weeks	0	64.6±19.0	
		1	61.2±23.0	
		10	70.9±34.9	
		300	88.9±27.0	
		750	102.5±22.2*	

* - significantly different from control, $p < 0.01$
Interquartile Range - the difference between the 75th and the 25th percentile

Urinalysis: There were no changes which were considered to be related to treatment wih CGA 184927.

Organ Weights: Findings considered to be treatment-related were as follows:
i) At 53 weeks (refer to Table 3): Mean relative liver and kidney weights, both sexes, and mean absolute liver weight, females only, were increased in the high-dose group. Mean relative liver and kidney weights were also increased in the 300 ppm group, females only. Statistical significance was attained as indicated.

Table 3 - Mean Organ Weights, with the Interquartile Range, absolute (g) and relative (0/00 of bodyweight)

Dose (ppm)	Male		Female	
	absolute	relative	absolute	relative
1. Liver				
0	21.16±2.26	32.56±1.84	13.45±3.41	32.64±3.88
1	24.34±2.36	33.33±1.38	13.80±1.92	32.96±4.18
10	23.11±3.67	34.09±5.81	12.10±1.94	30.73±6.77
300	21.87±2.21	33.03±4.08	13.80±1.34	36.42±3.22
750	24.43±6.30	39.25±3.94*	15.90±2.62	41.83±3.50*

2. Kidney				
0	3.44±0.44	5.05±0.58	2.30±0.47	5.58±0.55
1	3.64±0.42	5.00±0.57	2.40±0.40	5.75±0.97
10	3.48±0.65	5.13±0.56	2.34±0.23	5.97±1.61
300	3.50±0.61	5.30±0.69	2.43±0.57	6.41±1.39
750	3.78±0.76	5.75±0.82*	2.47±0.46	6.51±1.12*

* - significantly different from control, $p < 0.01$

ii) At 105 weeks (refer to Table 4): Mean absolute and relative liver weights were increased in the 300 and 750 ppm groups, both sexes. Mean absolute and relative kidney weights were increased in the high-dose group, both sexes, and in the 300 ppm group, males only. A decrease in the mean absolute and relative testicular weights was seen in the mid- and high-dose groups. Statistical significance was attained as indicated.

Table 4 - Mean Organ Weights, with the Interquartile Range, absolute (g) and relative (0/00 of bodyweight)

Dose (ppm)	Male		Female	
	absolute	relative	absolute	relative
1. Liver				
0	21.34±4.73	30.14±5.60	18.08±4.76	37.18±7.73
1	21.37±3.08	29.05±5.70	17.42±5.29	34.65±5.96
10	21.36±6.07	29.07±6.47	17.56±5.47	34.40±7.75
300	24.10±3.05*	34.99±6.34*	19.53±4.69	38.85±7.51*
750	25.97±4.73*	39.66±7.49*	20.86±5.70*	43.23±7.48*
2. Kidney				
0	4.18±0.47	6.02±1.05	3.19±0.43	6.64±1.39
1	4.21±0.63	5.78±1.13	3.05±0.40	6.26±1.09
10	4.29±0.88[a]	5.87±1.04[a]	2.94±0.50	5.88±1.16
300	4.69±0.68*	6.85±1.68*	3.25±0.55	6.60±1.31
750	5.11±0.65*	7.87±1.32*	3.42±0.71*	7.16±1.89*
3. Testes				
0	6.45±3.34	9.03±3.74		
1	6.28±2.69	8.56±5.08		
10	5.95±1.38	8.01±2.55		
300	4.78±0.91*	6.82±1.51*		
750	4.88±1.10*	7.54±2.36		

* - significantly different from control, $p < 0.01$
[a] - a single, outlying value of 41.40 g was excluded from calculation of the mean values. The high weight was the

result of a unilateral transitional cell carcinoma of the renal pelvis (not considered to be treatment-related).

The authors considered that the significant increase in the mean absolute and relative ovary weights in the high-dose group were treatment-related. However, examination of the individual animal data revealed that 2 females in the high-dose group had grossly enlarged ovaries. Since the causes of the ovary enlargements were unrelated to treatment, it was considered more appropriate to recalculate the mean ovary weights for the high-dose group excluding these 2 outlying values. The recalculated values were found to be comparable to the mean values for the control and other treatment groups. Hence, it was concluded that there was no treatment-related effect on mean ovary weight.
(The enlarged ovaries noted in 2 females in the high-dose group were the result of: i) unilateral benign granulosa/theca cell tumor, and ii) unilateral follicular cyst.)

Gross Pathology: For males, an increase in the incidence of enlarged and mottled livers, and an increased incidence of mottled lungs was noted in the high-dose group. In addition, the number of cystic kidneys was increased in the mid- and high-dose groups, i.e.,

	Dose (ppm)				
Incidence	0	1	10	300	750
1. Liver					
enlarged	2/80	0/80	4/80	3/80	6/80
mottled	0/80	0/80	0/80	1/80	7/80
2. Lungs					
mottled	1/80	1/80	0/80	3/80	6/80
3. Kidneys					
cystic	4/80	1/80	1/80	7/80	7/80

For females, a slight increase in the incidence of mottled lungs and livers was noted in the high-dose group, i.e.,

	Dose (ppm)				
Incidence	0	1	10	300	750
1. Liver					
mottled	0/80	0/80	1/80	0/80	3/80
2. Lung					
mottled	2/80	0/80	4/80	2/80	5/80

There were no other findings which were clearly associated to treatment with CGA 184927.

Histopathology: i) Non-neoplastic: Refer to Table 5a. The primary target organ was the liver. An increased incidence of the following treatment-related findings were noted: hepatocyte hypertrophy in the 300 and 750 ppm groups, both sexes, and in the 10 ppm group, males only; "recent" necrosis in the 300 and 750 ppm groups, both sexes; nodular hyperplasia, fibrosis of the liver parenchyma and capsule in the 750 ppm group, both sexes, and in the 300 ppm group, males only; necrosis of hepatocytes in the 750 ppm group, both sexes; and focal hyperplasia in the 300 and 750 ppm groups, males only. In the absence of any other hepatic effects at 10 ppm, the slightly increased incidence of hepatocyte hypertrophy noted at this dose level, males only, was not considered to be an adverse effect, but rather an adaptive response to treatment.

An increased incidence of hypertrophy of the thyroid follicular epithelium was noted in the high-dose group, females only, i.e., incidence rates of 1/80, 1/80, 0/80, 3/80 and 11/80 for the 0, 1, 10, 300 and 750 ppm groups, respectively. In the absence of an associated, treatment-related, neoplastic response (i.e., adenomas/carcinomas of the thyroid follicular epithelium), this was not considered to be an adverse finding.

In the ovary, an increased incidence of medullary tubular hyperplasia in the high-dose group was considered to be treatment-related by the authors, i.e., incidence rates were 2/80 (2.5%), 0/80 (0%), 5/80 (5.13%), 6/80 (7.5%) and 11/80 (13.75%) for the 0, 1, 10, 300 and 750 ppm groups, respectively. However, incidence rates in all groups fell well within the range of values obtained from in-house historical control data. [In-house historical control data obtained from 10 studies conducted between 1985 and 1989, 49 to 80 females per study, total of 752 females examined revealed incidence rates ranging from 0% to 22.37%, mean 7.85%.] Hence, the slightly higher incidence of ovarian medullary tubular hyperplasia seen in the high-dose group was considered to be an incidental finding, unrelated to treatment with CGA 184927.

In the kidney, an increase in the incidence of chronic progressive nephropathy was noted in the 300 and 750 ppm groups, both sexes, and an increase in tubular pigmentation was seen in the 10, 300 and 750 ppm groups, both sexes. In the absence of any other renal effects at 10 ppm, the slightly increased incidence of tubular pigmentation noted

at this dose level was not considered to be an adverse effect.

In the lung, there was an increase in the accumulation of alveolar foam cells in the high-dose group, both sexes. The findings noted in the kidneys and lungs are quite commonly seen in aging rats, and so are considered to be secondary, treatment-related changes.

ii) Neoplastic: Findings considered to be treatment-related were as follows (Table 5b):

For males, an increased incidence of prostate adenoma was seen in the high-dose group, i.e., incidence rates were 8/80 (10.0%), 9/80 (11.25%), 12/80 (15.0%), 13/80 (16.25%) and 19/80 (23.75%) in the 0, 1, 10, 300 and 750 ppm groups, respectively.

[NOTE: The incidence rates for prostate adenoma seen in the control group and all treated groups were well above the reported range of incidence rates seen in the in-house historical control data. In-house historical control data obtained from 10 studies conducted between 1985 and 1989, 49 to 80 males per study, total of 749 males examined, revealed incidence rates ranging from 0% to 4.08%, mean 0.80%.] The single finding of carcinoma of the prostate, seen in the high-dose group (incidental finding at terminal sacrifice), was not considered to be treatment-related. Although there were no cases of these tumors reported in the in-house historical control data, they are occasionally observed in a control population of aging rats.

For females, an increased incidence of tubular adenomas of the ovary was noted in the high-dose group, i.e., incidence rates of 2/80 (2.5%), 1/80 (1.25%), 1/80 (1.25%), 1/80 (1.25%) and 9/80 (11.25%) for the 0, 1, 10, 300 and 750 ppm groups, respectively. In-house historical control data revealed incidence rates ranging from 0% to 4.08%, mean 1.46%.

Overall, the total number of rats with one or more primary tumors was not affected by treatment with CGA 184927, i.e., incidence rates for males were 63/80, 57/80, 62/80, 52/80 and 57/80, and for females were 65/80, 68/80, 66/80, 55/80 and 54/80, in the 0, 1, 10, 300 and 750 ppm groups, respectively.

SUMMARY AND CONCLUSIONS Male and female Tif: RAIf (SPF) hybrid albino rats were continuously fed test diets containing CGA 184927, purity 93.7%, at dietary concentrations of 0, 1, 10, 300 or 750 ppm, 80 rats per sex per group, for a period of up to 24 months. An interim sacrifice was conducted on 10 randomly chosen rats per sex per group during week 53.

Mean final bodyweight was slightly lower in the 750 ppm group, both sexes. For males, this was primarily due to decreased mean food consumption and lower mean bodyweight gain for the first study week. For females, this was due to lower mean bodyweight gains seen sporadically between study weeks 42 and 91. A slight increase in mean water intake noted in all treatment groups, males only, was not considered to be an adverse health effect.

A decrease in RBC count, HCT and Hgb was seen in the 300 and 750 ppm groups at most time intervals measured. However, these values fell within at the lower limit of the normal range of values, and although the findings were suggestive of a marginal, treatment-related effect, they were not considered to be toxicologically significant.

Serum alkaline phosphatase was increased in the 300 and 750 ppm groups, males only. Serum cholesterol, triglycerides and phospholipids were increased in the 750 ppm group, females only; slight increases were noted in the 300 ppm group. In addition, slight increases were noted in serum ASAT and/or ALAT levels in the high-dose group, both sexes, and in the 300 ppm group, males only.

At interim sacrifice, mean relative liver and kidney weights (both sexes) and mean absolute liver weight (females only) were increased in the high-dose group; mean relative liver and kidney weights were also increased in the 300 ppm group, females only. At terminal sacrifice, mean absolute and relative liver weights were increased in the 300 and 750 ppm groups, both sexes; mean absolute and relative kidney weights were increased in the 750 ppm group, both sexes, and in the 300 ppm group, males only. In addition, mean absolute and relative testicular weights were decreased in the high-dose group.

At necropsy, an increased incidence of enlarged and/or mottled livers, and of mottled lungs, was noted in the high-dose group, both sexes. An increase in the number of cystic kidneys was observed in the 300 and 750 ppm groups, males only.

H3

18

Histopathological findings in the liver considered to be treatment-related were an increased incidence of hepatocyte hypertrophy in the 300 and 750 ppm groups, both sexes, and in the 10 ppm group, males only; "recent" necrosis in the 300 and 750 ppm groups, both sexes; nodular hyperplasia, fibrosis of the liver parenchyma and capsule in the 750 ppm group, both sexes, and in the 300 ppm group, males only; necrosis of hepatocytes in the 750 ppm group, both sexes; and focal hyperplasia in the 300 and 750 ppm groups, males only. In the absence of any other hepatic effects at 10 ppm, the slightly increased incidence of hepatocyte hypertrophy noted at this dose level, males only, was not considered to be an adverse effect, but rather an adaptive response to treatment.

In the thyroid, an increase in the incidence of hypertrophy of the follicular epithelium was noted in the high-dose group, females only. In the kidneys, there was an increased incidence of chronic progressive nephropathy (300 and 750 ppm groups, both sexes), and of tubular pigmentation (10, 300 and 750 ppm groups, both sexes). In the lung, an increase in the accumulation of alveolar foam cells was observed in the high-dose group, both sexes. These findings in the kidneys and lungs are commonly seen in aging rats, and so were considered to be secondary, treatment-related changes. In the absence of any other renal effects at 10 ppm, tubular pigmentation noted at this dose level was not considered to be an adverse effect.

Based on the results of this study, the NOAEL for general toxicity was determined to be 10 ppm, equivalent to 0.324 mg/kg bw/day for males, and 0.366 mg/kg bw/day for females. The increased incidence of renal tubular pigmentation (both sexes) and hepatocyte hypertrophy (males only) noted at this dose level were not considered to be adverse effects, as explained above.

Treatment-related neoplastic findings were an increased incidence of prostate adenomas and tubular adenomas of the ovary in the 750 ppm group. Overall, the total number of male and female rats with one or more primary tumors was unaffected by treatment with CGA 184927.

<u>Toxicology Branch 1 Reviewer's Comments:</u> Although there was 11-15% increase in water consumption among treated males during weeks 4-88, it occurred in a non-dose-related manner. Contrary to the mortality rates reported on page 6 of the DER, the incidence of mortality, as calculated by this

114

19

reviewer, is shown below. The mortality in treated groups was lower than the control groups.

CGA 184927™ - Tif:RAIf(SPF) Albino Rat Study male Mortality Rates*

Dose (ppm)	Weeks 1-26	27-52	53[i]	53-78	79-106[f]	Total
0	0/80	3/80	9/77	7/68	14/61	24/71 (34)
1	0/80	2/80	10/78	9/68	13/59	24/70 (34)
10	0/80	1/80	10/79	8/69	22/60[a]	31/69 (45)
300	0/80	2/80	10/78	8/68	11/60	21/70 (30)
750	0/80	1/80	10/79	5/69	15/64	21/70 (30)

*Number of animals that died during interval/Number of animals alive at the beginning of the interval.
( )Percent.

CGA 184927™ - Tif:RAIf(SPF) Albino Rat Study female Mortality Rates

Dose (ppm)	Weeks 1-26	27-52	53[i]	53-78	79-107[f]	Total
0	0/80	1/80	10/79	7/68[a]	18/60[b]	26/68 (38)
1	1/80	2/79	10/77	2/66[c]	22/63[d]	27/68 (40)
10	0/80	0/80	10/80	7/70	18/63	25/70 (36)
300	0/80	1/80	10/79	5/68[e]	14/63	20/69 (29)
750	1/80	2/79	10/77	3/67	16/63[f]	22/69 (32)

*Number of animals that died during interval/Number of animals alive at the beginning of the interval.

115
20

The treatment-related increase in the incidence of hypertrophy of hepatocytes, chronic progressive nephropathy and accumulation of pigment in the renal tubules was noted in both sexes at ≥10 ppm (Table 5a). The pigment resembled bilirubin. Therefore, it was considered secondary to the changes in the liver. Metastatic calcification noted in males at 300 ppm and in males and females at 750 ppm was indicative of reduced renal function and was caused by renal lesions (see Table 5a). Increased incidence of hypertrophy of the thyroid follicular epithelium noted at 750 ppm was considered to be secondary to the liver changes and was treatment-related. This finding is known to occur in response to increased metabolism of thyroid hormone by induced hepatic enzymes.

Under the conditions of this study, dietary administration of CGA 184927 increased the incidence of prostate and ovarian adenomas in rats at 750 ppm (Table 5b). The chemical was administered at a dose sufficient to test its carcinogenic potential.

The LOAEL for systemic toxicity is 10 ppm (0.32 and 0.36 mg/kg/day in males and females, respectively) based on hepatocytic hypertrophy, chronic progressive nephropathy and tubular pigmentation. The systemic NOAEL is 1 ppm (0.031 and 0.034 mg/kg/day in males and females, respectively) .

Table 5a. Non-neoplastic changes in male and female rats

Dose (ppm)	0.00	1	10	300	750
# Animals/group	80	80	80	80	80
Liver:					
- Focal hyperplasia, males	8	6	6	14	15
- Nodular hyperplasia, males	1	1	1	10	10
females	1	0	0	2	16
- Hypertrophy of hepatocytes,					
males	0	0	6	56	71
females	1	0	1	52	63
- Fibrosis of liver capsule,					
males	1	3	4	23	33
females	8	2	5	1	11
- Fibrosis of liver					
parenchyma, males	2	0	3	19	26
females	2	0	0	1	8
- Recent necrosis, males	12	5	9	29	35
females	4	2	4	7	10
- Necrosis of hepatocyte, males	0	1	0	2	6
females	3	2	1	2	5
Lung:					
- Alveolar foam cells, males	21	23	15	23	37
females	28	16	21	21	40
Thyroid					
- Follicular epith.					
hypertrophy, females	1	1	0.00	3	11
Kidney					
- Chronic progressive					
nephropathy,					
males	32	29	22	46	63
females	30	31	37	55	63
- Tubular pigment, males	0	0	4	15	22
females	3	5	10	25	24
-Metastatic calcification,					
males	0	1	1	2	3
females	0	0	0	0	2
Ovary:					
-Medullary tubular hyperplasia	2	0.00	5	6	11

Table 5b. Tumor incidences in male and female rats a

Dose (ppm)	0.00	1	10	300	750
# Animals/group	80	80	80	80	80
Liver (Males)					
- Hepatoma	1 (1.25%)	1	0.00	1	3 (3.75%)
- Hepatocarcinoma	0	0		0	1
Prostate:					
- Adenoma	8 (10%)	9 (11.25%)	12 (15%)	13 (16.25%)	19 *(23.75%)
- Carcinoma	0	0	0	0	1
Ovary:					
- Tubular adenoma	2 **(2.5%)	1	1	1	9* (11.25%)

a Historical control data:
Liver tumors: Range: 0-2.86%, mean, 0.93%; 0% carcinoma
Prostate adenoma: range: 0-4.08%, mean 0.80%;
Ovary tubular adenoma: range: 0-4.08%, mean 1.46%.
Tumor data statistically analyzed Lori Brunsman
** $p<0.01$; *$p<0.05$; Significant trend for ovary tubular adenomas, $p<0.01$; Significant pair-wise comparisons for prostate adenomas and ovary tubular adenomas, at $p<0.05$. Analyzed by the Exact test for trend. Pair-wise comparisons analyzed by the Fisher's Exact test.

THE FOLLOWING ATTACHMENT IS NOT AVAILABLE ELECTRONICALLY

Page_____ is not included in this copy.

Pages 25 through 38 are not included.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ FIFRA registration data.

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

_____ The document is not responsive to the request.

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

THE FOLLOWING ATTACHMENT IS NOT AVAILABLE ELECTRONICALLY

01/04/1999 01:06 PM

	Column A	Column B	Total
Row 1	4	76	80
	(3%)	(48%)	(50%)
Row 2	7	73	80
	(4%)	(46%)	(50%)
Total	11	149	160
	(7%)	(93%)	(100%)

Fisher's Exact Test

The two-sided P value is 0.5341, considered not significant.
There is not a significant association between rows and columns.

Odds Ratio = 0.5489
95% Confidence Interval: 0.1541 to 1.955
(using the approximation of Woolf.)

* * *

~~140~~

40

01/04/1999 01:07 PM

	Column A	Column B	Total
Row 1	4	76	80
	(3%)	(48%)	(50%)
Row 2	20	60	80
	(13%)	(38%)	(50%)
Total	24	136	160
	(15%)	(85%)	(100%)

Fisher's Exact Test
The two-sided P value is 0.0006, considered extremely significant.
There is a significant association between rows and columns.

Odds Ratio = 0.1579
95% Confidence Interval: 0.05122 to 0.4868
(using the approximation of Woolf.)

* * *

Page 42 is not included in this copy.

Pages _____ through _____ are not included.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ FIFRA registration data.

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

_____ The document is not responsive to the request.

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

01/04/1999 01:09 PM

	Column A	Column B	Total
Row 1	21	59	80
	(13%)	(37%)	(50%)
Row 2	37	43	80
	(23%)	(27%)	(50%)
Total	58	102	160
	(36%)	(64%)	(100%)

Fisher's Exact Test
The two-sided P value is 0.0133, considered significant.
There is a significant association between rows and columns.

Odds Ratio = 0.4137
95% Confidence Interval: 0.2129 to 0.8038
(using the approximation of Woolf.)

* * *

~~143~~

43

01/04/1999 01:10 PM

	Column A	Column B	Total
Row 1	28	52	80
	(18%)	(33%)	(50%)
Row 2	40	40	80
	(25%)	(25%)	(50%)
Total	68	92	160
	(43%)	(58%)	(100%)

Fisher's Exact Test

The two-sided P value is 0.0782, considered not quite significant.
There is not a significant association between rows and columns.

Odds Ratio = 0.5385
95% Confidence Interval: 0.2853 to 1.016
(using the approximation of Woolf.)

* * *

144

44

01/04/1999 01:11 PM

	Column A	Column B	Total
Row 1	28	52	80
	(18%)	(33%)	(50%)
Row 2	40	40	80
	(25%)	(25%)	(50%)
Total	68	92	160
	(43%)	(58%)	(100%)

Fisher's Exact Test
The one-sided P value is 0.0391, considered significant.
There is a significant association between rows and columns.

Odds Ratio = 0.5385
95% Confidence Interval: 0.2853 to 1.016
(using the approximation of Woolf.)

* * *

Page 46 is not included in this copy.

Pages _____ through _____ are not included.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

1 _____ FIFRA registration data.

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

_____ The document is not responsive to the request.

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

01/04/1999 01:03 PM

	Column A	Column B	Total
Row 1	8	71	79
	(5%)	(45%)	(50%)
Row 2	13	67	80
	(8%)	(42%)	(50%)
Total	21	138	159
	(13%)	(87%)	(100%)

Fisher's Exact Test

The two-sided P value is 0.3493, considered not significant.
There is not a significant association between rows and columns.

Odds Ratio = 0.5807
95% Confidence Interval: 0.2264 to 1.490
(using the approximation of Woolf.)

* * *

~~136~~

~~47~~

01/04/1999 01:04 PM

	Column A	Column B	Total
Row 1	8	71	79
	(5%)	(45%)	(50%)
Row 2	19	59	78
	(12%)	(38%)	(50%)
Total	27	130	157
	(17%)	(83%)	(100%)

Fisher's Exact Test
The two-sided P value is 0.0207, considered significant.
There is a significant association between rows and columns.

Odds Ratio = 0.3499
95% Confidence Interval: 0.1429 to 0.8568
(using the approximation of Woolf.)

* * *

137

95

01/04/1999 01:05 PM

	Column A	Column B	Total
Row 1	8	71	79
	(5%)	(45%)	(50%)
Row 2	20	58	78
	(13%)	(37%)	(50%)
Total	28	129	157
	(18%)	(82%)	(100%)

Fisher's Exact Test
The two-sided P value is 0.0127, considered significant.
There is a significant association between rows and columns.

Odds Ratio = 0.3268
95% Confidence Interval: 0.1341 to 0.7961
(using the approximation of Woolf.)

* * *

~~138~~
49

Page 50 is not included in this copy.

Pages _____ through _____ are not included.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ FIFRA registration data.

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

_____ The document is not responsive to the request.

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