272E 4-23-90

007871

CASWELL FILE

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

APR 23 1990

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: CYPROCONAZOLE - DOG CHRONIC FEEDING AND RAT CHRONIC FEEDING/ONCOGENICITY STUDIES

TO: SUSAN LEWIS/GRABLE
PRODUCT MANAGER (21)
REGISTRATION DIVISION (H7505C)

FROM: LINDA L. TAYLOR, PH.D. 4/17/90
TOXICOLOGY BRANCH II, SECTION II
HEALTH EFFECTS DIVISION (H7509C)

THRU: K. CLARK SWENTZEL 4/18/90
SECTION II HEAD, TOXICOLOGY BRANCH II
HEALTH EFFECTS DIVISION (H7509C)

AND

MARCIA VAN GEMERT, PH.D. 4/19/90
CHIEF, TOXICOLOGY BRANCH/HFAS/HED (H7509C)

REGISTRANT: SANDOZ CROP PROTECTION CORPORATION
CHEMICAL: CYPROCONAZOLE
SYNONYMS: SAN 619 F
PROJECT: 9-2056
CASWELL NO.: 272E
MRID NO.: 412129-01 & 411647-01
RECORD NO.: NONE PROVIDED
IDENTIFYING NO.: 55947-RGG
ACTION REQUESTED: NONE. TWO CHRONIC STUDIES SUBMITTED.

COMMENT: IN A LETTER DATED JULY 10, 1989, THE REGISTRANT SUBMITTED THE TWO STUDIES REFERENCED ABOVE, IN ORDER TO PROVIDE THE AGENCY WITH A COMPLETE PICTURE OF THE CHRONIC TOXICOLOGY PACKAGE FOR SAN 619 F. A MOUSE ONCOGENICITY STUDY (MRID # 411472-01) WAS SUBMITTED UNDER SEPARATE COVER "FYI". THE DER FOR EACH (DOG AND RAT) STUDY IS ATTACHED.

DOG STUDY - THE ADMINISTRATION OF SAN 619 F TO BEAGLE DOGS FOR 52 WEEKS AT DOSE LEVELS OF 30, 100, AND 350 PPM [1.0, 3.2, AND 12.1 (MALES); 12.6 (FEMALES) MG/KG/DAY, RESPECTIVELY] RESULTED IN DIFFERENCES IN SEVERAL CLINICAL LABORATORY PARAMETERS BETWEEN THE CONTROL AND TREATED ANIMALS. ABSOLUTE AND RELATIVE LIVER WEIGHTS WERE INCREASED IN THE HIGH-DOSE ANIMALS OF BOTH SEXES COMPARED TO CONTROLS, BUT STATISTICAL SIGNIFICANCE WAS ATTAINED ONLY IN THE MALES. RELATIVE KIDNEY WEIGHT WAS INCREASED (SIGNIFICANTLY) IN BOTH THE LOW- AND HIGH-DOSE FEMALES. THE NOEL CAN BE SET AT 30 PPM (1.0 MG/KG/DAY) AND THE LEL AT 100 PPM (3.2 MG/KG/DAY), BASED ON LIVER EFFECTS.

CLASSIFICATION: CORE MINIMUM UNDER GUIDELINE 83-1, CHRONIC TOXICITY.

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RAT STUDY - THE ADMINISTRATION OF SAN 619 F TO MALE RATS FOR 118 WEEKS AND TO FEMALE RATS FOR 121 WEEKS AT DOSE LEVELS OF 0, 20, 50, OR 350 PPM (MALES - 1.0, 2.2, AND 15.6 MG/KG; FEMALES - 1.2, 2.7, 21.8 MG/KG) RESULTED IN DECREASED BODY WEIGHTS IN HIGH-DOSE FEMALES AND INCREASED INCIDENCE OF FATTY INFILTRATION OF THE LIVER IN THE HIGH-DOSE MALES. THE NOEL FOR SYSTEMIC TOXICITY CAN BE SET AT 50 PPM, THE LEL AT 350 PPM, BASED ON DECREASED BODY WEIGHT IN FEMALES AND FATTY INFILTRATION IN THE LIVER OF MALES.

UNDER THE CONDITIONS OF THE STUDY, SAN 619 F WAS NOT CARCINOGENIC. BASED ON THE LACK OF: 1) ANY BIOLOGICALLY SIGNIFICANT BODY WEIGHT DECREMENT; 2) ANY SIGNIFICANT HISTOPATHOLOGICAL CORRELATE ACCOMPANYING THE INCREASED RELATIVE LIVER WEIGHT; 3) ANY INCREASE IN THE LIVER ENZYME ACTIVITIES IN THE FEMALES; 4) ANY CONSISTENT CHANGE IN THE LIVER ENZYME ACTIVITIES IN THE HIGH-DOSE MALES, SUGGESTS THAT THE DOSE LEVELS CHOSEN WERE NOT ADEQUATE TO DETERMINE THE CARCINOGENIC POTENTIAL OF THE TEST MATERIAL.

CLASSIFICATION: CORE SUPPLEMENTARY UNDER GUIDELINE 83-2, CARCINOGENICITY STUDY; CORE MINIMUM UNDER GUIDELINE 83-1, CHRONIC TOXICITY STUDY.

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CASWELL FILE
272-00787

REVIEWED BY: LINDA L. TAYLOR, PH.D. Linda Lee Taylor 11/21/89
TOX. BRANCH II, SECTION II (H7509C)
SECONDARY REVIEWER: K. CLARK SWENTZEL K. Clark Swentzel 11/21/89
HEAD SECTION II, TOX. BRANCH II (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: ONE-YEAR CHRONIC - DOG TOX. CHEM. NO.: 272E

MRID NO.: 412129-01

TEST MATERIAL: ALPHA-(4-CHLOROPHENYL)-ALPHA-(1-CYCLOPROPYLETHYL)-1H-1,2,4-TRIAZOLE-1-ETHANOL; SAN 619F

SYNONYMS: CYPROCONAZOLE

STUDY NUMBER: PROJECT NO. 394-D

SPONSOR: SANDOZ CROP PROTECTION CORPORATION

TESTING FACILITY: SANDOZ LTD. AGRO DEVELOPMENT - TOXICOLOGY DEPARTMENT BASLE/SWITZERLAND

TITLE OF REPORT: CHRONIC ORAL TOXICITY BY DIETARY ADMINISTRATION TO BEAGLE DOGS FOR ONE YEAR

AUTHOR(S): S.F.P. WARREN, F. HAMBURGER, S. CARPY, AND F. MILLER

REPORT ISSUED: APRIL 18, 1988

QUALITY ASSURANCE: A QUALITY ASSURANCE STATEMENT WAS PROVIDED.

CLASSIFICATION: CORE-MINIMUM.

CONCLUSION: THE ADMINISTRATION (DIET) OF SAN 619 F TO BEAGLE DOGS FOR 52 WEEKS AT DOSE LEVELS OF 30, 100, AND 350 PPM [1.0, 3.2, AND 12.1 (MALES); 12.6 (FEMALES) MG/KG/DAY, RESPECTIVELY] RESULTED IN DIFFERENCES IN SEVERAL CLINICAL LABORATORY PARAMETERS BETWEEN THE CONTROL AND TREATED ANIMALS, WHICH ARE CONSISTENT WITH EFFECTS ON THE LIVER (ELEVATED ALKALINE PHOSPHATASE AND ALAT LEVELS; DECREASED TOTAL PROTEIN, ALBUMIN, AND CHOLESTEROL LEVELS). ABSOLUTE AND RELATIVE LIVER WEIGHTS WERE INCREASED IN THE HIGH-DOSE ANIMALS OF BOTH SEXES COMPARED TO CONTROLS, BUT STATISTICAL SIGNIFICANCE WAS ATTAINED ONLY IN THE MALES. RELATIVE KIDNEY WEIGHT WAS INCREASED (SIGNIFICANTLY) IN BOTH THE LOW- AND HIGH-DOSE FEMALES.

STATISTICALLY SIGNIFICANT INCREASES WERE OBSERVED IN CYTOCHROME P_{450} IN BOTH SEXES OF THE HIGH-DOSE AND IN THE MID-DOSE FEMALES. LAMINAR EOSINOPHILIC INTRAHEPATOCYTIC BODIES WERE OBSERVED IN ALL HIGH-DOSE MALES, ONE MID-DOSE MALE, AND TWO HIGH-DOSE FEMALES AND WERE CONSIDERED TO REPRESENT ADAPTIVE HYPERTROPHY OF THE ENDOPLASMIC RETICULUM.

THE NOEL CAN BE SET AT 30 PPM (1.0 MG/KG/DAY) AND THE LEL AT 100 PPM (3.2 MG/KG/DAY), BASED ON LIVER EFFECTS.

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A. MATERIALS:

1. TEST COMPOUND: SANDOZ 619F, TECHNICAL; DESCRIPTION: A LIGHT BROWN POWDER; BATCH #: 8507; PURITY: 95+ 1%; STABILITY: DOCUMENTED.

2. TEST ANIMALS: SPECIES: DOG ; STRAIN: PUREBRED BEAGLES (CANIS FAMILIARIS); AGE: APPROXIMATELY 5 MONTHS; WEIGHT: MALES: 7.6-8.0 KG, FEMALES: 7.0-7.5 KG; SOURCE: MARSHALL FARMS BREEDING LABORATORIES, NORTH ROSE, NEW YORK.

B. STUDY DESIGN:

1. ANIMAL ASSIGNMENT

ANIMALS WERE ASSIGNED RANDOMLY TO THE FOLLOWING TEST GROUPS:

GROUP	DOSE IN DIET (PPM)	EXPOSURE PERIOD (52 MONTHS) MALES	FEMALES
1 CONTROL	0	4	4
2 LOW	30	4	4
3 MID	100	4	4
4 HIGH	350	4	4

2. DIET PREPARATION

THE TEST ARTICLE WAS ADMINISTERED IN THE DIET (POWDERED DIET # 24-335-1; KLINGENTALMUHLE, CH-BASLE). A DIET PREMIX WAS PREPARED MONTHLY [40 GRAMS OF SAN 619F MIXED WITH 3960 GRAMS OF POWDERED FODDER CONCENTRATION OF 10 MG SAN 619F PER GRAM (1%)] WHICH WAS THEN MIXED WEEKLY BY ADDING ADDITIONAL POWDERED FODDER TO MAKE THE APPROPRIATE DOSE LEVELS. THE CONTROLS RECEIVED UNTREATED DIET. EACH DOG WAS OFFERED APPROXIMATELY 400 GRAMS OF FOOD DAILY AND WATER AD LIBITUM.

RESULTS

DATA PROVIDED INDICATE THE DIETS TO BE WITHIN +/-10% OF THE TARGET CONCENTRATIONS THROUGHOUT THE STUDY.

3. STATISTICS - THE PROCEDURES UTILIZED IN ANALYZING THE NUMERICAL DATA ARE EXPLAINED ON PAGE 17 OF THE FINAL REPORT (COPY ATTACHED).

C. METHODS AND RESULTS:

1. OBSERVATIONS

ALL DOGS WERE OBSERVED TWICE DAILY FOR SIGNS OF ILL HEALTH, AND THE NOSE, EYES, ANUS, AND BUCCAL CAVITY WERE CHECKED DAILY.

RESULTS:

TOXICITY/MORTALITY (SURVIVAL)

THERE WERE NO DEATHS OR UNSCHEDULED SACRIFICES DURING THE STUDY.

CLINICAL OBSERVATIONS

SUBDUED BEHAVIOR (DURING WEEKS 4 TO 8) AND LOWER BODY-WEIGHT GAIN (DURING THE FIRST 4 WEEKS) WERE OBSERVED IN ONE HIGH-DOSE FEMALE. FOOD CONSUMPTION ALSO TENDED TO BE LOW IN THIS ANIMAL UP TO WEEK 10. THEREAFTER, THIS ANIMALS DISPLAYED COMPARABLE BEHAVIOR TO THE OTHER DOGS. ONE MID-DOSE FEMALE DISPLAYED SUBDUED BEHAVIOR WITH BODY WEIGHT LOSS AND LOW FOOD CONSUMPTION DURING WEEK 2.

ONE HIGH-DOSE FEMALE FAILED TO COME INTO HEAT DURING THE STUDY, AND TERMINAL HISTOLOGICAL EXAMINATION REVEALED IMMATURE OVARIES.

2. BODY WEIGHT AND FOOD CONSUMPTION

ANIMALS WERE WEIGHED WEEKLY AND FOOD CONSUMPTION WAS DETERMINED WEEKLY. GROUP MEAN WEEKLY INTAKE OF TEST MATERIAL WAS CALCULATED FROM INDIVIDUAL BODY WEIGHT AND FOOD CONSUMPTION.

RESULTS

THE AUTHOR REPORTED AN INITIAL EFFECT ON BODY-WEIGHT GAIN FOR THE HIGH-DOSE MALES; A DECREASE WAS NOTED INITIALLY, WHICH WAS GREATEST AT WEEK 9 AND THEN BECAME COMPARABLE TO CONTROL THEREAFTER.

BODY WEIGHT (% CONTROL)

WEEK	0	1	3	6	9	14	15	16	26	50
MALES										
LOW	96	100	100	97	97	97	98	98	102	117
MID	101	104	105	103	103	103	104	105	104	114
HIGH	100	100	99	95	94	93	93	93	97	105

WEEK	0	1	3	6	9	14	27	44	47	50
FEMALES										
LOW	103	100	101	98	100	100	104	98	95	101
MID	101	101	100	100	107	111	107	107	104	111
HIGH	96	93	94	90	95	98	99	93	92	93

NOTE: DUE TO A COMPUTER PROBLEM AT THE TESTING FACILITY, PRE-TREATMENT VALUES FOR BOTH BODY WEIGHT AND FOOD CONSUMPTION WERE NOT AVAILABLE.

BODY-WEIGHT GAIN (KG)

	WEEK 0 - 9	WEEK 0 - 13	WEEK 13 - 26	WEEK 26 - 52	WEEK 0 - 52
MALES					
C	1.9	2.3	1.1	-0.1	3.3
L	1.9	2.5	1.4	1.5	5.4
M	2.1	2.7	1.1	0.7	4.5
H	1.3	1.8	1.3	0.5	3.6
FEMALES					
C	1.0 (1.0)*	1.1	0.6	0.5	2.2
L	0.8 (0.6)	0.9	0.6	0.5	2.0
M	1.5 (0.9)	1.9	0.4	0.9	3.2
H	0.9 (0.5)	1.1	0.7	0.0	1.8

* VALUE FOR BODY-WEIGHT GAIN BETWEEN WEEKS 0 AND 6

IN GENERAL, MEAN FOOD CONSUMPTION OF ALL OF THE MALE GROUPS WAS SIGNIFICANTLY GREATER THAN CONTROL AT VARIOUS TIME POINTS DURING THE STUDY. FOR FEMALES, FOOD CONSUMPTION VARIED CONSIDERABLY, WITH THE HIGH-DOSE GROUP SHOWING DECREASED INTAKE, COMPARED TO THE CONTROLS AND OTHER TREATED GROUPS FOR THE FIRST 3 WEEKS OF THE STUDY AND DURING WEEKS 31, 36, 42, 47, AND 51 (NOT STATISTICALLY SIGNIFICANT). THE LOW-DOSE FEMALES SHOWED DECREASED FOOD CONSUMPTION FROM WEEK 23 TO WEEK 48 (STATISTICALLY SIGNIFICANT AT WEEK 26 ONLY), AND THE MID DOSE SHOWED A DECREASE AT WEEKS 31, 36, 37, AND DURING WEEKS 42-47 (NONE STATISTICALLY SIGNIFICANT BUT $\geq$ 10% BELOW CONTROL VALUE).

FOOD EFFICIENCY DATA PROVIDED IN THE REPORT INDICATE THAT THERE WAS A SLIGHTLY REDUCED EFFICIENCY AT THE HIGH DOSE FOR MALES OVER THE FIRST 26 WEEKS. FOR THE FIRST 9 WEEKS, BOTH SEXES AT THE HIGH DOSE DISPLAYED A REDUCED FOOD EFFICIENCY (NO STATISTICS WERE PERFORMED ON THESE DATA).

3. COMPOUND INTAKE

AVERAGE DAILY DOSES OF THE TEST MATERIAL WERE CALCULATED FROM NOMINAL DIETARY CONCENTRATIONS, INDIVIDUAL BODY WEIGHT, AND FOOD CONSUMPTION.

	CONSUMED (MG/KG/DAY)	
	MALES	FEMALES
LOW	0.99	0.99
MID	3.15	3.23
HIGH	12.05	12.58

4. OPHTHALMOLOGICAL EXAMINATIONS

OCULAR EXAMINATIONS WERE PERFORMED ON ALL OF THE DOGS PRIOR TO TREATMENT AND DURING WEEK 50, USING A FUNDUS CAMERA FOLLOWING ADMINISTRATION OF A MYDRIATIC.

RESULTS

THERE WERE NO TREATMENT-RELATED OCULAR CHANGES IN EITHER SEX.

5. BLOOD ANALYSIS

CLINICAL LABORATORY STUDIES WERE CONDUCTED ON ALL DOGS (FASTED 16-18 HOURS) PRIOR TO STUDY INITIATION (WEEKS -1 & -2), AT 3, 6, AND 9 MONTHS, AND AT STUDY TERMINATION. THE 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 CONC.(MCHC)
X	ERYTHROCYTE COUNT (RBC)*	X	MEAN CORPUSCULAR VOLUME (MCV)
X	PLATELET COUNT*	X	RETICULOCYTE COUNT
	THROMBOCYTE COUNT		METHEMOGLOBIN
X	PROTHROMBIN TIME		HEINZ BODIES
	ERYTHROCYTE INDICES		HOWELL-JOLLY BODIES

* REQUIRED FOR CHRONIC STUDIES

RESULTS

INCREASED PLATELET COUNTS WERE OBSERVED AT THE HIGH DOSE IN BOTH SEXES THROUGHOUT THE STUDY. MID-DOSE MALES ALSO DISPLAYED MARGINALLY INCREASED COUNTS AT WEEKS 26, 38, AND 52. PROTHROMBIN TIME WAS MEASURED AT WEEK 48 TO ASSESS WHETHER THE DISTURBED PLATELET COUNT WAS ASSOCIATED WITH DISTURBED CLOTTING FUNCTION. THE INCREASE IN PROTHROMBIN TIME OBSERVED WAS CONSIDERED (BY THE AUTHOR) TO BE THE RESULT OF THE OCCASIONAL LOW VALUES IN THE LOW-DOSE AND CONTROL GROUPS, AND NOT TO TREATMENT. HOWEVER, IT IS TO BE NOTED THAT THE LOW- AND MID-DOSE FEMALES SHOWED LOWER VALUES THAN THE CONTROL FEMALES.

HEMATOLOGICAL VALUES (% OF CONTROL)

PARAMETER	GROUP	WEEK -1	WEEK 13	WEEK 26	WEEK 38	WEEK 48	WEEK 52
MALES							
PLATELETS TH/CMM	CONTROL	403	305	287	269	291	274
	LOW	334(83)	269(88)	256(89)	248(92)	266(91)	258(94)
	MID	386(96)	335(110)	356(124)	307(114)	332(114)	318(116)
	HIGH	358(89)	461(151)	423(147)	384(143)	409(140)	383(140)
PROTHROMB. SEC.	CONTROL					9.60	
	LOW					10.50(109)	
	MID					10.80(113)	
	HIGH					10.85(113)	
FEMALES	GROUP	WEEK 0	WEEK 13	WEEK 26	WEEK 38	WEEK 48	WEEK 52
PLATELETS TH/CMM	CONTROL	374	319	324	323	310	305
	LOW	352(94)	291(91)	317(98)	308(95)	322(104)	324(106)
	MID	362(97)	344(108)	351(108)	328(102)	371(120)	332(109)
	HIGH	344(92)	456(143)*	433(134)	415(129)	442(143)*	438(144)**
PROTHROMB. SEC.	CONTROL					10.08	
	LOW					9.88(98)	
	MID					9.83(98)	
	HIGH					11.05(110)	

B. CLINICAL CHEMISTRY

THE CHECKED (X) PARAMETERS WERE MEASURED.

	ELECTROLYTES:		OTHER:
X	CALCIUM*	X	ALBUMIN*
X	CHLORIDE*	X	BLOOD CREATININE*
	MAGNESIUM*	X	BLOOD UREA NITROGEN*
X	PHOSPHORUS*	X	CHOLESTEROL*
X	POTASSIUM*	X	GLOBULINS
X	SODIUM*	X	GLUCOSE*
	ENZYMES	X	TOTAL BILIRUBIN*
X	ALKALINE PHOSPHATASE	X	TOTAL SERUM PROTEIN*
	CHOLINESTERASE#	X	TRIGLYCERIDES
X	CREATININE PHOSPHOKINASE*		SERUM PROTEIN ELECTROPHORESIS
X	LACTIC ACID DEHYDROGENASE	X	GAMMA GLUTAMYLTRANSFERASE
X	SERUM ALANINE AMINOTRANSFERASE (ALSO SGPT)*		
X	SERUM ASPARTATE AMINOTRANSFERASE (ALSO SGOT)*		
	GAMMA GLUTAMYL TRANSPEPTIDASE	X	LEUCINE ARYLAMIDASE
X	GLUTAMATE DEHYDROGENASE		

* REQUIRED FOR CHRONIC STUDIES
# SHOULD BE REQUIRED FOR OP

RESULTS

THERE WAS A STATISTICALLY SIGNIFICANT DECREASE IN TOTAL PROTEIN, ALBUMIN, AND CHOLESTEROL VALUES AT VARIOUS TIME POINTS THROUGHOUT THE STUDY IN BOTH SEXES AT THE HIGH-DOSE. TOTAL BILIRUBIN VALUES ALSO TENDED TO BE DEPRESSED, ESPECIALLY IN THE HIGH-DOSE FEMALES, BUT STATISTICAL SIGNIFICANCE WAS NOT ATTAINED. ALKALINE PHOSPHATASE VALUES WERE INCREASED IN BOTH SEXES OF THE HIGH DOSE THROUGHOUT THE STUDY (STATISTICALLY SIGNIFICANT AT ALL TIME POINTS IN THE FEMALE, BUT ONLY AT WEEK 51 FOR MALES). THE MID-DOSE FEMALES DISPLAYED A SIMILAR INCREASE OF LESSER MAGNITUDE, BUT STATISTICAL SIGNIFICANCE WAS NOT ATTAINED. THE MID-DOSE MALES DISPLAYED AN INCREASE ONLY AT THE 51-WEEK TIME POINT, WHICH WAS NOT STATISTICALLY SIGNIFICANT. CALCIUM LEVELS WERE DECREASED ($P<0.01$) AT THE 13-WEEK TIME POINT IN BOTH SEXES OF THE HIGH DOSE AND AT THE 25-WEEK TIME POINT IN THE HIGH-DOSE MALES. ALAT VALUES FOR THE HIGH-DOSE MALES WERE ELEVATED AT ALL TIME POINTS DURING THE STUDY COMPARED WITH CONTROL VALUES, BUT STATISTICAL SIGNIFICANCE WAS ATTAINED ONLY AT WEEK 51. SIMILAR EFFECTS WERE NOT OBSERVED IN THE FEMALES. GLOB % WAS ELEVATED SIGNIFICANTLY IN THE HIGH-DOSE (BOTH SEXES) AT WEEKS 13 AND 25, AND IN THE HIGH-DOSE MALES AT WEEK 38. TRIGLYCERIDE VALUES WERE SIGNIFICANTLY DEPRESSED IN THE HIGH-DOSE FEMALE AT WEEKS 13 AND 38.

CLINICAL CHEMISTRY VALUES (% OF CONTROL)

PARAMETER	GROUP	WEEK -1	WEEK 13	WEEK 25	WEEK 38	WEEK 51
MALES	CONTROL	59	65	69	70	67
T. PROTEIN G/L	LOW	58(98)	63(97)	67(98)	68(97)	66(99)
	MID	58(98)	62(96)	69(101)	67(95)	66(98)
	HIGH	58(99)	56(86)**	61(89)**	59(85)**	62(92)
ALBUMIN G/L	CONTROL	25.7	28.6	31.3	30.1	32.9
	LOW	25.7(100)	27.8(97)	30.1(96)	28.4(94)	31.0(94)
	MID	25.3(98)	26.9(94)	29.0(93)	27.0(90)	30.3(92)
	HIGH	23.6(92)	21.2(76)**	23.6(76)**	20.2(67)**	25.6(78)**
CHOLESTEROL MMOL/L	CONTROL	2.89	3.82	3.29	3.48	3.59
	LOW	2.66(92)	2.96(78)	2.93(89)	3.04(87)	3.38(94)
	MID	2.39(83)	2.76(72)	2.80(85)	2.56(74)	3.05(85)
	HIGH	2.37(82)	1.38(36)**	1.80(55)	1.72(49)*	2.07(58)
BILIRUBIN UMOL/L	CONTROL	1.453	1.557	1.570	1.608	1.648
	LOW	1.495(103)	1.403(90)	1.648(105)	2.140(133)	1.708(104)
	MID	1.413(97)	1.420(91)	0.918(58)	1.713(107)	1.570(95)
	HIGH	1.565(108)	1.185(76)	1.500(96)	1.300(81)	1.340(81)
ALKALINE PHOSPHATASE U/L	CONTROL	403.3	298.0	137.8	126.6	96.1
	LOW	273.0(65)	169.0(57)	105.4(76)	107.4(85)	80.5(84)
	MID	299.5(69)	206.3(69)	140.8(102)	128.8(102)	117.4(122)
	HIGH	268.0(61)	380.3(128)	287.8(209)	362.3(286)	375.5(391)**
ALAT U/L	CONTROL	20.28	21.77	27.98	32.53	28.85
	LOW	24.38(120)	25.15(116)	28.10(100)	29.48(91)	27.00(94)
	MID	21.03(104)	25.08(115)	27.43(98)	27.83(86)	27.13(94)
	HIGH	19.10(94)	38.58(177)	40.05(143)	46.85(144)	48.57(16)
CALCIUM MMOL/L	CONTROL	2.740	2.698	2.675	2.545	2.593
	LOW	2.725(99)	2.608(97)	2.543(95)	2.425(95)	2.505(97)
	MID	2.628(96)	2.578(96)	2.528(95)	2.403(94)	2.483(96)
	HIGH	2.673(98)	2.408(89)**	2.400(90)**	2.353(92)	2.473(95)
GLOB. % %	CONTROL	56.55	56.11	54.68	57.14	51.17
	LOW	55.78(99)	55.82(99)	55.22(101)	58.22(102)	53.38(104)
	MID	56.26(99)	56.94(101)	58.23(106)	59.31(104)	54.06(106)
	HIGH	59.64(105)	62.14(111)*	61.50(112)*	65.99(115)*	58.56(114)

PARAMETER	GROUP	WEEK -1	WEEK 13	WEEK 25	WEEK 38	WEEK 51
FEMALES	CONTROL	58.4	62.3	63.9	72	65.2
T. PROTEIN G/L	LOW	59.8(102)	62.3(100)	68.1(107)	65.5(91)	64.7(99)
	MID	55.6(95)	59.4(95)	62.2(97)	63.6(88)	62.9(97)
	HIGH	59.9(103)	54.4(87)*	59.1(92)	58.3(81)	59.3(91)
ALBUMIN G/L	CONTROL	27.7	29.4	30.2	30.1	32.0
	LOW	27.3(99)	30.4(103)	29.6(98)	29.8(99)	30.7(96)
	MID	24.6(89)	28.3(96)	28.5(94)	27.9(93)	29.7(93)
	HIGH	26.9(97)	21.5(73)**	24.3(80)**	23.6(78)*	26.4(83)**
CHOLESTEROL MMOL/L	CONTROL	3.03	4.23	4.11	4.75	5.35
	LOW	2.87(94)	3.49(82)	5.19(126)	3.53(74)	4.56(85)
	MID	2.44(80)	3.98(94)	3.79(92)	4.79(101)	4.59(86)
	HIGH	2.51(83)	2.05(48)**	2.76(67)	2.45(52)**	2.80(52)*

PARAMETER	GROUP	WEEK -1	WEEK 13	WEEK 25	WEEK 38	WEEK 51
BILIRUBIN UMOL/L	CONTROL	1·815	2·013	1·925	2·550	2·090
	LOW	1·743(96)	1·950(97)	1·620(84)	1·955(77)	1·860(89)
	MID	1·673(92)	1·703(85)	1·320(69)	2·265(89)	1·803(86)
	HIGH	1·933(107)	1·368(68)	1·528(79)	1·455(57)	1·393(67)
ALKALINE PHOSPHATASE U/L	CONTROL	226·0	146·6	122·0	137·5	108·9
	LOW	197·8(88)	139·8(95)	105·6(87)	118·7(86)	98·6(91)
	MID	229·0(101)	216·8(148)	164·5(135)	158·5(115)	152·8(140)
	HIGH	248·3(110)	407·8(278)*	366·8(301)**	407·8(297)*	342·8(316)**
ALAT U/L	CONTROL	22·48	17·75	19·58	21·65	20·88
	LOW	21·08(94)	20·53(116)	16·30(83)	22·75(105)	17·80(85)
	MID	23·65(105)	20·90(118)	21·55(110)	22·65(105)	22·20(106)
	HIGH	22·23(99)	21·45(121)	22·13(113)	22·43(109)	22·85(109)
CALCIUM MMOL/L	CONTROL	2·628	2·665	2·465	2·323	2·540
	LOW	2·703(103)	2·635(99)	2·530(103)	2·348(94)	2·548(100)
	MID	2·603(99)	2·630(99)	2·455(100)	2·308(94)	2·578(101)
	HIGH	2·620(100)	2·455(92)**	2·318(94)	2·193(89)	2·365(93)
GLOB· % %	CONTROL	52·65	52·78	52·74	57·25	50·72
	LOW	54·44(103)	51·20(97)	56·52(107)	54·41(95)	52·56(104)
	MID	55·79(106)	52·39(99)	54·21(103)	56·12(98)	52·63(104)
	HIGH	55·18(105)	60·54(115)**	58·91(112)*	59·35(104)	55·43(109)

* $p<0.05$
** $p<0.01$

6. URINALYSIS

URINE WAS COLLECTED (AFTER A 16-18 HOUR FAST) FROM ALL ANIMALS PRE-DOSE, AND AT 3, 6, AND 9 MONTHS, AND PRIOR TO STUDY TERMINATION. THE CHECKED (X) PARAMETERS WERE EXAMINED.

	APPEARANCE*	X	GLUCOSE*
	VOLUME*	X	KETONES*
X	SPECIFIC GRAVITY*	X	BILIRUBIN*
X	PH	X	BLOOD*
X	SEDIMENT (MICROSCOPIC)*		NITRATE
X	PROTEIN*	X	UROBILINOGEN
	OSMOLALITY		

* REQUIRED FOR CHRONIC STUDIES

RESULTS

THERE WERE SPORADIC STATISTICALLY SIGNIFICANT ALTERATIONS IN A FEW URINARY PARAMETERS COMPARED TO CONTROL VALUES, BUT NONE THAT COULD BE ATTRIBUTED TO TREATMENT. THE pH OF THE HIGH-DOSE MALES WAS MORE ALKALINE THAN THE CONTROL VALUE AT WEEKS 12, 25, AND 38, BUT STATISTICAL SIGNIFICANCE WAS NOT ATTAINED.

GROSS PATHOLOGY

ALL ANIMALS WERE SACRIFICED AT STUDY TERMINATION AND WERE SUBJECTED TO GROSS PATHOLOGICAL EXAMINATION. ALL DOGS WERE EXAMINED EXTERNALLY BOTH VISUALLY AND

BY PALPATION, WITH PARTICULAR ATTENTION BEING PAID TO THE EYES, NOSE, BUCCAL CAVITY, EXTERNAL GENITALIA, AND ANUS. A MACROSCOPIC EXAMINATION WAS PERFORMED AFTER OPENING ALL CAVITIES AND OBSERVING THE TISSUES IN SITU. THE FOLLOWING ORGANS WERE WEIGHED:

ADRENAL	LIVER	SPLEEN
BRAIN	OVARIES	TESTES
KIDNEY	PITUITARY	THYROID WITH PARATHYROID

RESULTS

TWO HIGH-DOSE MALES DISPLAYED ENLARGED LIVERS AT NECROPSY, WITH PRONOUNCED LOBULAR PATTERNING. NO OTHER TREATMENT-RELATED FINDINGS WERE REPORTED.

ABSOLUTE AND RELATIVE LIVER WEIGHT WERE SIGNIFICANTLY INCREASED IN THE HIGH-DOSE MALES COMPARED TO CONTROLS. HIGH-DOSE FEMALES ALSO DISPLAYED AN INCREASE IN LIVER WEIGHT (BOTH ABSOLUTE AND RELATIVE), BUT A $P<0.05$ WAS NOT ATTAINED.

ABSOLUTE KIDNEY WEIGHT WAS SLIGHTLY INCREASED IN THE LOW- AND HIGH-DOSE FEMALES, BUT STATISTICAL SIGNIFICANCE WAS NOT ATTAINED. RELATIVE KIDNEY WEIGHT WAS SIGNIFICANTLY INCREASED IN BOTH THE LOW- AND HIGH-DOSE FEMALE GROUPS.

ABSOLUTE THYROID WEIGHT OF THE FEMALES SHOWED A SLIGHT INCREASE WITH DOSE, BUT THIS WAS NOT DOSE-RELATED. RELATIVE THYROID WEIGHT INCREASED WITH INCREASING DOSE, BUT THIS DID NOT ATTAIN STATISTICAL SIGNIFICANCE.

THE PITUITARY WAS ALSO FOUND TO BE HEAVIER IN THE HIGH-DOSE ANIMALS COMPARED TO THE RESPECTIVE CONTROLS, BUT STATISTICAL SIGNIFICANCE WAS NOT ATTAINED.

ORGAN WEIGHTS

	LIVER		KIDNEY		THYROID		PITUITARY	
	ABSOLUTE GRAMS	RELATIVE %	ABSOLUTE GRAMS	RELATIVE %	ABSOLUTE GRAMS	RELATIVE %	ABSOLUTE GRAMS	RELATIVE %
MALES								
CONTROL	251	2.34	45.0	0.43	0.79	0.0073	61.8	0.57
LOW	279	2.26	54.3	0.44	0.75	0.0061	84.8	0.69
MID	296	2.47	50.5	0.42	0.73	0.0061	67.0	0.56
HIGH	400**	3.64*	53.8	0.49	0.86	0.0077	75.3	0.68
FEMALES								
CONTROL	258	2.76	33.8	0.36	0.66	0.0070	89.5	0.96
LOW	297	3.24	37.4	0.41*	0.67	0.0073	82.5	0.89
MID	282	2.78	34.7	0.36	0.82	0.0080	70.8	0.69
HIGH	290	3.39	36.7	0.43*	0.77	0.0091	111.0	1.31

* $P<0.05$
** $P<0.01$

Liver Chemistry

At necropsy, liver samples were taken from all dogs for analysis of P_{450} content, glutathione content (GSH), glutathione-S-transferase activity (GST), and p-aminophenol hydroxylase activity (PAP).

Results

High-dose dogs of both sexes and mid-dose females displayed statistically significant increases in cytochrome P_{450} (see attached Special Liver Chemistry table). Measurement of PAP indicated no induction of activity with increasing dose (although the low-dose female value was significantly elevated above control value by the Dunnett's t-test performed by this reviewer). The author indicated that since PAP shows a slightly greater specificity of induction potential with P_{448} inducers, the data suggest that the test material is a P_{450} inducer and not a P_{448} inducer (often a marker of carcinogenic potential). There was no dose-related effect reported for either sex on GSH or GST, although statistical significance was reported in the mid-dose animals of both sexes for GSH. This reviewer found a dose-related decrease ($p<0.05$) in GST values in the mid- and high-dose females using Dunnett's t-test.

Histopathology

The following CHECKED (X) tissues/organs were collected from all animals.

	Digestive System
	Tongue
X	Salivary glands*
X	Esophagus*
X	Stomach*
X	Duodenum*
X	Jejunum*
X	Ileum*
X	Cecum*
X	Colon*
X	Rectum*
X	Liver*†
X	Gall bladder*
X	Pancreas*

	Respiratory
X	Trachea*
X	Lung*
	Nose
	Pharynx
	Larynx

	Cardiovasc./Hemat.
X	Aorta*
X	Heart*
	Bone marrow*
X	Lymph nodes*
X	Spleen*
X	Thymus*

	Urogenital
X	Kidneys*†
X	Urinary bladder*
X	Testes*†
X	Epididymides
X	Prostate
X	Seminal vesicle
X	Ovaries*†
X	Uterus*
	Cervix
X	Vagina

	Neurologic
X	Brain*†
X	Periph. nerve* (sciatic)
X	Spinal cord (3 levels)*
X	Pituitary*
X	Eyes (optic n.)*

	Glandular
X	Adrenals*
	Lacrimal gland
X	Mammary gland*
X	Parathyroids*††
X	Thyroids*††

	Other
X	Bone* (sternum/femur)
X	Skeletal muscle*
X	Skin*
X	All gross lesions and masses*
	Head

* Required for chronic studies
† Organ weights required in chronic studies/†† for non-rodent studies

RESULTS

THE LIVER WAS SHOWN TO BE THE TARGET ORGAN. LAMINAR EOSINOPHILIC INTRAHEPATOCYTIC BODIES WERE OBSERVED IN ALL HIGH-DOSE MALES AND IN ONE MID-DOSE MALE. TWO HIGH-DOSE FEMALES ALSO DISPLAYED THESE BODIES. TWO HIGH-DOSE MALES DISPLAYED CANALICULAR BILE PLUGS, AND ONLY TREATED MALES SHOWED AN INCREASE IN INTRAHEPATIC PIGMENT.

OTHER OBSERVATIONS INCLUDE ONE HIGH-DOSE FEMALE WITH IMMATURE OVARIES AND ONE MID-DOSE MALE WITH DEGENERATION OF THE TESTICULAR GERMINAL EPITHELIUM. SINCE THIS FEMALE HAD NOT SHOWN ANY SIGN OF ESTROUS CYCLING DURING THE STUDY, THE AUTHOR STATED THAT IT WOULD BE IMPRUDENT TO DISMISS THE POSSIBILITY OF THIS FINDING BEING A CONSEQUENCE OF STEROID BIOSYNTHESIS INHIBITION.

CONCLUSION:

THERE WERE NO DIFFERENCES OBSERVED IN SURVIVAL, OPHTHALMOSCOPIC PARAMETERS, OR HEMATOLOGIC PARAMETERS FOLLOWING THE ADMINISTRATION (DIET) OF SAN 619 F TO BEAGLE DOGS FOR 52 WEEKS AT DOSE LEVELS OF 30, 100, AND 350 PPM [1.0, 3.2, AND 12.1 (MALES); 12.6 (FEMALES) MG/KG/DAY, RESPECTIVELY].

BODY WEIGHT GAIN WAS LOWER IN THE HIGH-DOSE ANIMALS COMPARED WITH CONTROL, ALTHOUGH THE MAGNITUDE OF THE DIFFERENCE WAS NOT GREAT. THERE WERE DOSE-RELATED INCREASES IN PLATELETS THROUGHOUT THE STUDY IN BOTH SEXES, ALTHOUGH STATISTICAL SIGNIFICANCE WAS NOT ALWAYS ATTAINED. PROTHROMBIN TIMES WERE CHECKED AT WEEK 48 AND WERE SLIGHTLY ELEVATED IN THE MID-DOSE MALES AND THE HIGH-DOSE ANIMALS.

DIFFERENCES OBSERVED IN SEVERAL CLINICAL LABORATORY PARAMETERS BETWEEN THE CONTROL AND TREATED ANIMALS ARE CONSISTENT WITH EFFECTS ON THE LIVER (ELEVATED ALKALINE PHOSPHATASE AND ALAT LEVELS; DECREASED TOTAL PROTEIN, ALBUMIN, AND CHOLESTEROL LEVELS).

ABSOLUTE AND RELATIVE LIVER WEIGHTS WERE INCREASED IN THE HIGH-DOSE ANIMALS OF BOTH SEXES COMPARED TO CONTROLS, BUT STATISTICAL SIGNIFICANCE WAS ATTAINED ONLY IN THE MALES. RELATIVE KIDNEY WEIGHT WAS INCREASED (SIGNIFICANTLY) IN BOTH THE LOW- AND HIGH-DOSE FEMALES.

STATISTICALLY SIGNIFICANT INCREASES WERE OBSERVED IN CYTOCHROME P450 IN BOTH SEXES OF THE HIGH-DOSE AND IN THE MID-DOSE FEMALES. LAMINAR EOSINOPHILIC INTRAHEPATOCYTIC BODIES WERE OBSERVED IN ALL HIGH-DOSE MALES, ONE MID-DOSE MALE, AND TWO HIGH-DOSE FEMALES AND WERE CONSIDERED TO REPRESENT ADAPTIVE HYPERTROPHY OF THE ENDOPLASMIC RETICULUM.

THE NOEL CAN BE SET AT 30 PPM (1.0 MG/KG/DAY) AND THE LEL AT 100 PPM (3.2 MG/KG/DAY), BASED ON LIVER EFFECTS.

CYPROCONAZOLE Tox review 007871

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