DATA EVALUATION RECORD

BAS 670H

Study Type: §83-1b, Chronic Toxicity Study in Dogs

Work Assignment No. 1-01-11 A (MRIDs 45902215 and 45902216)

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DATA EVALUATION RECORD

STUDY TYPE: Chronic Toxicity in Dogs (feeding); OPPTS 870.4100b [§83-1b]; OECD 452.

PC CODE: 123009 **DP BARCODE**: D292904

TEST MATERIAL (PURITY): BAS 670H (95.8% a.i.)

SYNONYMS: [3-(4-5-Dihydro-isoxazol-3-yl)-4-methanesulfonyl-2-methyl-phenyl]-(5-hydroxy-1-methyl-1H-pyrazol-4-yl)-methanone

CITATION: Kaspers, U., K. Deckardt, W. Kaufmann, *et al.* (2002) BAS 670H: chronic oral toxicity study in beagle dogs: administration in the diet for 12 months. Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany. Laboratory Project ID: 33D0124/98123, December 4, 2002. MRID 45902215. Unpublished.

Kaspers, U., K. Deckardt, W. Kaufmann, *et al.* (2002) BAS 670H: Supplementary chronic oral toxicity study in beagle dogs: administration in the diet for 12 months. Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany. Laboratory Project ID: 33D0124/98144, December 20, 2002. MRID 45902216. Unpublished.

SPONSOR: BASF Corporation, Agricultural Products, P.O. Box 13528, Research Triangle Park, NC

EXECUTIVE SUMMARY - In a chronic toxicity study (MRID 45902215), BAS 670H (95.8% a.i., Batch No.: N26) was administered to beagle dogs (5/sex/dose) in the diet at doses of 0, 3000, 9000, or 25,000 ppm for 209 days and 0, 2600, 7800, or 22,000 for study days 210-364 (equivalent to 0/0, 81/92, 248/287, and 688/780 mg/kg/day in males/females over the entire study). Because a NOAEL was not established in the initial study, a supplementary study (MRID 45902216) was performed. The same test material (Batch No.: N26) was administered to 5 beagle dogs/sex/dose in the diet at doses of 0, 100, or 500 ppm (equivalent to 0/0, 2.9/3.1, and 15.3/15.4 mg/kg/day in males/females) for up to 12 months.

Two 25,000 ppm males died, one on Day 137 and the other on Day 280. The cause of death for both dogs were attributed to necrotizing cystitis and postrenal uremia. Observed clinical signs were limited to these two dogs that die. No other treatment-related adverse effects were seen on ophthalmology, food consumption, hematology, and clinical chemistry.

Slight decreases (not statistically significant [NS]) in body weight were frequently observed throughout the studies in males at ≥500 ppm and in females at ≥3000 ppm. This effect was clearly dose-dependent by Day 126 in the initial study and throughout the supplementary study. Cumulative body weight gains were decreased in all treated animals throughout the studies. Overall body weight gains (Day 0-364) were decreased in males at 3000 (↓9%, NS), 9000 (↓25%, NS), 25000 (↓34%, NS) ppm and in females at 3000 (↓14%, NS), 9000 (↓55%, $p \leq 0.05$), and 25,000 (↓29%, NS) ppm. Significant decreases ($p \leq 0.05$) were often observed in the 9000 ppm females from Day 77 to termination and in the 25,000 ppm females on Day 238. The effect on body weight gain in the females was not clearly dose-dependent.

In the supplementary study, slight decrease (NS) of body weight and body weight gains were observed in 500 ppm males compared to the control during the entire treatment period. Interestingly, increased body weight and body weight gains (NS) were observed in females at 500 ppm. Overall (Days 0-364) body weight gain was increased (NS) in the 100 and 500 ppm females by 5-46%. This increase (NS) may have been incidental as the effect of treatment in these studies is generally a decrease in body weight gain. For these reasons, the effect on body weight gain in the 100 and 500 ppm females was not considered adverse.

Although food consumption was limited and the ration was generally entirely consumed, food efficiency was affected as evidenced by the variation in body weight gains. The average food efficiency (calculated by the reviewer) was decreased dose-dependently in the males of both studies; however, the decrease in the 100 ppm males was minor. Food efficiency was decreased in the ≥3000 ppm females, but the effect was not clearly dose-dependent. Food efficiency was not decreased in the 100 and 500 ppm females.

No significant treatment-related adverse effects were observed in hematology and chemistry parameters; however, serum tyrosine level was not measured in this study. Urinalysis showed increased ketone level in the urine in all treated animals. This finding may be a false positive due to excretion of p-hydroxyphenylpyruvic acid (a keto-acid) which interferes with the reagent of the test strip. Decreased urine pH values (pH<6) were observed in all treated animals compared with the controls (pH>6). Examination of urinary sediment revealed crystals (it was identified as magnesium complex of the parent compound). The study authors stated that due to the known solubility characteristics of the compound which is heavily dependent on pH level, it is possible that the limit of solubility was surpassed, as indicated by crystals of the compound in urine sediment. This finding was supported by high concentration of BAS 670H detected in the urine of treated animals. The quantity detected in the urine was not linearly proportional to the administered dose.

Histopathology examinations showed increased incidences of minimal to moderate thyroid C-cell hyperplasia in males (3-4/5 treated vs 1/5 controls). No dose-response was observed in females

(3-5/5 treated vs 5/5 controls). It is known from other concurrently submitted studies that the compound affects the thyroid. Therefore, the thyroid c-cell hyperplasia is considered treatment-related.

Significant microscopic lesions were observed only in the two males of the 25000 ppm group that died: (i) renal/urinary system toxicity as evidenced by ureter dilation; urinary bladder cystitis; and pyelonephritis, perinephritis, and concretion in the kidney; (ii) ilium Peyer patch atrophy; (iii) brain glia cell reaction; (iv) indications of reproductive organ toxicity including hyperemia in the epididymides and prostatitis; (v) starry sky appearance of the thymus; (vi) serositis in the mesenteric lymph node; and (vii) hyperemia in the auxiliary lymph node.

One male dog of the 9000 ppm group showed multiple hemorrhages in the urinary bladder wall which corroborates with its gross pathological finding. This may be an indication for early toxic damage of the structures of the urinary bladder wall. The loss of the integrity of the transitional epithelium could lead to bacterial infection and other secondary effects.

All other histopathological findings were considered incidental as it occurred in single case or were equally distributed over the treated and control groups.

For males, the NOAEL is 100 ppm (equivalent to 2.9 mg/kg/day), and the LOAEL is 500 ppm (equivalent to 15.3 mg/kg/day) based on increased incidence of thyroid C-cell hyperplasia. For females, the NOAEL is 500 ppm (equivalent to 15.4 mg/kg/day), and the LOAEL is 3000 ppm (equivalent to 92 mg/kg/day) based on decreased body weights, body weight gains, and food efficiency. No serum tyrosine level was measured.

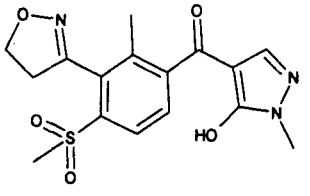
This study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.4100b, OECD 452) for a chronic oral toxicity study in dogs.

COMPLIANCE - Signed and dated GLP, Data Confidentiality, Quality Assurance, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. **Test material:** BAS 670H

Description:	Beige solid
Batch/Lot #:	N26
Purity (w/w):	95.8% a.i.
Stability of compound:	At room temperature, stable in the diet for up to 49 days, and in the wetted diet for 24 hours.
CAS #:	210631-68-8
Structure:	

2. **Vehicle** - Dietary paste (1 g of diet/mL of water)

3. **Test animals** (data presented below are for both the initial and supplemental studies)

Species:	Dog
Strain:	Beagle
Age/weight at initiation of treatment:	Approximately 6-9 months old; 9.5-14.9 kg males, 7.8-11.8 kg females
Source:	BASF's own beagle breed
Housing:	Individually in indoor/outdoor kennels (6-9 m^2)
Diet:	Dog Maintenance KLIBA Laboratory Diet (Provimi Kliba SA, Kaiseraugst, Switzerland); 350 g diet mixed with 350 mL water/day up to Day 209; 400 g diet mixed with 400 mL water/day from Day 210 onward in the initial study and each day of the supplementary test; diet was offered for 2 hours at late morning
Water:	Tap water, *ad libitum*; except allowed approximately 500 mL of water while in metabolism cages
Environmental conditions	The report stated that the animal rooms were ventilated by a forced ventilation system (with additional heating of the air supply in winter).
Temperature:	Not reported.
Humidity:	Not reported
Air changes:	Not reported
Photoperiod:	Natural day/night rhythm with artificial light as required during working hours.
Acclimation period:	7 days

B. STUDY DESIGN

1. **In life dates** - Initial study - Start: 8/14/00 End: 8/21/01
Supplemental study - Start: 7/04/01 End: 7/09/02

2. **Animal assignment** - The dogs were randomly assigned, stratified by body weight, to the test groups shown in Table1.

Table 1. Study design [a]

Test Group	Dose (ppm)	Achieved Intake (mg/kg/day, M/F)	# of Animals (M/F)
Initial Study			
Control	0	0/0	5/5
Low	3000/2600[b]	81/92	5/5
Mid	9000/7800[b]	248/287	5/5
High	25,000/22,000[b]	688/780	5/5
Supplementary Study			
Control	0	0/0	5/5
Low	100	2.9/3.1	5/5
High	500	15.3/15.4	5/5

a Data were obtained from MRID 45902215, pages 22 and 48, and MRID 45902216, pages 20 and 44.

b Due to lower than expected body weight gains in all groups in the initial study, including the controls, the amount of diet provided was increased from 350 g/day to 400 g/day beginning on Day 210 onward. This changed the nominal dose (ppm) as shown; the achieved intake (mg/kg/day) was calculated for the entire study.

3. **Dose selection rationale** - In a concurrently submitted subchronic oral study (MRID 45902205), BAS 670H was administered to 5 Beagle dogs/sex/dose in the diet at doses of 0, 3000, 9000, or 25,000 ppm (equivalent to 0/0, 182/205, 535/624, or 1511/1712 mg/kg/day in males/females) for up to 90 days. The LOAEL was 25,000 ppm, based on decreased body weight gain and impaired food efficiency in the males. Based upon these results, the doses summarized in Table 1 were selected for the initial chronic toxicity study (MRID 45902215). Doses for the supplemental chronic toxicity study (MRID 45902216) were selected based on the results from the initial chronic toxicity study.

4. **Treatment preparation, administration, and analysis** - The appropriate amount of test substance was mixed with a small amount of diet to form a premix. The premix was further diluted with diet to achieve the proper dose levels. Test diets were prepared approximately every two weeks and stored at room temperature until used. The control animals received the standard diet alone. Initially, all animals were fed daily using 350 g of ground diet mixed with 350 mL of water. However, due to lower than expected body weight gains in all groups (including controls), the amount of diet provided was increased to 400 g/day (mixed with 400 mL of water) on Day 210 and thereafter, and in each day of the supplementary study. Thus the nominal dose (ppm) changed at this time in the initial study. During the study, homogeneity was determined 1-3 times for each formulation by analyzing 3 samples (reviewers assume from the top, middle, and bottom) from each formulation. Stability in the dry diet for up to 49 days and in a wet diet (amount of water was not reported) for up to 24 hours was determined at room temperature prior

to initiation of the study using comparable batches (95.2-97.7% a.i.) of the test material in a 5000 ppm formulation. When not analyzed for homogeneity, concentration analyses were performed on each formulation at the start of treatment, at approximately 3-month intervals during the study, on Day 205 (initial study only), and one month prior to the end of treatment.

Results - **Homogeneity (range as % nominal, coefficient of variation):** During the study, the results for homogeneity were 103.0-106.1% for 2600/3000 ppm, 102.5-107.1% for 7800/9000 ppm, and 105.6-111.6% for 22000/25000 ppm, C.V.= 0.0-1.4% of target concentration, respectively.

Stability: 99.3-105.9% at 0-49 days (dry food at 5000 ppm) and 96.4-100% at 0-24 hours (wet food at 5000 ppm).

Concentration (range as % of nominal): During the study, the % of nominal concentrations were 103.0-106.1% for 2600/3000 ppm, 102.5-107.1% for 7800/9000 ppm, and 105.6-111.6% for 22000/25000 ppm.

The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the animals was acceptable.

6. Statistics - The following statistical procedures (2-sided) were employed:

Parameter	Statistical Test
Body weight and body weight gain	Parametric one-way analysis using the F-test (ANOVA) followed by Dunnett's test, if necessary.
Hematology and clinical chemistry parameters (except differential blood count)	Non-parametric one-way analysis using the Kruskal-Wallis test followed by the Mann-Whitney U-test for equal medians, if necessary.
Urinalysis parameters (except color, volume, turbidity, and specific gravity)	Fisher's exact test.
Organ weights	Non-parametric one-way analysis using Kruskal-Wallis test followed by the Wilcoxon test, if necessary.

All tests were performed at $p \leq 0.05$ and ≤ 0.01, except tests for hematology and clinical chemistry in the initial study were performed at $p \leq 0.05$, ≤ 0.02, and ≤ 0.002

C. METHODS

1. Observations

a. Cage-side observations - Animals were inspected at least once daily for clinical signs of toxicity, and twice daily (once daily weekends and holidays) for mortality and moribundity.

b. Clinical and neurological examinations - Open field observations of the animals in the kennel were performed prior to treatment and weekly thereafter (further details were not provided). The parameters evaluated included:

behavior during handling	activity/arousal level	feces
fur	tremors	(appearance/consistency)
skin	convulsions	urine (volume/color)
body posture	abnormal movements	pupil size
mucosal membranes	impairment of gait	visible swellings or masses
salivation	lacrimation	respiration
		other unspecified parameters

In addition, acute (MRID 45902303) and subchronic (MRID 45902201) neurotoxicity studies of the rat were submitted concurrently.

2. Body weight - All animals were weighed prior to the study (Days -7 and 0), weekly throughout the study, and at termination. Cumulative body weight gain was calculated weekly.

3. Food consumption, food efficiency, and compound intake - Food consumption (wetted diet, g/animal/day) was recorded daily (beginning on Day -7) for each dog. Test substance intake (mg/kg bw/day) was calculated weekly throughout the study. Food efficiency was calculated weekly based on the individual food consumption and body weight gain data.

4. Ophthalmoscopic examination - Ophthalmoscopic examinations were conducted on all dogs prior to initiation of treatment, at 6 months (initial study only), and prior to termination.

5. Hematology and clinical chemistry - Blood samples for hematology and clinical chemistry analyses were collected from the vena cephalica antebrachli of fasted animals without anesthesia prior to initiation of treatment and from survivors at 3, 6, and 12 months. The sampling procedure and the subsequent analysis of samples were performed according to a randomized sequence. The following CHECKED (X) parameters were examined.

a. Hematology

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB concentration (MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpuscular volume (MCV)*
X	Platelet count* (PLT)		Reticulocyte count
	Blood clotting measurements*		
X	(Activated partial thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time)		

* Recommended for chronic studies based on Guideline 870.4100

b. Clinical chemistry

	ELECTROLYTES		OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Creatinine*
X	Magnesium*	X	Urea nitrogen*
X	Phosphorus*	X	Total cholesterol*
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose (fasting)*
	ENZYMES (more than 2 hepatic enzymes)*	X	Total bilirubin
X	Alkaline phosphatase (ALK)*	X	Total protein *
	Cholinesterase (ChE)	X	Triglycerides
	Creatine phosphokinase		Serum protein electrophores
	Lactic acid dehydrogenase (LDH)		
X	Alanine aminotransferase (ALT/ SGPT)*		
X	Aspartate aminotransferase (AST/ SGOT)*		
X	Gamma glutamyltransferase (GGT)*		
	Glutamate dehydrogenase		

* Recommended for chronic studies based on Guideline 870.4100

6. Urinalysis - Urine samples were collected overnight while each individual animal was in a metabolism cage (fasted, but with 500 mL water) prior to initiation of treatment and at 3, 6, and 12 months. The urine samples were evaluated in randomized sequence. The CHECKED (X) parameters were examined.

X	Appearance*	X	Glucose*
X	Volume*	X	Ketones
X	Specific gravity*	X	Bilirubin
X	pH*	X	Occult blood*
X	Sediment (microscopic)		Nitrites
X	Protein*	X	Urobilinogen
X	Turbidity		
X	BAS 670H concentration		

* Recommended for chronic studies based on Guideline 870.4100

7. Sacrifice and pathology - At study termination, all animals were sacrificed via exsanguination under anesthesia, weighed, and subjected to a gross pathological examination. The following CHECKED (X) tissues were collected and fixed in 4% neutral buffered formaldehyde. Additionally, the (XX) organs were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
	Tongue	X	Aorta, thoracic*	XX	Brain (multiple sections)*+
X	Salivary glands*	XX	Heart*+	X	Peripheral nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	XX	Spleen*+	X	Eyes (with optic nerve)*
X	Jejunum*	X	Thymus		GLANDULAR
X	Ileum*			XX	Adrenal gland*+
X	Cecum*		UROGENITAL		Lacrimal gland
X	Colon*	XX	Kidneys*+	XX	Parathyroids*
X	Rectum*	X	Urinary bladder*	XX	Thyroid*
XX	Liver*+	XX	Testes*+		OTHER
X	Gall bladder*	XX	Epididymides*+	X	Bone (sternum and/or femur)
X	Pancreas*	XX	Prostate*	X	Skeletal muscle
	RESPIRATORY	XX	Ovaries*+	X	Skin*
X	Trachea*	XX	Uterus*+	X	Joint (femur/tibia)
X	Lung*++	X	Mammary gland*	X	All gross lesions and masses*
X	Nasal structures*		Cervix		
X	Pharynx*	X	Vagina		
X	Larynx*	X	Oviducts		

* Required for chronic studies based on Guideline 870.4100.
\+ Organ weight required in chronic studies.
++ Organ weight required if inhalation route.

Tissues from all animals were processed routinely, stained with hematoxylin and eosin, and were examined microscopically.

II. RESULTS

A. OBSERVATIONS

1. **Clinical signs of toxicity** - All animals in the 25,000 ppm group had light brown feces beginning on Day 1 and generally throughout the study. One male dog in the 25000 ppm group was found to have vomit, diarrhea, reduced general condition, abdominal and lateral position. This dog was found dead on day 137. Another male dog in this group showed lateral position, slight tremor, hypothermia, slight apathy, diarrhea, moderate polyuria and unsteady gait. This dog was sacrificed on day 280 due to its severe condition. Other clinical signs were transient and considered incidental.

2. **Mortality** - One 25,000 ppm male was found dead on Day 137; another 25,000 ppm male was sacrificed moribund on Day 280. Pathology revealed the cause of death for both dogs were

attributed to necrotizing cystitis and postrenal uremia. All other animals survived throughout the study.

B. BODY WEIGHT AND WEIGHT GAIN - It is to be noted that the study indicated that lower than expected body weight gains were observed in all dose groups (including controls) in the initial study; therefore, the amount of dietary formulations given to all groups was increased from 350 g to 400 g/day beginning on Day 210 and continuing throughout the study.

In the initial study, slight decreases in body weight were frequently observed throughout the studies in treated animals at ≥3000 ppm of both sexes (Table 2a). Statistically significant decreases ($p \leq 0.05$) of body weight were observed in the mid-dose (9000 ppm) females from Day 119 to termination (↓12-15%). Cumulative body weight gains were decreased in all treated animals throughout the studies (Table 2b). Decreases of overall body weight gain (Day 0-364) were observed in males at 3000 (↓9%, NS), 9000 (↓25%, NS), 25000 (↓34%, NS) ppm and in females at 3000 (↓14%, NS), 9000 (↓55%, $p \leq 0.05$), and 25,000 (↓29%, NS) ppm. Significant decreases ($p \leq 0.05$) were observed in the 9000 ppm females from Day 77 to termination and in the 25,000 ppm females on Day 238. The effect on body weight gain in the females was not clearly dose-dependent.

In the supplementary study, slight decreases (NS) of body weight and body weight gains were observed in males at 500 ppm compared to the control during the entire treatment period. Interestingly, increased body weight and body weight gains (NS) were observed in females at 500 ppm. Overall (Days 0-364) body weight gain was increased (NS) in the 100 and 500 ppm females by 5-46%. This increase (NS) may have been incidental as the effect of treatment in these studies is generally a decrease in body weight gains. For these reasons, the increases of body weight gains in the 100 and 500 ppm females were not considered adverse.

Table 2a. Mean (±SD) body weights (kg) at selected intervals in dogs treated with BAS 670H in the diet for up to 364 days. [a]

Days on Study	Dose (ppm)						
	Supplementary Study			Initial Study			
	0	100	500	0	3000	9000	25,000
Males							
0	11.1±1.1	11.1±1.1	11.3±1.1	12.0±1.4	12.3±1.1	12.0±1.4	12.4±1.8
7	11.3±1.0	11.3±1.0	11.2±1.0	12.0±1.2	12.2±1.0	12.0±1.3	12.4±1.7
91	14.1±1.4	14.0±0.8	13.7±1.5	13.1±0.7	12.7±1.0	12.5±0.7	12.7±1.5
210	14.1±1.5	14.3±0.8	13.3±1.9	12.9±0.8	12.3±1.1	12.0±0.7	12.9±1.3
364	14.4±1.6	14.2±0.8	13.2±2.3	14.8±0.8	14.8±1.2	14.1±0.7	14.2±0.7
Females							
0	9.8±1.2	10.1±1.0	9.8±1.2	10.2±1.1	10.2±0.8	10.1±0.9	10.3±0.9
7	10.0±1.1	10.3±1.0	10.0±1.3	10.3±1.0	10.2±0.7	10.2±0.8	10.3±0.9
91	11.8±1.2	12.2±1.1	12.6±1.6	11.6±1.1	10.8±0.5	10.5±0.6	10.9±0.7
119	12.2±1.3	12.1±1.0	12.7±1.7	11.7±1.1	10.7±0.5	10.4±0.6* (↓12)	11.1±0.8
210	11.9±1.5	12.7±0.6	12.9±1.5	12.1±1.3	10.8±0.4	10.3±0.9*	10.9±0.8
364	12.3±1.7	12.9±0.7	13.6±1.7	13.8±1.4	13.3±0.8	11.8±0.5*(↓15)	12.9±1.1

a Data were obtained from pages 137-148 of MRID 45902215 and pages 115-126 of MRID 45902216.
* Significantly different from controls, p≤0.05

Table 2b. Mean (±SD) cumulative body weight gains (kg) at selected intervals in dogs treated with BAS 670H in the diet for up to 364 days. [a]

Days on Study	Dose (ppm)						
	Supplementary Study			Initial Study			
	0	100	500	0	3000	9000	25,000
Males							
0-7	0.2±0.2	0.2±0.3	-0.1±0.2	0.0±0.2	-0.1±0.2	0.0±0.1	-0.1±0.1
0-91	3.0±0.8	2.8±0.4	2.4±0.8	1.1±0.7	0.4±0.5	0.5±0.8	0.3±0.4
0-210	3.1±1.2	3.2±0.5	2.0±1.4	0.9±1.6	0.0±0.7	0.0±1.2	-0.1±0.8
0-364	3.4±1.2	3.1±0.7 (↓8)	1.9±1.8 (↓44)	2.8±1.1	2.5±0.5 (↓9)	2.1±0.9 (↓25)	1.8±1.0 (↓34)
Females							
0-7	0.2±0.1	0.1±0.2	0.2±0.2	0.1±0.1	0.1±0.2	0.0±0.2	0.0±0.1
0-140	2.4±0.5	2.1±0.5	3.1±0.9	1.4±0.9	0.4±0.7	0.0±0.7* (↓99)	0.4±0.2
0-210	2.1±0.9	2.5±0.8	3.1±0.5	1.9±1.0	0.7±0.8	0.1±0.9**	0.6±0.1
0-364	2.6±0.9	2.7±0.6 (↑5)	3.8±0.7 (↑46)	3.6±1.1	3.1±1.3 (↓14)	1.6±0.8* (↓55)	2.6±1.0 (↓29)

a Data were obtained from pages 149-160 of MRID 45902215 and pages 127-138 of MRID 45902216.
* Significantly different from controls, p≤0.05

C. FOOD CONSUMPTION AND COMPOUND INTAKE

1. Food consumption - One 25,000 ppm male showed reduced food consumption on Days 130-136; this animal was found dead on Day 137. Another 25,000 ppm male showed reduced food consumption on Day 279; this animal was sacrificed in moribund condition on Day 280. These findings were short-term effects and are likely secondary effects, considering the lack of effect on food consumption in the other treated males. All other males consumed their entire ration. A dose-dependent effect was not observed in the females in either study. Although the females generally consumed their entire ration, frequent decreases were observed in the control (initial study) and 9000 ppm females after Day 295. In the supplementary study, the entire ration or nearly the entire ration was often consumed, but frequent decreases were observed in all groups.

2. Compound intake - Mean test material intake values for the overall study are reported in Table 1.

3. Food efficiency - Although food consumption was limited and the ration was generally entirely consumed, food efficiency was affected as evidenced by the variation in body weight gains. The average food efficiency (calculated by the reviewer) was decreased dose-dependently in the males of both studies; however, the decrease in the 100 ppm males was minor (Table 3). Food efficiency was decreased in the ≥3000 ppm females, but the effect was not clearly dose-dependent. Food efficiency was not decreased in the 100 and 500 ppm females.

Table 3. Average food efficiency in dogs treated with BAS 670H in the diet for up to 364 days.[a]

Dose (ppm)						
Supplementary Study			Initial Study			
0	100	500	0	3000	9000	25,000
Males						
2.3	2.1	1.3	2.00	1.74	1.43	1.34
Females						
1.5	1.5	2.6	2.64	2.13	0.92	1.81

a Values calculated by the reviewers from data obtained from pages 161-170 of MRID 45902215 and page 231 of MRID 45902216.

D. OPHTHALMOSCOPIC EXAMINATION - No significant treatment-related abnormalities were observed during ophthalmoscopic examinations.

E. BLOOD ANALYSES

1. Hematology - No significant treatment-related adverse effects were observed. Statistically significant increase of platelet counts ($p \leq 0.05$) were observed in the 25,000 ppm females on Days 184 and 365; however, it was within the normal historical control ranges. In all other parameters, differences ($p \leq 0.05$) were minor, transient, and/or unrelated to dose in both studies.

2. Clinical chemistry - No significant treatment-related effects were observed. Decreased ($p \leq 0.05$) creatinine was observed in the ≥3000 ppm males on Days 92 and 364 (↓8-15%), but the

effect was not clearly dose-dependent. All other differences ($p \leq 0.05$) were minor, unrelated to dose, and/or transient. No serum tyrosine level was measured.

F. URINALYSIS - Urinalysis showed increased ketone level in the urine in all treated animals. The study authors stated that the mode of action of the test material is inhibition of the enzyme p-hydroxyphenylpyruvate-dioxygenase, an enzyme involved in tyrosine catabolism in animals. The inhibition of this enzyme results in increased tyrosine levels in the blood and urine and leads to an excretion of large amounts of p-hydroxyphenylpyruvic acid (a keto-acid), which results in a false positive test for ketone.

Decreased urine pH values (pH<6) were observed in all treated animals while pH>6 was observed in the controls. Examination of urinary sediment revealed crystals (the crystal was later identified as magnesium complex of the parent compound). The study authors stated that due to the known solubility characteristics of the compound which is heavily dependent on pH level, it is possible that the limit of solubility was surpassed, as indicated by crystals of the compound in urine sediment. Precipitation of the compound may have played a role in the observed renal/urinary system pathology.

In addition, urine samples were analyzed for concentration of BAS 670H. High levels of BAS 670H was detected in the urine of treated animals (Table 4). However, the quantity detected in the urine was not linearly proportional to the administered dose.

Table 4. Quantity (mg, range [mean]) of BAS 670H found in urine in dogs treated with BAS 670H in the diet for up to 364 days. [a]

0 ppm	3000 ppm	9000 ppm	25,000 ppm
Males			
<10	26.3-209.8 (147.2)	16.6-188.9 (118.2)	204.7-364.1 (281.3)
Females			
<10	29.6-262.4 (153.4)	162.8-368.5 (250.9)	119.0-371.4 (273.3)

a Data (n=5, except n=3 in 25,000 ppm males) were obtained from pages 628-629 of MRID 45902215.

G. SACRIFICE AND PATHOLOGY:

There was excessive mortality in the 25,000 ppm males (2 deaths in 5 tested animals), which could confound the detection of primary treatment-related effects. Furthermore, historical control data were not provided for pathology in either study, and could not be used to dismiss incidental findings.

1. Organ weight - In the initial study, increased absolute and relative kidney weights were observed in all treated males, statistical significances were observed in the 3000 and 9000 ppm groups. No significant difference was observed in females (Table 5a,b). Slight increases (not statistically significant) of thyroid weight were observed in the treated animals of both sexes. In the supplementary study, decreases ($p \leq 0.05$) of absolute and relative ovary weights and relative uterus weights were observed at 500 ppm; however, a difference ($p \leq 0.05$) was not observed in the initial study.

Table 5a. Initial study: Selected mean (±SD) absolute (g) and relative (%) organ weights in dogs treated with BAS 670H in the diet for one year [a]

Parameter	Dose (ppm)			
	0	3000/2600	9000/7800	25,000/22000
Males				
Terminal body weight (kg)	15.06±0.82 (n=5)	14.84±1.32 (n=5)	14.38±0.78 (n=5)	14.53±0.77 (n=3)
Kidney - absolute (g)	57.57±5.01	65.94±2.15* (↑15)	68.20±2.31** (↑18)	67.58±5.75 (↑17)
relative (%)	0.38±0.05	0.45±0.05	0.48±0.04* (↑24)	0.47±0.03
Thyroid - absolute (g)	1.09±0.16	1.12±0.22	1.26±0.11	1.15±0.28
relative (%)	0.007±0.001	0.008±0.002	0.009±0.002	0.008±0.002
Females				
Terminal body weight (kg)	14.36±1.38 (n=5)	13.92±0.86 (n=5)	12.04±0.52* (n=5)	13.28±1.05 (n=5)
Kidney - absolute (g)	51.34±5.19	56.08±6.03	47.09±4.49	53.41±7.35
relative (%)	0.36±0.02	0.40±0.05	0.39±0.04	0.40±0.05
Thyroid -absolute (g)	1.06±0.13	1.15±0.04	1.05±0.17	1.12±0.23
relative (%)	0.007±0.001	0.008±0.00	0.009±0.001	0.008±0.002

a Data were obtained from pages 247-250 of the study report (MRID 45902215). Percent difference from controls, calculated by the reviewers, is included in parentheses.
* Significantly different from the control group at $p \leq 0.05$
** Significantly different from the control group at $p \leq 0.01$

Table 5b. Supplementary Study: Selected mean (±SD) absolute (g) and relative (%) organ weights in dogs treated with BAS 670H in the diet for one year [a]

Parameter	Males/ Dose (ppm)			Females/ Dose (ppm)		
	0	100	500	0	100	500
Terminal body weight (kg)	14.48±1.70 (n=5)	14.32±0.84 (n=5)	13.34±2.28 (n=5)	12.62±1.74 (n=5)	13.08±0.84 (n=5)	13.86±1.76 (n=5)
Kidney-absolute (g)	63.85±8.96	76.78±9.17	66.20±11.67	53.91±7.62	57.56±5.89	60.62±5.97
relative (%)	0.44±0.06	0.54±0.08	0.49±0.02	0.43±0.03	0.44±0.05	0.44±0.02
Thyroid-absolute (g)	1.00±0.26	0.94±0.17	1.00±0.24	0.86±0.21	1.02±0.19	0.93±0.22
relative (%)	0.007±0.002	0.007±0.001	0.008±0.003	0.007±0.001	0.008±0.02	0.007±0.002

a Data were obtained from pages 225-228 of the study report (MRID 45902216).
* Significantly different from the control group at $p \leq 0.05$
** Significantly different from the control group at $p \leq 0.01$

2. Gross pathology - The following macroscopic lesions were observed exclusively in two of the animals at 25000 ppm that died: (i) renal/urinary system toxicity as evidenced by ureter dilation; urinary bladder cystitis, dilation, and thickening of wall; and kidney enlargement, pelvic dilation, and concretion; (ii) abdominal cavity effusion; (iii) epididymides focus; (iv) prostate hemorrhage and inflammation; and (v) enlarged spleen. One male of the 9000 ppm group showed multifocal hemorrhages in the mucosa of the urinary bladder. Other observations included kidney retraction

in one 25,000 ppm female vs 0/5 in the other female groups; however, renal toxicity was not corroborated in the females.

3. **Microscopic pathology** - Increased incidences of minimal to moderate thyroid C-cell hyperplasia were observed in the males at ≥500 ppm (3-4/5 treated vs 1/5 controls) and in all females include control group (3-5/5 treated vs 5/5 controls) (Table 6). No dose-response was observed in females. It is known from other studies that BAS 670H affects the thyroid; therefore, the C-cell hyperplasia is considered treatment-related.

The two males of 25000 ppm that died showed significant microscopic lesions: (i) renal/urinary system toxicity as evidenced by ureter dilation; urinary bladder cystitis; and pyelonephritis, perinephritis, and concretion in the kidney; (ii) ilium Peyer patch atrophy; (iii) brain glia cell reaction; (iv) indications of reproductive organ toxicity including hyperemia in the epididymides and prostatitis; (v) starry sky appearance of the thymus; (vi) serositis in the mesenteric lymph node; and (vii) hyperemia in the auxiliary lymph node.

One male dog of the 9000 ppm group showed multiple hemorrhages in the urinary bladder wall which corroborates with its gross pathological finding.

All other histopathological findings were considered incidental as it occurred in single case or were equally distributed over the treated and control groups.

Table 6. Incidence (# animals affected/5) of thyroid C-cell hyperplasia in dogs treated with BAS 670H in the diet for up to 364 days. [a]

Dose (ppm)						
Supplementary Study			Initial Study			
0	100	500	0	3000	9000	25,000
Males (n=5)						
1/5	1/5	3/5	1/5	3/5	3/5	4/5
Females (n=5)						
5/5	5/5	5/5	5/5	4/5	3/5	3/5

a Data were obtained from page 254 of MRID 45902215 and page 231 of MRID 45902216.

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS - In the initial study, the high dose group (25,000 ppm) was treated with more than the maximum tolerated dose. The LOAEL was 3000 ppm based on: decreased body weights in males and body weight gain and food efficiency in both sexes. At 3000 ppm, there were also increased urinary ketones and decreased urinary pH in both sexes. The Sponsor regarded the kidneys and urinary bladder as target organs. In the supplementary study, the LOAEL was 500 ppm, based on decreased body weights, body weight gain, and food efficiency in males. The NOAEL was 100 ppm.

B. REVIEWER COMMENTS - No treatment-related adverse effect was observed on clinical signs, ophthalmology, food consumption, hematology, and clinical chemistry.

Two 25,000 ppm males died, one on Day 137 and the other on Day 280. The cause of death for both dogs were attributed to necrotizing cystitis and postrenal uremia.

Slight decreases (not statistically significant [NS]) in body weight were frequently observed throughout the studies in males at ≥500 ppm and in females at ≥3000 ppm. This effect was clearly dose-dependent by Day 126 in the initial study and throughout the supplementary study. There was a statistically significant decreases ($p \leq 0.05$) of body weight in the mid-dose (9000 ppm) females from Day 119 to termination (↓12-15%). Cumulative body weight gains were decreased in all treated animals throughout the studies. Overall body weight gains (Day 0-364) were decreased in males at 3000 (↓9%, NS), 9000 (↓25%, NS), 25000 (↓34%, NS) ppm and in females at 3000 (↓14%, NS), 9000 (↓55%, $p \leq 0.05$), and 25,000 (↓29%, NS) ppm. Significant decreases ($p \leq 0.05$) were often observed in the 9000 ppm females from Day 77 to termination and in the 25,000 ppm females on Day 238. The effect on body weight gain in the females was not clearly dose-dependent.

In the supplementary study, slight decrease (NS) of body weight and body weight gains were observed in 500 ppm males compared to the control during the entire treatment period. Interestingly, increased body weight and body weight gains (NS) were observed in females at 500 ppm. Overall (Days 0-364) body weight gain was increased (NS) in the 100 and 500 ppm females by 5-46%. This increase (NS) may have been incidental as the effect of treatment in these studies is generally a decrease in body weight gain. For these reasons, the effect on body weight gain in the 100 and 500 ppm females was not considered adverse.

Although food consumption was limited and the ration was generally entirely consumed, food efficiency was affected as evidenced by the variation in body weight gains. The average food efficiency (calculated by the reviewer) was decreased dose-dependently in the males of both studies; however, the decrease in the 100 ppm males was minor. Food efficiency was decreased in the ≥3000 ppm females, but the effect was not clearly dose-dependent. Food efficiency was not decreased in the 100 and 500 ppm females.

No significant treatment-related adverse effects were observed in hematology and chemistry parameters; however, serum tyrosine level was not measured in this study. Urinalysis showed increased ketone level in the urine in all treated animals. The study authors stated that the mode of action of the test material is inhibition of the enzyme p-hydroxyphenylpyruvate-dioxygenase, an enzyme involved in tyrosine catabolism in animals. The inhibition of this enzyme results in increased tyrosine levels in the blood and urine and leads to an excretion of large amounts of p-hydroxyphenylpyruvic acid (a keto-acid), which interferes with the reagent of the test strip and causes false positive results for ketone bodies in the urine.

Decreased urine pH values (pH<6) were observed in all treated animals while pH>6 was observed in the controls. Examination of urinary sediment revealed unknown crystals (the crystal was later identified as the parent compound). The study authors stated that due to the known solubility characteristics of the compound which is heavily dependent on pH level, it is possible that the limit of solubility was surpassed, as indicated by crystals of the compound in urine sediment. This finding was supported by high levels of BAS 670H detected in the urine of treated animals. The quantity detected in the urine was not linearly proportional to the administered

dose. Precipitation of the compound may have played a role in the observed renal/urinary system pathology.

Histopathology examination showed increased incidence of minimal to moderate thyroid C-cell hyperplasia in males (3-4/5 treated vs 1/5 controls). No dose-response was observed in females (3-5/5 treated vs 5/5 controls). It is known from other concurrently submitted studies that the compound affects the thyroid. Therefore, the thyroid c-cell hyperplasia is treatment-related.

Treatment at 25,000 ppm resulted in excessive mortality. Microscopic and macroscopic lesions were generally observed only in the two males that died. These observed lesions including (i) renal/urinary system toxicity as evidenced by ureter dilation; urinary bladder cystitis; and pyelonephritis, perinephritis, and concretion in the kidney; (ii) ilium Peyer patch atrophy; (iii) brain glia cell reaction; (iv) indications of reproductive organ toxicity including hyperemia in the epididymides and prostatitis; (v) starry sky appearance of the thymus; (vi) serositis in the mesenteric lymph node; and (vii) hyperemia in the auxiliary lymph node.

One male dog of the 9000 ppm group showed multiple hemorrhages in the urinary bladder wall which corroborates with its gross pathological finding. This may be an indication for early toxic damage of the structures of the urinary bladder wall. The loss of the integrity of the transitional epithelium could lead to bacterial infection and other secondary effects as observed at the higher dose.

All other histopathological findings were considered incidental as it occurred in single case or were equally distributed over the treated and control groups.

For males, the NOAEL is 100 ppm (equivalent to 2.9 mg/kg/day), and the LOAEL is 500 ppm (equivalent to 15.3 mg/kg/day) based on increased incidence of thyroid C-cell hyperplasia. For females, the NOAEL is 500 ppm (equivalent to 15.4 mg/kg/day), and the LOAEL is 3000 ppm (equivalent to 92 mg/kg/day) based on decreased body weights, body weight gains, and food efficiency.

This study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.4100b, OECD 452) for a chronic oral toxicity study in dogs.

C. **STUDY DEFICIENCIES** - In general, historical control data was not provided and is not required; however, historical control data would have been helpful in determining treatment-related effects.

IV. APPENDIX

BASF IC- 6
PATHOLOGY REPORT 33D0124/98123
Chronic Toxicity Study in Beagle Dogs Jun/26/2002 WERA
acopat system

INCIDENCE OF MICROSCOPIC FINDINGS

Sacrifice group	F1							
Sex	M				F			
Dose group	0	1	2	3	0	1	2	3
Animals in selected Group	5	5	5	5	5	5	5	5
Pharynx	5	5	5	5	5	5	5	5
- Inflammatory cells	1	.	.	.	.	.	.	.
Parotid glands	5	5	5	5	5	5	5	5
- Inflammatory cells	.	1	2	.	2	1	3	3
Mandibular glands	5	5	5	5	5	5	5	5
- Inflammatory cells	1	1	3	1	.	1	2	2
- Focal sclerosis	.	.	1	.	.	.	.	.
Esophagus	5	5	5	5	5	5	5	5
- Mononuclear cells	.	.	2	1	1	1	.	.
- Erosions	.	.	.	1	.	.	.	.
Stomach	5	5	5	5	5	5	5	5
- Hyperemia, (m)foc.	.	.	1	.	.	.	.	.
- Hyperplasia, lymph	.	.	.	.	.	2	1	.
- Ulcer	.	.	.	1	.	.	.	.
- Inflammatory cells	.	.	.	1	.	.	.	.
Duodenum	5	5	5	5	5	5	5	5
- Hyperemia, (m)foc.	.	.	.	.	1	1	.	.
- Hyperplasia, lymph	1	1	.	.	.	1	.	1
Jejunum	5	5	5	5	5	5	5	5
- Hyperemia, (m)foc.	.	.	1	1	1	1	.	.
Ileum	5	5	5	5	5	5	5	5
- Atrophy Peyer patch	.	.	.	2	.	.	.	.
- Hyperemia, (m)foc.	.	.	.	.	1	1	.	.
Cecum	5	5	5	5	5	5	5	5
- Atrophy of GALT	.	.	.	1	.	.	.	.
Colon	5	5	5	5	5	5	5	5
- Serositis, sero-fib.	.	.	.	1	.	.	.	.
- Inflammatory cells	.	.	.	.	.	.	1	.
- Hyperemia, (m)foc.	.	.	.	.	1	.	1	.
Rectum	5	5	5	5	5	5	5	5
Liver	5	5	5	5	5	5	5	5
- Kupffer cell granul.	5	5	5	5	5	5	5	5
- Single cell necrosis	.	1	1	1	.	1	1	.
- Hemosiderosis	1	1	.	.	.	.	.	.
- Fat storage	.	.	.	2	.	1	.	.
- Pigmentation,bile d.	.	.	1	.	.	.	.	.
- Inflammatory cells	1	1	3	2	.	1	1	1
- Bile duct prolifera.	.	.	2	.	.	.	.	.
- Increased mitosis	.	.	.	1	.	.	.	.
- Prominent glycogen	.	.	.	.	.	1	.	.
Gallbladder	5	5	5	5	5	5	5	5
- Hyperplasia, lymph	.	2	3	.	1	.	.	1
Pancreas	5	5	5	5	5	5	5	5
- Atrophy of islets	.	.	.	1	.	.	.	.
- Fibrosis, interstit.	.	.	.	1	.	.	.	.
- Inflammatory cells	.	.	3	.	.	.	.	.

BASF IC- 7
PATHOLOGY REPORT 33D0124/98123
Chronic Toxicity Study in Beagle Dogs Jun/26/2002 WEKA
acopat system

INCIDENCE OF MICROSCOPIC FINDINGS

Sacrifice group	F1							
Sex	M				F			
Dose group	0	1	2	3	0	1	2	3
Animals in selected Group	5	5	5	5	5	5	5	5
Abdominal cavity	.	.	.	.	.	1	.	.
- Hernia	.	.	.	.	.	1	.	.
Nasal cavity	5	5	5	5	5	5	5	5
Larynx	5	5	5	5	5	5	5	5
- Inflammatory cells	1	2	2	.	2	1	.	3
Trachea	5	5	5	5	5	5	5	5
- Inflammatory cells	2	.	1	1	1	.	.	1
Lungs	5	5	5	5	5	5	5	5
- Pulmonary abscess	.	.	.	.	.	1	.	.
- Pneumonia, intersti.	.	.	.	2	.	1	.	.
- Granuloma(s), focal	3	4	3	3	3	5	5	3
- Pneumonia verminous	3	1	5	2	2	2	3	2
Kidneys	5	5	5	5	5	5	5	5
- Calcification	5	5	5	3	5	5	5	5
- Aplasia	.	.	.	.	.	.	1	.
- Nephritis, interst.	.	1	.	1	.	2	.	1
- Pyelonephritis	.	.	.	2	.	.	.	.
- Perinephritis	.	.	.	2	.	.	.	.
- Concretion	.	.	.	2	.	.	.	.
Ureter	5	5	5	5	5	5	5	5
- Dilation	.	.	.	2	.	.	.	.
- Hemorrhage, acute	.	.	.	1	.	.	.	.
Urinary bladder	5	5	5	5	5	5	5	5
- Hemorrhage, (m)foc.	.	.	1	.	.	.	.	.
- Cystitis, necrotic	.	.	.	2	.	.	.	.
Testes	5	5	5	5	.	.	.	.
- Giant cells	1	.	3	3	.	.	.	.
- Tubular atrophy	2	.	1	.	.	.	.	.
- Tubular degeneration	1	.	.	1	.	.	.	.
- Inflammatory cells	1	.	.	.	.	.	.	.
Epididymides	5	5	5	5	.	.	.	.
- Hyperemia, pampinif.	.	.	.	2	.	.	.	.
Prostate	5	5	5	5	.	.	.	.
- Cyst(s)	1	.	1	.	.	.	.	.
- Inflammatory cells	1	.	1	.	.	.	.	.
- Prostatitis,necrotic	.	.	.	2	.	.	.	.
Ovaries	.	.	.	.	5	5	5	5
- Cyst(s)	.	.	.	.	.	1	1	.
Oviducts	.	.	.	.	5	5	5	5
Uterus	.	.	.	.	5	5	5	5
Vagina	.	.	.	.	5	5	5	5
- Cyst of Gartner duct	.	.	.	.	.	1	.	.
Mammary gland	.	.	.	.	5	5	5	5
- Lactatio falsa	.	.	.	.	2	1	3	1
- Pigment storage	.	.	.	.	1	.	1	1
- Hyperemia	.	.	.	.	.	2	1	2
- Hyperemia,lymph node	.	.	.	.	1	.	.	.

BASF IC- 8
PATHOLOGY REPORT 33D0124/98123
Chronic Toxicity Study in Beagle Dogs Jun/26/2002 WEKA
acopat system

INCIDENCE OF MICROSCOPIC FINDINGS

Sacrifice group	F1							
Sex	M				F			
Dose group	0	1	2	3	0	1	2	3
Animals in selected Group	5	5	5	5	5	5	5	5
Heart	5	5	5	5	5	5	5	5
Aorta	5	5	5	5	5	5	5	5
Bone marrow	5	5	5	5	5	5	5	5
Spleen	5	5	5	5	5	5	5	5
- Atrophy	.	.	.	1	.	.	.	.
- Acute congestion	.	.	.	1	.	.	.	.
- Nodular hyperplasia	.	1	.	.	.	.	.	.
- Hematoma in organiz.	.	1	1	1	.	1	1	.
- Focal hyperemia	.	.	.	.	2	2	.	.
Thymus	5	5	5	5	5	5	5	5
- "Starry sky" appear.	.	.	.	2	.	.	.	.
Mesenteric lymph n.	5	5	5	5	5	5	5	5
- Serositis, fibrinous	.	.	.	2	.	.	.	.
- Hyperemia	.	.	.	1	.	.	.	1
- Sinus histiocytosis	.	.	.	.	.	.	.	1
Axillary lymph nodes	5	5	5	5	5	5	5	5
- Hyperemia	.	.	.	2	.	1	.	1
- Hemosiderin storage	.	1	.	.	.	2	.	2
Iliac lymph nodes	.	.	.	.	.	1	.	.
- Hyperplasia	.	.	.	.	.	1	.	.
Inguinal lymph nodes	.	.	.	.	.	1	.	.
- Hyperplasia	.	.	.	.	.	1	.	.
Brain	5	5	5	5	5	5	5	5
- Glia cell reaction	1	1	1	3	4	3	4	2
- Calcification, focal	1	1	2	.	2	.	3	.
Cervical cord	5	5	5	5	5	5	5	5
- Calcification	.	.	.	.	.	.	.	1
Thoracic cord	5	5	5	5	5	5	5	5
Lumbar cord	5	5	5	5	5	5	5	5
- Calcification	.	.	.	1	3	2	.	1
Sciatic nerve	5	5	5	5	5	5	5	5
Eyes with opt. nerve	5	5	5	5	5	5	5	5
Adrenal cortex	5	5	5	5	5	5	5	5
- Accessory adrenal t.	.	.	.	.	1	.	.	1
Adrenal medulla	5	5	5	5	5	5	5	5
Thyroid glands	5	5	5	5	5	5	5	5
- C-cell hyperplasia	1	3	3	4	5	4	3	3
- Lymphoid cells	.	1	4	.	.	.	.	.
- Cyst(s)	1	1	.	.	.	.	.	.
Parathyroid glands	5	5	5	5	5	5	5	5
- Cyst(s)	1	3	.	1	3	1	2	2
Pituitary gland	5	5	5	5	5	5	5	5
- Cyst(s)	1	2	3	1	3	4	2	4
Sternum, with marrow	5	5	5	5	5	5	5	5
Femur with joint	5	5	5	5	5	5	5	5
Skeletal muscle	5	5	5	5	5	5	5	5
- Segmental regenerat.	.	.	1	.	.	.	.	.

BASF IC- 6
PATHOLOGY REPORT 33D0124/98144
Chronic Toxicity Study in Beagle Dogs Oct/31/2002 WEKA acopat system

INCIDENCE OF MICROSCOPIC FINDINGS

Sacrifice group	F1					
Sex	M			F		
Dose group	0	1	2	0	1	2
Animals in selected Group	5	5	5	5	5	5
Pharynx	5	5	5	5	5	5
Parotid glands	5	5	5	5	5	5
- Inflammatory cells	1	1	1	.	2	2
Mandibular glands	5	5	5	5	5	5
- Inflammatory cells	.	3	2	3	2	2
- Focal sclerosis	.	1	.	.	.	.
Esophagus	5	5	5	5	5	5
- Mononuclear cells	.	.	.	2	1	3
Stomach	5	5	5	5	5	5
- Hyperplasia, lymph	1	2	1	1	.	2
Duodenum	5	5	5	5	5	5
- Mononuclear cells	.	.	.	.	4	1
- Hyperplasia, lymph	.	.	.	1	1	.
Jejunum	5	5	5	5	5	5
Ileum	5	5	5	5	5	5
- Hyperplasia, lymph	.	.	.	.	.	1
Cecum	5	5	5	5	5	5
Colon	5	5	5	5	5	5
Rectum	5	5	5	5	5	5
Liver	5	5	5	5	5	5
- Granuloma(s), Kupff.	5	5	5	5	5	5
- Microabscess, focal	.	.	1	.	.	.
- Hemosiderosis	.	.	.	1	.	1
- Pigmentation,bile d.	1	.	.	.	.	1
- Inflammatory cells	.	1	2	1	1	2
Gallbladder	5	5	5	5	5	5
- Hyperplasia, lymph	.	.	.	.	1	.
Pancreas	5	5	5	5	5	5
Nasal cavity, III	5	5	5	5	5	5
Larynx	5	5	5	5	5	5
- Inflammatory cells	1	2	.	1	1	4
- Metaplasia, focal	.	.	.	.	1	.
Trachea	5	5	5	5	5	5
- Inflammatory cells	1	.	.	2	.	.
Lungs	5	5	5	5	5	5
- Granuloma(s), focal	2	.	3	1	4	4
- Pneumonia verminous	3	3	3	4	2	2
Kidneys	5	5	5	5	5	5
- Calcification	5	5	5	5	5	5
- Nephritis, interst.	1	.	1	.	.	1
- Pyelonephritis	.	.	.	.	1	.
- Pyelitis	1	1	1	3	2	.
Urinary bladder	5	5	5	5	5	5
Testes	5	5	5	.	.	.
- Giant cells	4	5	4	.	.	.
- Tubular atrophy	.	1	2	.	.	.
- Tubular degeneration	.	1	2	.	.	.

INCIDENCE OF MICROSCOPIC FINDINGS

Sacrifice group	F1					
Sex	M			F		
Dose group	0	1	2	0	1	2
Animals in selected Group	5	5	5	5	5	5
Epididymides	5	5	5	.	.	.
Prostate	5	5	5	.	.	.
- Inflammatory cells	1	1	2	.	.	.
- Fibrosis, focal	.	1	2	.	.	.
Ovaries	.	.	.	5	5	5
- Cyst(s)	.	.	.	2	.	.
Oviducts	.	.	.	5	5	5
Uterus	.	.	.	5	5	5
Vagina	.	.	.	5	5	5
Mammary gland	.	.	.	5	5	5
- Lactatio falsa	.	.	.	4	.	3
Heart	5	5	5	5	5	5
Aorta	5	5	5	5	5	5
Bone marrow (femur)	5	5	5	5	5	5
Spleen	5	5	5	5	5	5
- Focal hyperemia	.	.	1	.	.	1
- Splenoma	.	.	1	.	.	.
- Hematoma in organiz.	.	.	.	.	1	1
Thymus	5	5	5	5	5	5
Mesenteric lymph n.	5	5	5	5	5	5
Axillary lymph nodes	5	5	5	5	5	5
- Hemosiderin storage	.	.	2	2	.	.
- Hyperemia	.	.	.	1	.	.
- Hyperplasia	.	.	.	.	.	1
Mandibular lymph n.	.	.	2	.	.	.
- Hyperplasia	.	.	2	.	.	.
- Hemosiderin storage	.	.	1	.	.	.
- Abscess formation	.	.	1	.	.	.
Pancreatic lymph nod	.	.	1	.	.	.
- Hemosiderin storage	.	.	1	.	.	.
Brain	5	5	5	5	5	5
- Calcification	.	.	1	3	1	1
Cervical cord	5	5	5	5	5	5
Thoracic cord	5	5	5	5	5	5
- Calcification	.	.	.	.	.	1
Lumbar cord	5	5	5	5	5	5
- Calcification	4	4	1	4	5	2
Sciatic nerve	5	5	5	5	5	5
- Demyelination, focal	.	.	.	.	1	.
Eyes with opt. nerve	5	5	5	5	5	5
Adrenal cortex	5	5	5	5	5	5
Adrenal medulla	5	5	5	5	5	5
Thyroid glands	5	5	5	5	5	5
- C-cell hyperplasia	1	1	3	5	5	5
- Lymphoid cells	.	.	2	.	.	.
- Cyst(s)	2	1	.	.	.	.

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INCIDENCE OF MICROSCOPIC FINDINGS

Sacrifice group	F1					
Sex	M			F		
Dose group	0	1	2	0	1	2
Animals in selected Group	5	5	5	5	5	5
Thyroid glands cont.						
- Hypoplasia	1	.	.	.	.	.
- Thyroiditis, lympho.	.	1	.	1	1	1
- Remnants, ultiomobr.	.	.	1	.	.	.
- Ectopic thymic tiss.	.	.	1	.	.	.
- Fibrosis, focal	.	.	.	.	.	1
Parathyroid glands	5	5	5	5	5	5
- Cyst(s)	4	4	1	3	4	.
Pituitary gland	5	5	5	5	5	5
- Cyst(s)	5	3	2	1	1	3
Sternum, with marrow	5	5	5	5	5	5
Femur with joint	5	5	5	5	5	5
Skeletal muscle	5	5	5	5	5	5
- Myofiber degenerat.	.	.	.	1	.	.
Skin	5	5	5	5	5	5
- Folliculitis, focal	.	.	1	1	.	.

DATA FOR ENTRY INTO ISIS

Chronic Study - dogs (870.4100b)

PC code	MRID	Study	Species	Duration	Route	Admin	Dose range mg/kg/day	Doses mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Endpoints	Comments
123009	45902215 45902216	Chronic	dog	1 year	oral	diet	2.9-780	0/0, 2.9/3.1, 15.3/15.4, 81/92, 248/287, 688/780 [M/F]	2.9(M) 15.4(F)	15.3(M) 92(F)	BW, BWG, FE thyroid	