In the Segment II teratology study in rats (report #93/GYS006/054), rats were treated by oral gavage at 0, 120, 600 and 2000 mg/kg/day from gestation days 6 though 17. Two-thirds of pregnant rats were sacrificed on day 20 of gestation and the remaining one-third of the dams were allowed to deliver and rear their offspring. The body weight and food consumption of the dams were not affected. No teratogenic potential was identified in all groups. No adverse effects on postnatal development and fertility of the offspring were seen at doses up to the high dose (2000 mg/kg/day). In conclusion, BSZ was not teratogenic in this study.

In the Segment II teratology study in rabbits (report #93/GYS009/0802), rabbits were treated by oral gavage at 0, 120, 600 and 1200 mg/kg/day from gestation days 6 through 19. No teratogenic potential was seen at doses up to high dose (1200 mg/kg/day).

In the Segment III perinatal and postnatal study in rats (report #93/GYS008/0618), rats were treated by oral gavage at 0, 120, 600 and 2000 mg/kg/day from gestation day 15 through day 25 after parturition. There were no treatment related changes in clinical signs of toxicity, body weight and food consumption. There were no adverse effects on dams and fetuses (F1 and F2). In conclusion, perinatal and postnatal performance were not adversely affected by oral administration of BSZ at doses up to 2000 mg/kg/day.

Following mutagenicity studies were conducted: for BSZ, Ames tests, *in vitro* chromosomal aberration test in human lymphocytes, *in vivo* mouse micronucleus test, CHO/HGPRT forward gene mutation test, L5178Y mouse lymphoma cells assay; for 4-ABA, Ames test, L5178Y mouse lymphoma cells assay, *in vitro* chromosomal aberration test in human lymphocytes and for N-acetyl-4-ABA, Ames test, L5178Y mouse lymphoma cells assay and *in vitro* chromosomal aberration test in human lymphocytes. BSZ was not mutagenic when tested in the Ames test, *in vitro* chromosomal aberration test in human lymphocytes and *in vivo* mouse micronucleus test. However, BSZ had mutagenic potential in CHO/HGPRT forward gene mutation test. To confirm this, sponsor conducted a forward gene mutation test at tk locus in L5178Y mouse lymphoma cells in response to our request and the results indicated that BSZ was not mutagenic in this test. 4-ABA was not mutagenic in Ames test, L5178Y mouse lymphoma cells assay but had clastogenic activity in the *in vitro* chromosomal aberration test in human lymphocytes. N-acetyl-4-ABA was not mutagenic in the Ames test, L5178Y mouse lymphoma cells assay and *in vitro* chromosomal aberration test in human lymphocytes.

The toxicity of BSZ was adequately studies in rats (26-week oral study), in ferrets (26-week oral study) and in dogs (52-week oral study). Following target organs of toxicity were identified in rats: stomach (gastritis), kidney (corticomedullary mineralization and papillary urothelial hyperplasia and mineralization) and bladder (urothelial hyperplasia). Increased incidence of renal pelvic mineralization, tubular dilatation, urothelial hyperplasia, hydronephrosis, urinary bladder distention, cystitis and prostatitis were also seen in the 104-week dietary carcinogenicity study in rats. However, these changes were not seen in other species such as ferrets and dogs. The target organs of toxicity were not identified in ferrets and dogs.

RECOMMENDATION:

From a preclinical standpoint, this NDA is approvable. Sponsor should be asked to revise the labeling as recommended.

/S/ 11/3/97
Ke Zhang, Ph.D.

/S/ 11/4/97

cc:
NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Choudary
HFD-180/Dr. Talarico
HFD-180/Dr. Zhang
HFD-345/Dr. Viswanathan

R/D Init.: J. Choudary 9/19/97

KZ/hw/10/2/97, 10/7/97 & 10/23/97
C:\WPFILES\PHARM\N\20610709.0KZ

Attachments: APPENDIX I: Tumor and Non-tumor Data for 104-Week Dietary Carcinogenicity Study in Rats

APPENDIX I

Tumor and Non-tumor Data for 104-Week Dietary
Carcinogenicity Study in Rats
(Study # 1067/6-1050)

TABLE 9.6
Group incidence: histopathology data - all animals - neoplastic

Dose levels (mg/kg/day): Gp 1 = 0, Gp 2 = 120, Gp 3 = 600, Gp 4 = 2000, Gp 5 = 0

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STUDY NUMBER: 10676

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=B,M;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		--- NUMBER OF ANIMALS AFFECTED ---									
SEX:		----------MALE----------					---------FEMALE---------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:		60	60	60	60	60	60	60	60	60	60
** TOP OF LIST **											
SKIN SUBCUTIS	NUMBER EXAMINED:	60	52	58	60	60	60	59	57	60	60
--B-FIBROMA		8	8	8	4	12	5	2	1	2	2
--B-DERMAL FIBROMA		15	6	8	7	13	0	0	0	0	0
--B-NEUROFIBROMA		0	0	0	0	0	1	0	0	0	0
--B-LIPOMA		5	3	3	3	5	2	3	0	0	4
--B-FIBROLIPOMA		1	0	0	0	2	0	0	0	0	0
--B-SQUAMOUS CELL PAPILLOMA		3	1	1	1	0	0	1	0	0	0
--B-BASAL CELL ADENOMA		2	1	2	0	0	1	0	0	1	0
--B-KERATOACANTHOMA		10	6	8	6	10	1	0	2	2	0
--M-SARCOMA		1	2	4	5	3	1	0	0	0	0
--M-FIBROSARCOMA		0	2	1	2	0	0	0	0	0	0
--M-HISTIOCYTIC SARCOMA		0	1	0	1	0	0	1	0	1	1
--M-SQUAMOUS CELL CARCINOMA		0	0	0	0	0	0	1	0	0	1
MAMMARY GLAND	NUMBER EXAMINED:	3	3	5	1	4	60	58	57	60	59
--B-FIBROADENOMA		1	1	2	0	3	37	32	35	31	33
--B-ADENOMA		0	0	0	0	0	1	0	2	2	3
--B-ADENOLIPOMA		0	0	0	0	0	0	1	0	0	0
--M-CARCINOMA		0	0	0	0	0	7	2	4	1	7
LIVER	NUMBER EXAMINED:	60	49	54	60	60	60	52	48	60	60
--B-HEPATOCELLULAR ADENOMA		4	1	2	1	1	0	0	1	0	1
SPLEEN	NUMBER EXAMINED:	60	42	49	60	60	60	47	45	59	60
--B-HAEMANGIOMA		1	0	0	0	1	0	0	0	0	0
--M-SARCOMA		0	0	0	0	0	0	0	0	0	1
--M-HAEMANGIOSARCOMA		0	0	0	0	1	0	0	0	0	0
PANCREAS	NUMBER EXAMINED:	60	41	47	60	59	60	46	45	59	60
--B-ACINAR CELL ADENOMA		1	0	0	0	0	0	0	0	0	0

** CONTINUED ON NEXT PAGE **

TABLE 9.6
Group Incidence: histopathology data - all animals - neoplastic

Dose levels (mg/kg/day): Gp 1 = 0, Gp 2 = 120, Gp 3 = 600, Gp 4 = 2000, Gp 5 = 0

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STUDY NUMBER: 10676

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=B,M;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		--- NUMBER-OF-ANIMALS-AFFECTED ---									
SEX:		----------MALE----------					---------FEMALE--------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:		60	60	60	60	60	60	60	60	60	60
** FROM PREVIOUS PAGE **											
PANCREAS	NUMBER EXAMINED:	60	41	47	60	59	60	46	45	59	60
--B-ISLET CELL ADENOMA		2	3	2	4	3	2	2	1	0	2
--M-ISLET CELL CARCINOMA		0	0	2	1	1	0	0	0	1	1
MES.LYMPH NODE	NUMBER EXAMINED:	60	41	48	60	60	60	46	45	59	60
--B-HAEMANGIOMA		0	0	2	0	1	0	0	0	0	0
--B-LYMPHANGIOMA		1	0	0	0	0	0	0	0	0	0
STOMACH	NUMBER EXAMINED:	56	41	44	58	54	60	47	45	58	59
--B-SQUAMOUS CELL PAPILLOMA		0	1	0	0	0	0	0	0	0	0
ADRENAL	NUMBER EXAMINED:	60	60	60	60	60	60	48	46	60	60
--B-BENIGN PHAEOCHROMOCYTOMA		8	8	9	18	4	3	2	0	4	3
--B-ADENOMA		0	0	1	0	1	1	0	1	0	0
--M-CARCINOMA		0	0	1	1	0	0	0	1	1	0
--M-MALIGNANT PHAEOCHROMOCYTOMA		2	0	1	1	1	0	0	0	1	0
KIDNEY	NUMBER EXAMINED:	60	60	60	60	60	60	60	60	60	60
--B-LIPOMA		0	0	0	0	0	0	0	0	1	0
--M-NEPHROBLASTOMA		0	0	0	0	0	0	0	0	1	0
--M-TUBULAR CELL CARCINOMA		0	0	0	0	1	0	0	0	0	0
--M-MESENCHYMAL TUMOUR		0	1	0	0	0	0	0	0	0	0
--M-LIPOSARCOMA		0	0	0	0	0	0	1	2	0	0
TESTIS	NUMBER EXAMINED:	60	46	51	60	60	0	0	0	0	0
--B-HAEMANGIOMA		0	0	0	0	1	0	0	0	0	0
--B-INTERSTITIAL CELL ADENOMA		4	3	3	3	2	0	0	0	0	0
--M-MALIGNANT MESOTHELIOMA		0	0	0	0	1	0	0	0	0	0

TABLE 9.6
Group incidence: histopathology data - all animals - neoplastic

Dose levels (mg/kg/day): Gp 1 = 0, Gp 2 = 120, Gp 3 = 600, Gp 4 = 2000, Gp 5 = 0

STUDY NUMBER: 10676

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=B,M;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		--- NUMBER-OF-ANIMALS-AFFECTED ---									
SEX:		----------MALE----------					---------FEMALE---------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:		60	60	60	60	60	60	60	60	60	60
OVARY	NUMBER EXAMINED:	0	0	0	0	0	60	50	52	60	59
--B-BENIGN GRANULOSA CELL TUMOUR		0	0	0	0	0	2	0	0	0	0
--B-GRANULOSA-THECA TUMOUR		0	0	0	0	0	0	1	0	0	0
--B-BENIGN MESOTHELIOMA		0	0	0	0	0	0	0	0	0	1
--B-TUBULOSTROMAL ADENOMA		0	0	0	0	0	0	0	1	0	1
URINARY BLADDER	NUMBER EXAMINED:	59	42	47	60	59	59	47	45	60	60
--B-TRANSITIONAL CELL PAPILLOMA		0	0	0	0	0	0	0	0	0	1
--M-TRANSITIONAL CELL CARCINOMA		0	0	1	0	0	0	0	0	0	0
PROSTATE	NUMBER EXAMINED:	60	42	49	60	59	0	0	0	0	0
--M-CARCINOMA		1	1	0	0	0	0	0	0	0	0
UTERUS	NUMBER EXAMINED:	0	0	0	0	0	60	50	47	60	60
--B-POLYP		0	0	0	0	0	3	2	2	4	3
--M-CARCINOMA		0	0	0	0	0	0	0	0	1	0
--M-STROMAL SARCOMA		0	0	0	0	0	0	0	0	1	0
--M-GRANULAR CELL TUMOUR		0	0	0	0	0	0	0	0	0	1
--M-MALIGNANT SCHWANNOMA		0	0	0	0	0	0	1	0	1	0
THYMUS	NUMBER EXAMINED:	53	40	44	56	57	59	44	45	57	58
--B-THYMOMA		0	0	1	0	1	2	3	1	2	1
LUNG	NUMBER EXAMINED:	60	47	49	60	60	60	51	49	60	60
--B-BRONCHIOLO-ALVEOLAR ADENOMA		0	1	1	0	0	0	0	0	0	0
--M-BRONCHIOLO-ALVEOLAR CARCINOMA		0	0	0	0	0	0	0	0	1	0
HEART	NUMBER EXAMINED:	60	43	49	60	60	60	47	45	60	60
--B-SCHWANNOMA		0	0	0	0	0	0	0	1	0	1
--B-HAEMANGIOMA		0	0	0	0	0	0	0	0	1	0

** CONTINUED ON NEXT PAGE **

TABLE 9.6
Group Incidence: histopathology data - all animals - neoplastic

Dose levels (mg/kg/day): Gp 1 = 0, Gp 2 = 120, Gp 3 = 600, Gp 4 = 2000, Gp 5 = 0

STUDY NUMBER: 10676

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=B,M;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		--- NUMBER OF ANIMALS AFFECTED ---									
SEX:		----------MALE----------					---------FEMALE--------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:		60	60	60	60	60	60	60	60	60	60
** FROM PREVIOUS PAGE **											
HEART	NUMBER EXAMINED:	60	43	49	60	60	60	47	45	60	60
--M-MALIGNANT SCHWANNOMA		0	1	0	0	0	0	0	0	0	0
THYROID	NUMBER EXAMINED:	55	39	41	57	58	59	45	44	58	57
--B-C-CELL ADENOMA		11	4	5	4	8	10	5	2	9	5
--B-FOLLICULAR CELL ADENOMA		5	0	1	1	3	0	1	0	0	0
--M-C-CELL CARCINOMA		0	0	0	0	0	0	1	0	2	1
PARATHYROID	NUMBER EXAMINED:	56	42	44	55	58	56	45	44	56	57
--B-ADENOMA		0	0	0	1	0	0	0	0	0	0
PITUITARY	NUMBER EXAMINED:	60	45	53	60	60	60	58	55	60	59
--B-ADENOMA		28	26	26	23	27	47	44	41	47	44
--M-CARCINOMA		0	0	0	0	0	1	2	4	0	1
BRAIN	NUMBER EXAMINED:	60	42	48	60	60	60	47	45	60	59
--B-MENINGIOMA		2	0	0	2	0	3	0	0	0	0
--M-GLIOMA		0	2	0	1	1	0	0	0	0	0
SPINAL CORD	NUMBER EXAMINED:	60	42	48	60	60	60	47	45	60	60
--M-GLIOMA		0	0	0	1	0	0	1	0	0	0
HAEM/LYMPH/RETIC	NUMBER EXAMINED:	60	42	49	60	60	60	47	45	60	60
--M-LYMPHOMA-LYMPHOCYTIC		0	0	1	1	0	0	0	0	1	1
--M-LEUKAEMIA-LYMPHOCYTIC		4	0	1	3	2	1	0	0	0	3
FOOT/LEG	NUMBER EXAMINED:	12	14	13	8	10	2	11	6	2	6
--M-SARCOMA		0	0	1	1	0	0	0	0	0	0

HE Study no 10676

TABLE 9.6
Group incidence: histopathology data - all animals - neoplastic

Dose levels (mg/kg/day): Gp 1 = 0, Gp 2 = 120, Gp 3 = 600, Gp 4 = 2000, Gp 5 = 0

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STUDY NUMBER: 10676

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=B,M;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		--- NUMBER-OF-ANIMALS-AFFECTED ---									
SEX:		----------MALE----------					---------FEMALE--------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:		60	60	60	60	60	60	60	60	60	60
TAIL	NUMBER EXAMINED:	26	21	32	45	22	27	26	31	25	21
--B-FIBROMA		1	0	0	0	0	0	0	0	0	0
--B-SQUAMOUS CELL PAPILLOMA		0	2	0	1	0	0	0	0	0	0
ORAL CAVITY	NUMBER EXAMINED:	2	2	5	4	4	11	7	11	9	7
--M-SQUAMOUS CELL CARCINOMA		0	0	1	0	0	0	0	0	0	0
EAR	NUMBER EXAMINED:	10	7	11	6	9	9	11	6	10	3
--B-NEUROFIBROMA		0	0	1	0	0	0	1	0	0	0
THORACIC CAVITY	NUMBER EXAMINED:	2	3	3	7	2	1	0	2	2	1
--M-MESOTHELIOMA		0	0	0	0	0	0	0	0	1	0
ABDOMINAL CAVITY	NUMBER EXAMINED:	2	3	4	2	2	1	1	1	1	2
--B-LIPOMA		1	0	0	0	0	0	0	0	0	0
--M-CARCINOMA		0	0	0	0	0	1	0	0	0	0
--M-SARCOMA		0	0	1	0	1	0	0	0	0	0
--M-SCHWANNOMA		0	0	1	0	0	0	0	0	0	0
BONE	NUMBER EXAMINED:	0	0	1	3	0	0	1	0	0	1
--B-FIBROMA		0	0	1	0	0	0	0	0	0	0
--M-OSTEOSARCOMA		0	0	0	2	0	0	1	0	0	1
--M-SARCOMA		0	0	0	1	0	0	0	0	0	0
CONNECTIVE TISS	NUMBER EXAMINED:	0	0	0	0	1	0	1	1	0	0
--M-HISTIOCYTIC SARCOMA		0	0	0	0	1	0	1	1	0	0
PREPUT/CLIT GL	NUMBER EXAMINED:	1	0	0	1	2	3	1	1	0	2
--M-CARCINOMA		0	0	0	0	0	1	0	0	0	0

TABLE 9.6
Group incidence: histopathology data - all animals - neoplastic

Dose levels (mg/kg/day): Gp 1 = 0, Gp 2 = 120, Gp 3 = 600, Gp 4 = 2000, Gp 5 = 0

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PAGE: 6

STUDY NUMBER: 10676

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=D,M;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		--- NUMBER OF ANIMALS AFFECTED ---									
	SEX:	----------MALE----------					---------FEMALE---------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
	NUMBER:	60	60	60	60	60	60	60	60	60	60
CRANIAL CAVITY	NUMBER EXAMINED:	0	0	0	0	1	0	0	0	0	0
--D-OSTEOMA		0	0	0	0	1	0	0	0	0	0

** END OF LIST **

APPEARS THIS WAY
ON ORIGINAL

TABLE 9.2
Group incidence: histopathology data - terminal kill - non-neoplastic
Dose levels (mg/kg/day): Gp 1 = 0, Gp 2 = 120, Gp 3 = 600, Gp 4 = 2000, Gp 5 = 0

STUDY NUMBER: 10676

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=T;FIND=P;SUBSET=T

ORGAN AND FINDING DESCRIPTION		--- NUMBER-OF-ANIMALS-AFFECTED ---									
SEX:		----------MALE----------					----------FEMALE----------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:		25	18	13	28	19	13	14	15	27	17
RECTUM	NUMBER EXAMINED:	0	0	0	0	0	0	0	0	0	1
--NO EQUIVALENT SAMPLE		0	0	0	0	0	0	0	0	0	1
SCIATIC NERVE	NUMBER EXAMINED:	2	0	1	0	1	0	0	0	0	0
--NEUROPATHY		2	0	1	0	1	0	0	0	0	0
VAS DEFERENS	NUMBER EXAMINED:	0	0	1	0	0	0	0	0	0	0
--CONGESTION /HAEMORRHAGE		0	0	1	0	0	0	0	0	0	0
PREPUT/CLIT GL	NUMBER EXAMINED:	1	0	0	0	2	1	0	0	0	1
--CYSTIC DISTENSION		0	0	0	0	1	1	0	0	0	1
--ABSCESS		1	0	0	0	1	0	0	0	0	0
JOINT	NUMBER EXAMINED:	1	0	0	0	0	0	0	0	0	0
--ARTHROPATHY		1	0	0	0	0	0	0	0	0	0
TRIGEMINAL NERVE	NUMBER EXAMINED:	0	1	0	0	0	0	0	0	0	0
--NEUROPATHY		0	1	0	0	0	0	0	0	0	0

** END OF LIST **

TABLE 9.3
Group incidence: histopathology data - all animals - non-neoplastic

Dose levels (mg/kg/day): Gp 1 = 0, Gp 2 = 120, Gp 3 = 600, Gp 4 = 2000, Gp 5 = 0

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PAGE: 1

STUDY NUMBER: 10676

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=P;SUBSET=T

ORGAN AND FINDING DESCRIPTION		--- NUMBER-OF-ANIMALS-AFFECTED ---									
SEX:		----------MALE----------					----------FEMALE----------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:		60	60	60	60	60	60	60	60	60	60
** TOP OF LIST **											
EYE	NUMBER EXAMINED:	56	39	41	57	54	58	45	45	58	58
--ONE		2	1	0	0	2	0	0	0	0	1
--HAEMORRHAGE		0	0	0	0	1	0	0	0	0	0
--DISTENSION		0	1	0	0	0	0	0	0	0	0
--CORNEAL MINERALISATION		0	1	0	0	0	0	0	0	1	2
--LENTICULAR DEGENERATION		2	1	0	0	1	0	0	1	1	0
--RETINAL ATROPHY		1	2	0	0	1	0	0	1	1	1
--DYSTROPHY		0	0	0	0	0	0	0	1	0	0
--KERATITIS		7	6	6	9	6	6	1	3	3	0
--UVEITIS		0	1	1	1	1	0	0	1	1	0
--PANOPHTHALMITIS		0	0	0	0	2	0	0	0	0	0
NERVE OPTIC	NUMBER EXAMINED:	58	43	46	60	57	59	47	44	60	59
--ONE SAMPLE		2	1	5	3	0	0	3	1	1	1
--NEUROPATHY		0	4	0	0	3	1	0	2	1	1
SKIN SUBCUTIS	NUMBER EXAMINED:	60	52	58	60	60	60	59	57	60	60
--EXTRA SAMPLE		37	19	27	28	37	52	31	35	36	48
--SQUAMOUS CYST		5	1	2	0	0	0	1	0	0	0
--ADNEXAL ATROPHY		2	3	2	0	1	10	4	3	1	10
--DERMATITIS / FOLLICULITIS		5	5	8	5	6	7	4	7	6	5
--CELLULITIS		1	0	0	0	1	0	1	0	0	0
--ABSCESS		2	1	1	2	0	1	0	0	0	2
--ACANTHOSIS		1	2	2	1	0	2	1	0	0	1
--FIBROSIS		0	0	0	0	0	0	1	0	0	0
MAMMARY GLAND	NUMBER EXAMINED:	3	3	5	1	4	60	58	57	60	59
--MASTITIS		0	0	0	0	0	0	0	0	1	0
--ACINAR HYPERPLASIA		0	0	0	0	0	14	10	7	10	9
--CYSTIC HYPERPLASIA		0	2	1	1	1	29	28	34	35	29

TABLE 9.3
Group Incidence: histopathology data - all animals - non-neoplastic
Dose levels (mg/kg/day): Gp 1 = 0, Gp 2 = 120, Gp 3 = 600, Gp 4 = 2000, Gp 5 = 0

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STUDY NUMBER: 10676

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=P;SUBSET=T

		--- NUMBER OF ANIMALS AFFECTED ---									
	SEX:	----------MALE----------					---------FEMALE---------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
ORGAN AND FINDING DESCRIPTION	NUMBER:	60	60	60	60	60	60	60	60	60	60
** TOP OF LIST **											
EYE	NUMBER EXAMINED:	56	39	41	57	54	58	45	45	58	58
--ONE		2	1	0	0	2	0	0	0	0	1
--HAEMORRHAGE		0	0	0	0	1	0	0	0	0	0
--DISTENSION		0	1	0	0	0	0	0	0	0	0
--CORNEAL MINERALISATION		0	1	0	0	0	0	0	0	1	2
--LENTICULAR DEGENERATION		2	1	0	0	1	0	0	1	1	0
--RETINAL ATROPHY		1	2	0	0	1	0	0	1	1	1
--DYSTROPHY		0	0	0	0	0	0	0	1	0	0
--KERATITIS		7	6	6	9	6	6	1	3	3	0
--UVEITIS		0	1	1	1	1	0	0	1	1	0
--PANOPHTHALMITIS		0	0	0	0	2	0	0	0	0	0
NERVE OPTIC	NUMBER EXAMINED:	58	43	46	60	57	59	47	44	60	59
--ONE SAMPLE		2	1	5	3	0	0	3	1	1	1
--NEUROPATHY		0	4	0	0	3	1	0	2	1	1
SKIN SUBCUTIS	NUMBER EXAMINED:	60	52	58	60	60	60	59	57	60	60
--EXTRA SAMPLE		37	19	27	28	37	52	31	35	36	48
--SQUAMOUS CYST		5	1	2	0	0	0	1	0	0	0
--ADNEXAL ATROPHY		2	3	2	0	1	10	4	3	1	10
--DERMATITIS / FOLLICULITIS		5	5	8	5	6	7	4	7	6	5
--CELLULITIS		1	0	0	0	1	0	1	0	0	0
--ABSCESS		2	1	1	2	0	1	0	0	0	2
--ACANTHOSIS		1	2	2	1	0	2	1	0	0	1
--FIBROSIS		0	0	0	0	0	0	1	0	0	0
MAMMARY GLAND	NUMBER EXAMINED:	3	3	5	1	4	60	58	57	60	59
--MASTITIS		0	0	0	0	0	0	0	0	1	0
--ACINAR HYPERPLASIA		0	0	0	0	0	14	10	7	10	9
--CYSTIC HYPERPLASIA		0	2	1	1	1	29	28	34	35	29

TABLE 9.3
Group incidence: histopathology data - all animals - non-neoplastic

Dose levels (mg/kg/day): Gp 1 = 0, Gp 2 = 120, Gp 3 = 600, Gp 4 = 2000, Gp 5 = 0

STUDY NUMBER: 10676

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=P;SUBSET=T

ORGAN AND FINDING DESCRIPTION		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	----------MALE----------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
	NUMBER:	60	60	60	60	60	60	60	60	60	60
STERNUM + MARROW	NUMBER EXAMINED:	60	43	49	60	60	60	47	45	60	60
--EXTRA SAMPLE		0	0	1	3	0	2	2	2	4	4
--DEFORMITY		0	1	2	3	0	2	2	2	4	4
--THROMBUS		0	1	0	0	0	0	0	0	0	0
--PIGMENT		0	1	0	0	0	0	0	0	0	0
--FATTY ATROPHY		0	2	0	0	1	0	0	0	0	0
--FIBROUS OSTEODYSTROPHY		0	0	0	0	0	0	0	0	1	0
--MARROW HYPERPLASIA		1	6	8	8	12	3	5	4	4	1
LIVER	NUMBER EXAMINED:	60	49	54	60	60	60	52	48	60	60
--EXTRA SAMPLE		5	2	1	3	5	1	0	4	2	5
--AGONAL CONGESTION / HAEMORRHAGE		12	10	14	8	13	2	3	4	4	3
--HAEMOPOIESIS		1	0	0	0	1	1	1	0	1	0
--PIGMENT		0	0	0	1	0	2	1	0	0	0
--BILE DUCT DISTENSION		0	0	0	1	0	0	0	0	0	0
--TELANGIECTASIS		3	2	2	1	2	3	3	2	7	4
--MICROCYSTIC DEGENERATION		10	15	19	9	13	1	0	1	0	0
--HEPATOCYTE VACUOLATION		22	22	29	13	24	25	32	21	23	25
--VACUOLATED AREA		0	0	1	1	0	0	0	1	0	1
--INFLAMMATORY CELL FOCI		8	9	12	8	9	9	5	3	7	10
--CHOLANGITIS/PERICHOLANGITIS		0	0	0	0	0	0	0	1	1	1
--FIBROSIS		2	0	0	0	0	0	1	0	1	0
--FOCAL NECROSIS		2	2	6	2	4	6	2	4	5	2
--ZONAL NECROSIS		0	0	3	0	2	0	0	0	0	1
--CAUDATE LOBE NECROSIS		0	1	0	0	0	0	0	0	0	1
--BILIARY PROLIFERATION		34	18	20	20	29	23	20	13	18	16
--EOSINOPHILIC FOCUS		2	1	0	1	0	0	0	0	0	1
--EOSINOPHILIC / CLEAR CELL FOCUS		7	6	6	8	10	8	5	2	0	5
--VACUOLATED FOCUS		3	2	2	6	1	6	1	4	5	3
--BASOPHILIC FOCUS		14	11	12	19	14	32	27	25	26	28

** CONTINUED ON NEXT PAGE **

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TABLE 9.3
Group Incidence: histopathology data - all animals - non-neoplastic
Dose levels (mg/kg/day): Gp 1 = 0, Gp 2 = 120, Gp 3 = 600, Gp 4 = 2000, Gp 5 = 0

STUDY NUMBER: 10676

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=P;SUBSET=T

ORGAN AND FINDING DESCRIPTION		--- NUMBER-OF-ANIMALS-AFFECTED ---									
SEX:		----------MALE----------					---------FEMALE---------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:		60	60	60	60	60	60	60	60	60	60
** FROM PREVIOUS PAGE **											
LIVER	NUMBER EXAMINED:	60	49	54	60	60	60	52	48	60	60
--MIXED FOCUS		0	0	0	0	0	1	0	0	0	0
--NORMOCHROMIC FOCUS		0	0	0	0	0	0	0	1	1	0
SPLEEN	NUMBER EXAMINED:	60	42	49	60	60	60	47	45	59	60
--EXTRA SAMPLE		2	0	1	0	2	0	0	0	1	1
--ACCESSORY SPLEEN		0	0	1	0	0	0	0	0	0	0
--AGONAL CONGESTION/HAEMORRHAGE		5	1	0	1	0	0	0	0	0	0
--HAEMOPOIESIS		13	7	14	11	20	25	23	22	15	13
--CYST		1	0	0	0	1	0	0	0	0	0
--PIGMENT		11	13	4	21	16	36	24	24	43	44
--CAPSULAR FIBROSIS		0	0	0	0	1	3	0	0	1	1
--ATROPHY		0	0	0	0	0	0	0	0	0	3
--LYMPHOID ATROPHY		0	1	2	4	2	0	0	1	0	0
--GRANULOMA		0	0	0	0	0	1	0	0	0	0
--NECROSIS		0	0	0	0	0	0	0	0	0	1
--LYMPHOID HYPERPLASIA		0	0	0	0	3	2	0	3	1	1
--RED PULP HYPERPLASIA		1	0	1	1	1	1	0	0	1	2
PANCREAS	NUMBER EXAMINED:	60	41	47	60	59	60	46	45	59	60
--EXTRA SAMPLE		1	0	2	1	0	1	0	0	1	2
--ACCESSORY SPLEEN		0	0	0	0	0	1	0	0	0	0
--AGONAL CONGESTION/HAEMORRHAGE		0	0	0	0	1	0	0	0	0	0
--CYST		0	0	0	0	0	1	0	0	0	1
--VACUOLATION		1	1	0	0	0	0	0	0	0	0
--OEDEMA		0	1	1	1	0	0	0	2	0	0
--LOBULAR ATROPHY		24	11	7	14	23	21	12	13	11	12
--ARTERITIS		2	0	0	0	1	1	0	1	2	0
--PANCREATITIS		1	1	0	1	0	2	2	0	0	3
--ISLET FIBROSIS		26	15	17	15	29	13	8	8	8	15

** CONTINUED ON NEXT PAGE **

TABLE 9:3
Group incidence: histopathology data - all animals - non-neoplastic

Dose levels (mg/kg/day): Gp 1 = 0, Gp 2 = 120, Gp 3 = 600, Gp 4 = 2000, Gp 5 = 0

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STUDY NUMBER: 10676

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=P;SUBSET=T

ORGAN AND FINDING DESCRIPTION		--- NUMBER OF ANIMALS AFFECTED ---									
SEX:		----------MALE----------					---------FEMALE--------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:		60	60	60	60	60	60	60	60	60	60
** FROM PREVIOUS PAGE **											
PANCREAS	NUMBER EXAMINED:	60	41	47	60	59	60	46	45	59	60
--HEPATOCYTE METAPLASIA		0	0	0	0	0	0	0	0	0	1
--ACINAR CELL HYPERPLASIA		0	0	0	3	0	0	0	0	0	0
--ISLET CELL HYPERPLASIA		6	5	4	3	2	2	1	1	3	5
--BASOPHILIC FOCUS		14	5	13	8	11	10	9	10	14	8
MES.LYMPH NODE	NUMBER EXAMINED:	60	41	48	60	60	60	46	45	59	60
--AGONAL CONGESTION/HAEMORRHAGE		1	0	1	2	0	1	0	0	0	1
--LYMPHANGIOFIBROSIS		1	0	0	2	4	0	0	0	1	0
--LYMPHOID HYPERPLASIA		2	1	0	0	0	0	0	1	2	0
STOMACH	NUMBER EXAMINED:	56	41	44	58	54	60	47	45	58	59
--EXTRA SAMPLE		6	5	4	3	5	0	3	3	4	7
--BARBITURATE LYSIS		0	0	0	1	0	0	0	1	0	0
--HAEMORRHAGE		1	0	0	1	0	0	0	0	0	0
--MINERALISATION		1	0	1	0	0	0	0	0	1	1
--CYSTIC GLANDS		30	17	14	38	27	27	18	23	33	24
--FORESTOMACH GASTRITIS		1	3	4	3	1	1	4	5	4	8
--GASTRITIS		6	8	6	2	6	4	6	4	0	6
--EROSION / ULCER		5	3	2	1	3	4	4	3	3	10
--SQUAMOUS CELL HYPERPLASIA		1	0	1	0	0	2	1	1	1	1
DUODENUM	NUMBER EXAMINED:	51	37	37	55	49	59	44	41	57	56
--CONGESTION		0	0	1	0	0	0	0	0	0	0
--EROSION/ULCER		0	0	0	0	1	2	0	0	0	0
--FOCAL HYPERPLASIA		0	0	0	0	0	1	0	0	0	0
JEJUNUM	NUMBER EXAMINED:	50	32	37	53	46	58	44	41	56	56
--DISTENSION		2	0	2	2	2	0	0	0	2	1
--CONGESTION		0	0	1	0	0	0	0	0	0	0

TABLE 9.3
Group incidence: histopathology data - all animals - non-neoplastic
Dose levels (mg/kg/day): Gp 1 = 0, Gp 2 = 120, Gp 3 = 600, Gp 4 = 2000, Gp 5 = 0

STUDY NUMBER: 10676

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=P;SUBSET=T

ORGAN AND FINDING DESCRIPTION		--- NUMBER-OF-ANIMALS-AFFECTED ---									
SEX:		----------MALE----------					---------FEMALE---------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:		60	60	60	60	60	60	60	60	60	60
ILEUM	NUMBER EXAMINED:	50	31	35	54	47	58	43	41	56	55
--NECROPSY FINDING/NO EQUIVALENT SAMPLE		0	0	0	0	1	0	0	0	0	0
--NEMATODE(S)		2	0	0	0	0	0	0	0	0	0
--BARBITURATE LYSIS		0	0	0	1	0	0	0	0	1	0
--DISTENSION		0	0	0	2	1	0	0	0	2	0
--INFLAMMATORY CELL INFILTRATE		0	0	0	0	0	0	0	0	1	0
CAECUM	NUMBER EXAMINED:	50	31	34	53	47	58	43	42	56	55
--EXTRA SAMPLE		0	0	0	2	0	0	0	1	2	0
--NECROPSY FINDING/NO EQUIVALENT SAMPLE		0	0	0	0	1	0	0	0	0	0
--NEMATODE(S)		2	0	0	0	1	0	0	0	0	0
--BARBITURATE LYSIS		0	0	0	13	2	0	2	2	15	0
--HAEMORRHAGE		0	0	0	0	0	0	0	0	1	0
--DISTENSION		0	0	0	1	0	0	0	0	0	0
--OEDEMA		0	0	0	0	0	0	0	1	0	0
--CAECITIS		1	2	2	2	0	3	1	2	0	2
--ARTERITIS		0	0	0	0	0	1	0	0	0	0
COLON	NUMBER EXAMINED:	55	37	41	57	52	59	46	44	58	58
--EXTRA SAMPLE		1	0	0	0	0	0	0	0	0	0
--NEMATODE(S)		15	2	4	0	8	5	1	5	0	2
--OEDEMA		0	0	0	0	0	0	0	0	2	1
--DISTENSION		1	0	1	3	1	0	0	0	2	0
ADRENAL	NUMBER EXAMINED:	60	60	60	60	60	60	48	46	60	60
--ONE		0	1	1	0	1	0	0	0	1	0
--ONE MEDULLA		1	1	0	1	0	4	1	2	3	2
--NO MEDULLA		0	1	0	0	0	0	0	0	2	0
--AGONAL CONGESTION / HAEMORRHAGE		0	1	1	0	0	0	0	0	1	0
--PIGMENT		1	2	2	3	3	5	4	4	0	6

** CONTINUED ON NEXT PAGE **

TABLE 9.3
Group incidence: histopathology data - all animals - non-neoplastic

Dose levels (mg/kg/day): Gp 1 = 0, Gp 2 = 120, Gp 3 = 600, Gp 4 = 2000, Gp 5 = 0

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STUDY NUMBER: 10676

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=P;SUBSET=T

ORGAN AND FINDING DESCRIPTION		--- NUMBER OF ANIMALS AFFECTED ---									
SEX:		----------MALE----------					---------FEMALE--------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:		60	60	60	60	60	60	60	60	60	60
** FROM PREVIOUS PAGE **											
ADRENAL	NUMBER EXAMINED:	60	60	60	60	60	60	48	46	60	60
--MINERALISATION		0	0	0	0	0	0	0	0	0	1
--HAEMANGIECTASIS		1	0	1	2	2	43	36	39	51	49
--HAEMATOCYST		0	1	2	2	3	4	5	4	4	5
--CORTICAL VACUOLATION		1	0	0	0	0	0	0	0	0	0
--ATROPHY		1	1	0	0	1	2	1	1	0	2
--CORTICAL ATROPHY		0	1	1	0	1	1	0	1	2	3
--FIBROSIS		0	0	0	0	0	0	1	0	3	0
--NECROSIS		1	1	0	1	0	0	1	0	1	1
--HYPERTROPHY		0	1	1	1	2	0	2	0	2	0
--CORTICAL HYPERTROPHY		0	1	1	0	0	0	0	1	0	0
--FOCAL MEDULLARY HYPERPLASIA		16	14	20	10	14	6	9	6	7	6
--EOSINOPHILIC FOCUS		15	13	18	17	13	18	20	18	19	24
--EOSINOPHILIC NODULE		0	2	3	2	2	12	8	10	16	10
--VACUOLATED FOCUS		17	17	18	18	16	6	6	6	9	6
--CLEAR CELL FOCUS		11	7	3	9	9	9	9	5	6	5
--BASOPHILIC FOCUS		3	5	2	5	3	7	4	1	1	2
--NORMOCHROMIC FOCUS		16	18	13	17	11	7	2	7	12	10
--NORMOCHROMIC NODULE		0	0	0	1	1	0	0	0	1	0
KIDNEY	NUMBER EXAMINED:	60	60	60	60	60	60	60	60	60	60
--EXTRA SAMPLE		1	1	0	3	4	0	0	1	1	0
--AGONAL CONGESTION / HAEMORRHAGE		7	4	15	5	11	0	2	3	4	2
--THROMBUS		0	0	0	0	0	1	1	0	0	0
--CYST(S)		2	1	0	3	1	1	0	0	0	1
--PIGMENT		0	0	1	2	1	0	0	1	1	1
--ADHESION		0	0	0	1	0	0	0	0	0	0
--PELVIC MINERALISATION		7	10	22	46	7	46	54	57	51	45
--PAPILLARY MINERALISATION		0	0	1	2	0	4	1	2	2	2
--CORTICOMEDULLARY MINERALISATION		2	1	1	1	2	6	2	5	12	0

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TABLE 9.3
Group incidence: histopathology data - all animals - non-neoplastic

Dose levels (mg/kg/day): Gp 1 = 0, Gp 2 = 120, Gp 3 = 600, Gp 4 = 2000, Gp 5 = 0

STUDY NUMBER: 10676

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=P;SUBSET=T

ORGAN AND FINDING DESCRIPTION		--- NUMBER-OF-ANIMALS-AFFECTED ---									
SEX:		----------MALE----------					---------FEMALE---------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:		60	60	60	60	60	60	60	60	60	60
** FROM PREVIOUS PAGE **											
KIDNEY	NUMBER EXAMINED:	60	60	60	60	60	60	60	60	60	60
--CORTICAL MINERALISATION		0	3	0	2	1	1	1	0	3	0
--TUBULAR DILATION		2	2	9	11	3	0	2	6	6	1
--TUBULAR VACUOLATION		1	3	3	0	0	10	14	5	4	6
--TUBULAR LYSIS		0	0	0	0	1	0	0	1	0	0
--HYALINE DROPLETS		1	1	0	0	2	0	2	1	1	1
--SEGMENTAL CORTICAL ATROPHY		0	0	0	1	0	0	0	0	0	0
--INFLAMMATORY CELL FOCI		0	0	0	0	0	0	0	1	0	0
--BASOPHILIC TUBULES		1	0	3	2	3	1	0	1	1	1
--FOCAL NEPHROPATHY		8	8	3	2	6	1	1	2	2	1
--GLOMERULONEPHROPATHY		42	44	43	45	44	43	43	41	43	37
--INTERSTITIAL NEPHRITIS		0	0	1	1	1	0	0	0	0	0
--PYELITIS		4	3	8	5	5	5	3	4	7	5
--PYELONEPHRITIS		0	0	0	4	2	1	1	0	0	0
--PAPILLITIS		1	1	0	0	1	0	0	0	0	0
--ABSCESS		0	0	1	0	0	0	0	0	0	0
--MICROABSCESS		0	0	0	0	0	0	0	1	0	0
--HYDRONEPHROSIS		5	4	5	9	2	0	0	1	2	0
--NECROSIS		0	1	0	0	0	0	0	0	0	0
--PAPILLARY NECROSIS		3	2	0	2	0	1	0	0	0	0
--CORTICAL SCAR		0	0	0	0	0	0	1	0	0	0
--UROTHELIAL HYPERPLASIA		9	11	22	47	7	25	30	42	50	25
--TUBULAR CELL HYPERPLASIA		0	0	0	0	0	1	0	0	0	0
TESTIS	NUMBER EXAMINED:	60	46	51	60	60	0	0	0	0	0
--EXTRA SAMPLE		2	0	0	0	0	0	0	0	0	0
--AGONAL CONGESTION/HAEMORRHAGE		2	0	1	0	0	0	0	0	0	0
--MINERALISATION		8	3	3	6	6	0	0	0	0	0
--TUBULAR DILATATION		1	0	0	0	1	0	0	0	0	0
--ATROPHY		9	7	8	12	14	0	0	0	0	0

** CONTINUED ON NEXT PAGE **

TABLE 9.3
Group incidence: histopathology data - all animals - non-neoplastic

Dose levels (mg/kg/day): Gp 1 = 0, Gp 2 = 120, Gp 3 = 600, Gp 4 = 2000, Gp 5 = 0

STUDY NUMBER: 10676

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=P;SUBSET=T

		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	----------MALE----------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
ORGAN AND FINDING DESCRIPTION	NUMBER:	60	60	60	60	60	60	60	60	60	60
** FROM PREVIOUS PAGE **											
TESTIS	NUMBER EXAMINED:	60	46	51	60	60	0	0	0	0	0
--ARTERITIS		2	1	3	2	1	0	0	0	0	0
--ORCHITIS		0	1	0	0	0	0	0	0	0	0
--NECROSIS		0	1	1	0	0	0	0	0	0	0
--INTERSTITIAL CELL HYPERPLASIA		5	8	8	7	6	0	0	0	0	0
EPIDIDYMIS	NUMBER EXAMINED:	60	42	47	60	60	0	0	0	0	0
--MINERALISATION		1	0	0	0	0	0	0	0	0	0
--OEDEMA		0	0	1	0	0	0	0	0	0	0
--OLIGOSPERMIA		6	5	4	8	7	0	0	0	0	0
--INFLAMMATORY CELL FOCI		2	2	3	1	2	0	0	0	0	0
--EPIDIDYMITIS		1	4	2	1	1	0	0	0	0	0
--SPERM GRANULOMA		0	1	1	0	0	0	0	0	0	0
--NECROSIS		0	1	0	0	0	0	0	0	0	0
OVARY	NUMBER EXAMINED:	0	0	0	0	0	60	50	52	60	59
--ONE SAMPLE		0	0	0	0	0	1	0	0	1	1
--AGONAL CONGESTION / HAEMORRHAGE		0	0	0	0	0	0	1	0	1	0
--CYST(S)		0	0	0	0	0	28	20	20	17	23
--CYSTIC BURSA		0	0	0	0	0	1	2	2	0	1
--REDUCED CORPORA LUTEA		0	0	0	0	0	35	29	39	37	32
--PERSISTENT CORPORA LUTEA		0	0	0	0	0	0	0	0	0	1
--ARTERITIS		0	0	0	0	0	0	0	0	1	0
--TUBULOSTROMAL HYPERPLASIA		0	0	0	0	0	22	14	16	30	23
URINARY BLADDER	NUMBER EXAMINED:	59	42	47	60	59	59	47	45	60	60
--NECROPSY FINDING/NO EQUIVALENT SAMPLE		0	0	0	0	0	0	0	0	1	0
--CONGESTION / HAEMORRHAGE		3	1	2	3	0	1	0	0	0	0
--DISTENSION		6	2	5	12	5	3	1	2	1	0
--INFLAMMATORY CELL FOCI		0	0	0	1	0	0	0	0	0	0

** CONTINUED ON NEXT PAGE **

TABLE 9.3
Group incidence: histopathology data - all animals - non-neoplastic
Dose levels (mg/kg/day): Gp 1 = 0, Gp 2 = 120, Gp 3 = 600, Gp 4 = 2000, Gp 5 = 0

STUDY NUMBER: 10676

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=P;SUBSET=T

ORGAN AND FINDING DESCRIPTION		--- NUMBER-OF-ANIMALS-AFFECTED ---									
SEX:		----------MALE----------					----------FEMALE----------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:		60	60	60	60	60	60	60	60	60	60
** FROM PREVIOUS PAGE **											
URINARY BLADDER	NUMBER EXAMINED:	59	42	47	60	59	59	47	45	60	60
--CYSTITIS		2	3	1	7	1	0	0	1	0	0
--TRANSITIONAL CELL HYPERPLASIA		0	1	0	3	0	1	0	0	1	0
PROSTATE	NUMBER EXAMINED:	60	42	49	60	59	0	0	0	0	0
--COAGULATING GLAND DISTENSION		0	0	1	0	0	0	0	0	0	0
--CONTRACTION		0	1	0	0	0	0	0	0	0	0
--ATROPHY		2	1	1	3	2	0	0	0	0	0
--INFLAMMATORY CELL FOCI		0	0	1	0	0	0	0	0	0	0
--PROSTATITIS		26	19	23	42	26	0	0	0	0	0
--ABSCESS		0	0	0	1	1	0	0	0	0	0
--FOCAL HYPERPLASIA		0	0	2	0	0	0	0	0	0	0
UTERUS	NUMBER EXAMINED:	0	0	0	0	0	60	50	47	60	60
--EXTRA SAMPLE		0	0	0	0	0	1	1	0	5	1
--CYSTIC GLANDS		0	0	0	0	0	16	8	11	18	15
--LYMPHANGIECTASIS		0	0	0	0	0	1	0	0	0	0
--PIGMENT		0	0	0	0	0	0	0	0	0	1
--ATROPHY		0	0	0	0	0	1	1	0	0	0
--ADENOMYOSIS		0	0	0	0	0	0	0	0	1	0
--SQUAMOUS METAPLASIA		0	0	0	0	0	2	0	0	0	0
--ENDOMETRIAL HYPERPLASIA		0	0	0	0	0	0	0	0	1	1
SALIVARY GLAND	NUMBER EXAMINED:	56	40	48	60	59	58	47	44	60	58
--EXTRA SAMPLE		0	0	0	0	0	0	0	1	0	0
--AGONAL CONGESTION/HAEMORRHAGE		0	0	0	0	1	0	0	0	0	0
--SIALOLITH		0	1	1	0	0	0	0	0	0	0
--OEDEMA		0	0	0	1	0	0	0	0	0	0
--LOBULAR ATROPHY		1	0	0	0	0	0	0	0	0	1
--ADENITIS		1	2	0	1	0	1	1	2	1	0

** CONTINUED ON NEXT PAGE **

TABLE 9.3
Group incidence: histopathology data - all animals - non-neoplastic

Dose levels (mg/kg/day): Gp 1 = 0, Gp 2 = 120, Gp 3 = 600, Gp 4 = 2000, Gp 5 = 0

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STUDY NUMBER: 10676

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=P;SUBSET=T

ORGAN AND FINDING DESCRIPTION		--- NUMBER OF ANIMALS AFFECTED ---									
	SEX:	----------MALE----------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
	NUMBER:	60	60	60	60	60	60	60	60	60	60
** FROM PREVIOUS PAGE **											
SALIVARY GLAND	NUMBER EXAMINED:	56	40	48	60	59	58	47	44	60	58
--FIBROSIS		0	2	1	0	0	0	2	0	0	0
MAND.LYMPH NODE	NUMBER EXAMINED:	56	41	48	60	59	57	48	47	60	58
--EXTRA SAMPLE		1	0	0	0	0	0	0	0	0	0
--AGONAL CONGESTION / HAEMORRHAGE		7	6	3	7	8	15	6	9	8	10
--LYMPHANGIECTASIS		1	0	0	6	0	2	2	1	2	1
--PIGMENT		0	0	1	0	0	0	1	0	0	0
--TATTOO PIGMENT		0	0	0	0	0	0	0	1	0	1
--ATROPHY		0	0	0	0	0	0	0	1	0	0
--LYMPHOID HYPERPLASIA		10	7	11	15	14	14	16	12	13	21
THYMUS	NUMBER EXAMINED:	53	40	44	56	57	59	44	45	57	58
--EXTRA SAMPLE		0	0	0	0	0	0	0	0	0	1
--AGONAL CONGESTION / HAEMORRHAGE		1	1	1	1	2	2	3	1	1	3
--ECTOPIC PARATHYROID		1	0	0	0	0	0	0	0	0	0
--HAEMORRHAGE		1	0	1	0	2	0	0	0	0	0
--CYST(S)		5	1	3	3	3	27	16	21	25	25
--LYMPHOID ATROPHY		4	5	2	6	2	1	2	1	1	3
--ARTERITIS		0	0	0	0	0	0	0	0	1	0
--LYMPHOID HYPERPLASIA		0	0	0	0	0	2	0	0	0	1
--TUBULAR/CYSTIC HYPERPLASIA		0	1	0	0	0	2	1	2	2	1
LUNG	NUMBER EXAMINED:	60	47	49	60	60	60	51	49	60	60
--EXTRA SAMPLE		0	2	1	4	1	2	2	0	2	2
--AGONAL CONGESTION / HAEMORRHAGE		17	20	20	10	21	7	7	6	4	10
--THROMBUS		0	0	0	1	0	0	0	0	0	0
--ECTOPIC BONE		8	3	4	8	3	3	2	3	3	1
--INFLAMMATORY CELL FOCI		2	1	0	0	0	1	1	0	1	2
--PNEUMONITIS		7	1	6	3	4	1	1	2	5	2

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TABLE 9.3
Group incidence: histopathology data - all animals - non-neoplastic

Dose levels (mg/kg/day): Gp 1 = 0, Gp 2 = 120, Gp 3 = 600, Gp 4 = 2000, Gp 5 = 0

STUDY NUMBER: 10676

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=P;SUBSET=T

		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	----------MALE----------					---------FEMALE---------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
ORGAN AND FINDING DESCRIPTION	NUMBER:	60	60	60	60	60	60	60	60	60	60
** FROM PREVIOUS PAGE **											
LUNG	NUMBER EXAMINED:	60	47	49	60	60	60	51	49	60	60
--GRANULOMA		0	0	0	1	0	0	0	0	3	1
--FOAMY HISTIOCYTES		22	21	16	32	24	18	21	18	23	25
--PIGMENTED HISTIOCYTES		0	1	0	1	0	0	0	0	0	0
--PLEURAL FIBROSIS		1	0	1	0	0	0	0	1	1	0
--MYOID HYPERPLASIA		0	0	0	1	0	0	0	0	0	0
--BRONCHIO-ALVEOLAR HYPERPLASIA		1	1	1	0	6	1	0	2	1	2
HEART	NUMBER EXAMINED:	60	43	49	60	60	60	47	45	60	60
--EXTRA SAMPLE		1	0	0	0	0	0	0	0	0	0
--THROMBUS		0	0	1	0	0	0	0	0	0	0
--ATRIAL THROMBUS		3	1	2	0	0	0	0	0	0	0
--VALVULAR HAEMATOCYST		0	0	0	1	0	0	0	0	0	0
--MINERALISATION		2	0	1	0	0	0	0	0	0	0
--CHAMBER DISTENSION		0	3	1	0	0	0	0	0	1	0
--ARTERITIS		1	2	1	0	1	0	1	1	2	0
--ENDOCARDITIS		0	1	0	0	0	0	0	0	0	0
--MYOCARDITIS / FIBROSIS		58	39	46	58	57	55	40	39	55	48
--VALVULAR ENDOCARDITIS		0	0	1	1	0	0	0	0	0	0
--VALVULAR ENDOCARDIOSIS		0	0	0	1	0	0	0	0	0	0
--FOCAL NECROSIS		0	0	1	0	0	0	0	0	0	0
--SCAR		1	1	1	0	0	0	0	0	0	0
--HYPERTROPHY		1	1	0	0	0	0	0	1	0	0
--CARTILAGINOUS METAPLASIA		4	4	4	4	3	0	1	0	2	0
--ENDOCARDIAL HYPERPLASIA		1	1	0	0	0	0	0	0	0	0
TRACHEA	NUMBER EXAMINED:	60	42	48	60	60	60	47	45	60	60
--TRACHEITIS		0	1	0	0	1	0	0	0	0	0

TABLE 9.3
Group incidence: histopathology data - all animals - non-neoplastic

Dose levels (mg/kg/day): Gp 1 = 0, Gp 2 = 120, Gp 3 = 600, Gp 4 = 2000, Gp 5 = 0

STUDY NUMBER: 10676

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=P;SUBSET=T

ORGAN AND FINDING DESCRIPTION		--- NUMBER-OF-ANIMALS-AFFECTED ---									
SEX:		----------MALE----------					---------FEMALE--------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:		60	60	60	60	60	60	60	60	60	60
OESOPHAGUS	NUMBER EXAMINED:	60	42	48	60	60	60	47	45	60	60
--DISTENSION		0	0	0	1	0	0	0	0	0	0
--OESOPHAGITIS		0	0	0	0	1	0	0	0	0	0
THYROID	NUMBER EXAMINED:	55	39	41	57	58	59	45	44	58	57
--EXTRA SAMPLE		0	0	0	0	0	0	0	0	1	0
--ONE		0	0	0	0	0	0	1	1	0	0
--AGONAL CONGESTION/HAEMORRHAGE		2	0	0	0	0	0	0	0	0	0
--INFLAMMATORY CELL FOCI		0	0	0	0	0	1	0	0	0	0
--CYST		4	1	1	0	1	1	0	0	3	0
--CYSTIC FOLLICLES		2	0	2	0	2	0	0	1	0	0
--FOLLICULAR CELL HYPERTROPHY		0	0	0	1	0	0	0	0	0	0
--FOLLICULAR CYSTIC HYPERPLASIA		2	0	0	0	4	0	1	0	1	0
--C-CELL HYPERPLASIA		48	32	34	50	48	58	41	42	55	55
PARATHYROID	NUMBER EXAMINED:	56	42	44	55	58	56	45	44	56	57
--ONE		32	22	26	32	38	39	30	29	30	35
--HAEMANGIECTASIS		0	1	0	0	0	0	0	0	0	0
--FOCAL HYPERPLASIA		1	0	5	4	2	1	0	1	0	0
--HYPERPLASIA		1	0	0	0	0	0	0	0	1	0
PITUITARY	NUMBER EXAMINED:	60	45	53	60	60	60	58	55	60	59
--CYST(S)		3	5	4	5	1	0	1	1	2	2
--CYSTIC CLEFT		1	0	1	0	2	1	0	0	4	0
--FOCAL HYPERPLASIA		13	7	13	21	18	8	6	7	8	6
--HYPERPLASIA		0	0	0	0	0	0	0	1	0	2
BRAIN	NUMBER EXAMINED:	60	42	48	60	60	60	47	45	60	59
--EXTRA SAMPLE		0	0	0	0	0	0	0	1	0	0
--HAEMORRHAGE		0	0	0	1	1	1	0	0	0	0

** CONTINUED ON NEXT PAGE **

TABLE 9.3
Group incidence: histopathology data - all animals - non-neoplastic

Dose levels (mg/kg/day): Gp 1 = 0, Gp 2 = 120, Gp 3 = 600, Gp 4 = 2000, Gp 5 = 0

STUDY NUMBER: 10676

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=P;SUBSET=T

ORGAN AND FINDING DESCRIPTION		--- NUMBER-OF-ANIMALS-AFFECTED ---									
SEX:		----------MALE----------					---------FEMALE---------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:		60	60	60	60	60	60	60	60	60	60
** FROM PREVIOUS PAGE **											
BRAIN	NUMBER EXAMINED:	60	42	48	60	60	60	47	45	60	59
--MINERALISATION		0	0	1	0	0	1	0	0	1	0
--VENTRICULAR DILATATION		0	0	0	0	1	0	0	0	0	1
--COMPRESSION		7	12	10	12	6	27	27	21	27	30
--VACUOLATION		0	0	0	1	0	2	0	1	3	0
--OPTIC NEUROPATHY		0	1	0	0	0	0	0	0	0	0
--ENCEPHALOPATHY		1	1	0	0	0	1	0	1	0	2
--SPONGIFORM ENCEPHALOPATHY		0	0	0	0	1	0	0	0	0	0
--ARTERITIS		0	0	0	0	0	0	0	1	0	0
--GLIOSIS		0	0	0	1	0	0	1	0	0	1
SPINAL CORD	NUMBER EXAMINED:	60	42	48	60	60	60	47	45	60	60
--EXTRA SAMPLE		0	0	0	2	0	0	0	0	0	0
--DEFORMITY		0	0	0	1	0	0	0	0	0	0
--HAEMORRHAGE		0	0	0	0	1	1	0	0	0	0
--VACUOLATION		0	1	1	0	0	0	0	0	0	0
--MYELOPATHY		2	1	0	0	2	0	0	0	1	0
FOOT/LEG	NUMBER EXAMINED:	12	14	13	8	10	2	11	6	2	6
--NO EQUIVALENT SAMPLE		1	0	0	0	0	0	0	0	0	0
--CONGESTION		0	1	0	0	0	0	0	0	0	0
--SQUAMOUS CYST		0	0	0	0	0	0	1	0	0	0
--OEDEMA		0	0	1	1	0	0	0	0	0	0
--ARTHRITIS		4	2	1	1	3	2	1	2	0	0
--CELLULITIS		0	0	0	0	0	0	0	0	0	1
--DERMATITIS / FOLLICULITIS		1	6	3	3	5	0	4	3	1	1
--MYOSITIS		1	6	0	0	1	0	0	2	0	1
--PODODERMATITIS		7	6	9	3	3	2	6	2	1	4
--FIBROSIS		0	1	0	0	0	0	0	0	0	0

TABLE 9.3
Group incidence: histopathology data - all animals - non-neoplastic

Dose levels (mg/kg/day): Gp 1 = 0, Gp 2 = 120, Gp 3 = 600, Gp 4 = 2000, Gp 5 = 0

STUDY NUMBER: 10676

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=P;SUBSET=I

		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	----------MALE----------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
ORGAN AND FINDING DESCRIPTION	NUMBER:	60	60	60	60	60	60	60	60	60	60
TAIL	NUMBER EXAMINED:	26	21	32	45	22	27	26	31	25	21
--NO EQUIVALENT SAMPLE		0	0	1	1	0	1	0	1	0	0
--SQUAMOUS CYST		0	0	0	1	1	0	0	0	0	0
--FRACTURE/DISLOCATION		0	0	0	2	0	0	0	0	0	0
--DERMATITIS / FOLLICULITIS		25	21	28	41	21	26	26	29	24	20
--MYOSITIS		1	0	0	1	0	0	0	0	0	0
--PERIOSTEITIS		1	0	0	0	0	0	0	0	0	0
--ABSCESS		3	0	0	1	1	0	0	0	0	0
--FIBROSIS		0	0	1	0	0	0	0	0	0	0
--NECROSIS		0	0	0	1	1	0	0	0	0	0
ORAL CAVITY	NUMBER EXAMINED:	2	2	5	4	4	11	7	11	9	7
--NECROPSY FINDING/NO EQUIVALENT SAMPLE		2	2	4	4	4	11	6	11	8	7
--ODONTOGENIC DYSPLASIA		0	0	0	0	0	0	0	0	1	0
EAR	NUMBER EXAMINED:	10	7	11	6	9	9	11	6	10	3
--NECROPSY FINDING/NO EQUIVALENT SAMPLE		2	3	4	3	1	5	5	3	6	1
--SQUAMOUS CYST		0	1	0	0	0	0	0	0	0	0
--CHONDROPATHY		7	2	6	0	4	4	1	2	1	2
--DERMATITIS		3	3	2	3	6	2	4	3	2	1
THORACIC CAVITY	NUMBER EXAMINED:	2	3	3	7	2	1	0	2	2	1
--NECROPSY FINDING/NO EQUIVALENT SAMPLE		2	2	3	6	2	1	0	2	1	1
--SEROSITIS		0	1	0	0	0	0	0	0	0	0
URETER	NUMBER EXAMINED:	0	2	2	9	2	0	0	0	0	0
--DISTENSION		0	2	2	9	2	0	0	0	0	0
--URETERITIS		0	0	0	2	1	0	0	0	0	0

TABLE 9.3
Group incidence: histopathology data - all animals - non-neoplastic
Dose levels (mg/kg/day): Gp 1 = 0, Gp 2 = 120, Gp 3 = 600, Gp 4 = 2000, Gp 5 = 0

STUDY NUMBER: 10676

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=P;SUBSET=T

ORGAN AND FINDING DESCRIPTION		--- NUMBER-OF-ANIMALS-AFFECTED ---									
SEX:		----------MALE----------					---------FEMALE---------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:		60	60	60	60	60	60	60	60	60	60
ABDOMINAL CAVITY	NUMBER EXAMINED:	2	3	4	2	2	1	1	1	1	2
--NECROPSY FINDING / NO EQUIVALENT SAMPLE		0	2	1	2	1	0	1	1	1	0
--FIBROSIS/ADHESION		0	0	0	0	0	0	0	0	0	1
--PERITONITIS		0	0	0	0	0	0	0	0	0	1
--STEATITIS		0	0	1	0	0	0	0	0	0	0
MUSCLE	NUMBER EXAMINED:	4	4	6	2	6	0	2	2	1	0
--HAEMORRHAGE		0	1	0	0	0	0	0	0	0	0
--ATROPHY		3	3	6	2	5	0	1	2	0	0
AORTA	NUMBER EXAMINED:	1	1	1	3	0	1	0	0	3	1
--MINERALISATION		0	0	1	0	0	0	0	0	1	0
--DISTENSION		1	1	1	3	0	1	0	0	2	0
SEMINAL VESICLE	NUMBER EXAMINED:	5	7	5	9	5	0	0	0	0	0
--DISTENSION		0	0	1	1	1	0	0	0	0	0
--CONTRACTION		1	0	1	0	0	0	0	0	0	0
--ATROPHY		2	5	2	3	3	0	0	0	0	0
--VESICULITIS		1	2	0	4	0	0	0	0	0	0
RECTUM	NUMBER EXAMINED:	0	1	1	0	0	1	1	1	1	1
--NO EQUIVALENT SAMPLE		0	0	0	0	0	1	1	1	0	1
VAGINA	NUMBER EXAMINED:	0	0	0	0	0	2	3	3	1	2
--NECROPSY FINDING / NO EQUIVALENT SAMPLE		0	0	0	0	0	0	0	0	1	0
--MUCIFICATION		0	0	0	0	0	0	0	0	0	1
--VAGINITIS		0	0	0	0	0	1	2	1	0	1
NASAL CAVITY	NUMBER EXAMINED:	0	0	1	0	0	0	0	0	1	0
--RHINITIS		0	0	0	0	0	0	0	0	1	0

TABLE 9.3
Group incidence: histopathology data - all animals - non-neoplastic

Dose levels (mg/kg/day): Gp 1 = 0, Gp 2 = 120, Gp 3 = 600, Gp 4 = 2000, Gp 5 = 0

PRINTED: 28-JUN-95
PAGE: 16

STUDY NUMBER: 10676

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;SCREEN=ALL;WEEKS=ALL
DEATH=ALL;FIND=P;SUBSET=T

ORGAN AND FINDING DESCRIPTION		--- NUMBER-OF-ANIMALS-AFFECTED ---									
SEX:		----------MALE----------					---------FEMALE---------				
GROUP:		-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:		60	60	60	60	60	60	60	60	60	60
SCIATIC NERVE	NUMBER EXAMINED:	2	1	2	3	2	0	0	0	0	0
--NEUROPATHY		2	1	2	2	1	0	0	0	0	0
--FIBROSIS		0	0	0	0	1	0	0	0	0	0
VAS DEFERENS	NUMBER EXAMINED:	0	0	2	0	0	0	0	0	0	0
--CONGESTION /HAEMORRHAGE		0	0	1	0	0	0	0	0	0	0
--SPERM GRANULOMA		0	0	1	0	0	0	0	0	0	0
PREPUT/CLIT GL	NUMBER EXAMINED:	1	0	0	1	2	3	1	1	0	2
--CYSTIC DISTENSION		0	0	0	0	1	2	0	0	0	2
--DUCT ECTASIA		0	0	0	0	0	0	0	1	0	0
--ADENITIS		0	0	0	0	0	0	1	0	0	0
--ABSCESS		1	0	0	1	1	0	0	0	0	0
PENIS	NUMBER EXAMINED:	0	1	0	1	0	0	0	0	0	0
--BALANOPOSTHITIS		0	1	0	0	0	0	0	0	0	0
BLOOD VESSEL	NUMBER EXAMINED:	0	0	0	0	0	0	0	0	1	0
--MINERALISATION		0	0	0	0	0	0	0	0	1	0
JOINT	NUMBER EXAMINED:	1	0	0	0	0	0	0	0	0	0
--ARTHROPATHY		1	0	0	0	0	0	0	0	0	0
TRIGEMINAL NERVE	NUMBER EXAMINED:	0	1	0	0	0	0	0	0	0	0
--NEUROPATHY		0	1	0	0	0	0	0	0	0	0

** END OF LIST **

This information is in the Pharmacology review dated November 4, 1997

Melodi McNeil 5/22/98

Melodi McNeil, Regulatory Health Project Manager

also see attached correspondence

APPEARS THIS WAY
ON ORIGINAL

MAY 12 1997

Salix Pharmaceuticals, Inc.
Attention: Margie Nemcik-Cruz
3600 West Bayshore Road, Suite 205
Palo Alto, CA 94303

Dear Ms. Nemcik-Cruz:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for Colazide (balsalazide) Capsules.

We also refer to the following amendments:

1. September 27, 1996, which contained a proposal for a 26-week oral gavage toxicity study (carcinogenicity study) of balsalazide, to be conducted in a transgenic mouse model, in lieu of repeating the 18-month mouse carcinogenicity study (1067/31) conducted by Biorex.

2. November 5, 1996, which contained a revised protocol for the 26-week oral gavage study, referenced above, in addition to a proposed protocol for the 4-week range-finding study in the p 53 +/- transgenic mouse that will be used to establish the doses for the 26-week study.

3. May 1, 1997, which seeks the Division's agreement with the use of the C57BL/6 strain in place of the p 53 transgenic mice in the 4-week dose-ranging study.

In these submissions, among other things, you requested Agency review and comment on the design of the proposed studies.

We have completed our review of your submissions and our discussion with the Center's Executive Carcinogenicity Assessment Committee and have the following comments:

Regarding the proposed protocol for a 4-week dose-ranging study:

1. Your proposal to use C57BL/6 mice in place of p 53 transgenic mice for the 4-week dose-ranging study is acceptable. It will also permit the use of sufficient number of animals for monitoring toxicokinetics.

2. We recommend that drug exposure be monitored, i.e. plasma AUC values for Colazide, 5-ASA, and 4-ABA at various dose levels. This information, together with the exposure levels at the maximum recommended dose in humans and comparative metabolism and protein binding data in humans and the rodent, would be useful for determining doses for the carcinogenicity study in the absence of any manifested toxicity in the dose-ranging study.

Regarding the proposed 26 week carcinogenicity study in p 53 +/- transgenic mice:

1. The overall study design/protocol is acceptable. However, the dose selection for this study should be based on the results of the proposed dose-ranging study. If the toxicity endpoints are needed for dose selection, the highest dose should be the maximum tolerated dose (MTD). If the pharmacokinetic endpoints are used for dose selection, please base it on the above suggested information regarding exposure levels, comparative metabolism, and protein binding.

2. Consider using p-cresidine (0.5% in the diet) as a positive control, instead of bromodichloromethane which has not been tested in p 53 heterogenous transgenic mice.

The appropriateness of your future dose selection for the proposed carcinogenicity study will be evaluated once the complete report of the four week dose-ranging study, along with the dose proposals, have been submitted.

If you have any questions, please contact:

Melodi McNeil
Regulatory Health Project Manager
(301) 443-0483

Sincerely yours,

/S/
5-7-97

5/7/97

Lilia Talarico, M.D.
Acting Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Orig
HFD-180/Division Files
HFD-180/Choudary
HFD-180/CSO/MMcNeil
RD Init: KJohnson 5/2/97
JChoudary 5/4/97, 5/6/97
Final: May 7, 1997
MMcNeil/April 30, 1997
mm/April 30, 1997/c:\wpfiles\

ADVICE

MC/NC1

AUG 15 1996

Salix Pharmaceuticals
Attention: Margie Nemcik-Cruz
3600 W. Bayshore Road
Palo Alto, CA 94303

Dear Ms. Nemcik-Cruz:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for Colazide (balsalazide) Capsules.

We also refer to the following amendments:

1. August 21, 1995, annual report containing the final report of a 104 week dietary carcinogenicity study in rats (Report # 1067/6-1050)

2. August 31, 1995, containing:

   a. L5178Y TK$^{+/-}$ mouse lymphoma assay (Report # 1067/59-1052)

   b. Genotoxicity studies of 4-ABA ("carrier molecule"): L5178Y TK$^{+/-}$ mouse lymphoma assay and chromosomal aberration test in human lymphocytes (Reports # 1067/54-1052 and 1067/57, respectively)

   c. Genotoxicity Studies of N-acetyl-4-ABA: Ames test, L5178Y TK$^{+/-}$ mouse lymphoma assay and chromosomal aberration test in human lymphocytes (Reports # 1067/056-1052, 1067/55-1052, and 1067/058-1052, respectively)

   d. Chemo-prevention of intestinal tumor formation in B6-Min/+ mice by balsalazide

We also refer to your February 26, 1996 submission (Serial# 52) submitted in response to our June 22, 1994 and January 3, 1995 letters notifying you that the mouse carcinogenicity study [redacted], conducted by Biorex, was inadequate and that your reasons for not repeating the study were not acceptable. In this submission you also requested that the carcinogenicity assessment committee (CAC) be consulted regarding our decision.

We have completed the review of the preclinical portions of your submissions, and have the following comments and requests:

1. The mouse carcinogenicity study was not acceptable because the testing was done by one laboratory and reported by another, which did not accept the responsibility for the recording or the integrity of the raw data. The dose selection was inappropriately

based on the results of a previous study in rats. The highest tested dose (1000 mg/kg/day via diet) was not the maximum feasible dose. During the study, the test drug formulation was not analyzed for stability, homogeneity, or achieved concentration. In addition, there was no evidence of any quality assurance inspections.

2. Information to show that the study met GLP requirements was not provided as follows:

   a. Names of the Study Director, other scientists or professionals and the names of all supervisory personnel involved in the study were not provided as per 21 CFR, Subpart B, 58.33 and Subpart J, 58.185.

   b. No quality assurance unit (QUA) was identified or any evidence of QUA inspection provided as per 21 CFR 58.35 and 21 CFR 58.185.

   c. No evidence for the analysis of test drug formulation for purity, stability, homogeneity or achieved concentration was provided as per 21 CFR 58.105 and 21 CFR 58.113.

   d. No approved and signed protocol was provided as per 21 CFR 58.120.

   e. No final report including the signed and dated reports of each of the individual scientists or other professionals involved in the study and the signed QUA statements was provided as per 21 CFR 58.185.

3. The Agency at this time recommends that any drug administered for prolonged or repetitive periods be assessed for carcinogenicity potential in two rodent species. You should, therefore, conduct a 13-week oral (gavage) dose-ranging study in mice to define the maximum tolerated dose (MTD) and submit the report along with the protocol for a repeat carcinogenicity study (gavage) in mice for our evaluation. The Carcinogenicity Assessment Committee (CAC) will be consulted after you provide such information.

4. Regarding the 104 week rat (Sprague-Dawley) carcinogenicity study, (Report # 1067/6-1050) you state that the rate of incidence of benign adrenal pheochromocytoma of high dose treated males (30%) was "within laboratory historical control incidence range (10-46%)." Please provide complete historical control data for the incidence of adrenal pheochromocytoma in this strain of rat from the testing laboratory, [redacted] for the period from 1991-1995.

We also reiterate our previous request that you revise your Investigator's brochure to include a statement of the fact that balsalazide is mutagenic in the mammalian cell (CHL/HGPRT) forward gene mutation assay. You should also include the information that balsalazide, 4-ABA, and N-acetyl-4-ABA are not mutagenic in L5178Y mouse lymphoma cell assay.

If you have any questions, please contact:

Melodi McNeil
Consumer Safety Officer
(301) 443-0483

Sincerely yours,

/S/ 8/14/96

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Orig
HFD-180/Division Files
HFD-180/JChoudary
HFD-180/CSO/MMcNeil
HFD-150/CAC/JDeGeorge
HFD-345/Viswanathan
HFD-345/SKelly
HFD-345/Snipes
R/D init: KJohnson 7/29/96, 7/30/96, 8/2/96, 8/14/96
JChoudary 8/5/96, 8/5/96, 8/11/96
SFredd 8/7/96, 8/12/96
Final: August 14, 1996
MMcNeil/July 22, 1996
mm/July 22, 1996/c:\wpfiles\cs

ADVICE

MESSAGE CONFIRMATION

08/20/96 13:39
ID=DGCDP/HFD-180

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
08/20	01'35"	914158561555	CALLING	04	OK	0000

08/20/96 13:37 DGCDP/HFD-180 → 914158561555 NO.066 D01

FOOD AND DRUG ADMINISTRATION
DIVISION OF GASTROINTESTINAL
AND COAGULATION DRUG PRODUCTS
DOCUMENT CONTROL ROOM 6B-24
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE 8/20/96

Center for Drug Evaluation and Research
FDA

TO:

Name Margie Nemcik-Cruz

Fax No. (415) 856-1555

Phone No. (415) 856-1558

Location Salix Pharmaceuticals

FROM:

Name Melodi McNeil

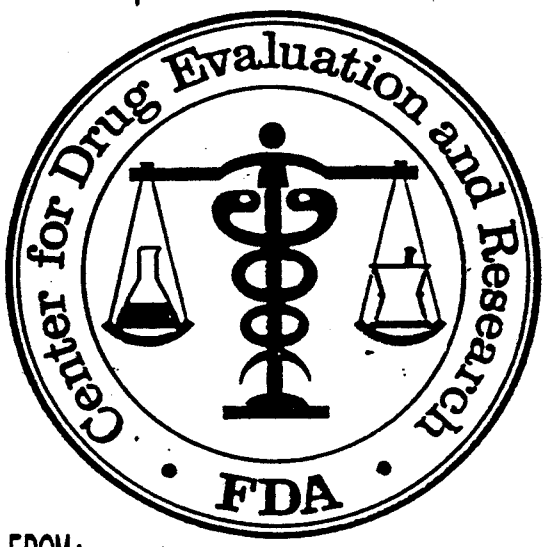
Fax No. (301) 443-9285

Phone No. (301) 443-0483

Total No. of Pages 4

FOOD AND DRUG ADMINISTRATION
DIVISION OF GASTROINTESTINAL
AND COAGULATION DRUG PRODUCTS
DOCUMENT CONTROL ROOM 6B-24
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE 8/20/96



TO:

Name Margie Nemcik-Cruz

Fax No. (415) 856-1555

Phone No. (415) 856-1558

Location Salix Pharmaceuticals

FROM:

Name Melodi McNeil

Fax No. (301) 443-9285

Phone No. (301) 443-0483

Total No. of Pages
Including Cover 4

Comments:

Here's the letter we discussed; I'm sorry you received an incomplete version.

Melodi McNeil

Salix Pharmaceuticals
Attention: Margie Nemcik-Cruz
3600 W. Bayshore Road, Suite 205
Palo Alto, CA 94303

Dear Ms. Cruz:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for Colazide (balsalazide) Capsules.

We also refer to your amendment dated September 20, 1994, serial number 039, submitted in response to our letter dated June 22, 1994 informing you of the inadequacy of the mouse (Report # ____), and rat (Report # ____), carcinogenicity studies conducted by Biorex, and requesting that you inform all investigators that balsalazide was mutagenic in the mammalian cell (CHL/HGPRT) forward gene mutation assay. In this amendment you acknowledge that carcinogenicity studies in mouse and rats were not conducted according to GLP regulations, were not inspected by QUA and the dose selection in bioassay in mouse and rat conducted by Biorex was not based on dose-ranging studies. However, you indicate that a repeat mouse carcinogenicity study is not needed since no tumorigenic potential of the drug was seen in the Biorex mouse carcinogenicity study.

We have completed the review of your submission, and have the following comments and requests:

1. Your reasons for not repeating the mouse carcinogenicity study are not acceptable because the mouse carcinogenicity study conducted by Biorex is inadequate. We reiterate our suggestion that you conduct a 13-week oral (gavage) dose-ranging study in mice and submit the report along with the protocol for repeat carcinogenicity study in mice for our review and evaluation.

2. We note that you have decided to conduct a mouse lymphoma cell L15178/TK forward gene mutation assay to further clarify the observed positive results in the CHL/HGPRT forward gene mutation assay. In the meantime, we ask that you amend the present Investigator's brochure (pages 1016 and 1020 of Volume 1 of the initial submission) which inaccurately depicts the results of CHL/HGPRT forward gene mutation assay as negative. Your amended brochure should reflect the positive results of the test accurately.

If you have any questions, please contact:

Kati Johnson
Consumer Safety Officer
(301) 443-0487

Sincerely yours,

1/3/95

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Orig IND
HFD-180
HFD-180/JChoudary
HFD-180/CSO
R/D init: JChoudary 12/13/94
SFredd 12/28/94
kj/November 28, 1994
kj/November 28, 1994/c:\wpfiles\cso

AD

APPEARS THIS WAY
ON ORIGINAL

JUN 22 1994

Salix Pharmaceuticals
Attention: Margie Nemcik-Cruz
3600 W. Bayshore Road
Palo Alto, CA 94303

Dear Ms. Nemcik-Cruz:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for Colazide (balsalazide sodium) Capsules.

We also refer to your amendments dated January 15 and 29, 1992, August 18, November 3, December 1, 1993, and January 6, 1994.

We have completed the pharmacology review of the preclinical portions of your submissions, and have the following recommendations and requests:

1. The carcinogenicity studies in mouse (Report # ——— No. 2) and rats (Report ——— No. 1) are inadequate for the following reasons:

   a. These studies were presumably conducted by ——— ——— in the early 1980's and ——— ——— "reconstructed or reassembled" the information for submission in November 1993.

   b. ——— accepts no responsibility for the recording or integrity of the raw data.

   c. There was no evidence that the conduct of the studies complied with FDA GLP guidelines and quality assurance was also lacking.

   d. There were no previous dose-ranging studies for the selection of the doses for the mouse and rat carcinogenicity studies and sufficiently high doses were not employed in the carcinogenicity studies.

2. We recommend that you conduct oral gavage dose-ranging studies of balsalazide in mice and rats for selecting appropriate doses for the oral (gavage) carcinogenicity studies in the same strains of animals. We recommend that you submit the full reports of such dose-ranging studies along with the protocols for the proposed repeat carcinogenicity studies of balsalazide in mice and rats for our consideration.

3. You should inform all the investigators that balsalazide was mutagenic in the mammalian cell (CHO/HGPRT) forward gene mutation assay. In addition, you should conduct forward gene mutation assay at the TK locus in L15178 mouse lymphoma cells.

If you have any questions, please contact:

Kati Johnson
Consumer Safety Officer
(301) 443-0487

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Orig IND
HFD-180
HFD-180/JChoudary
HFD-180/CSO
R/D init: JChoudary 6/21/94
SFredd 6/21/94
kj/June 17, 1994
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AD

APPEARS THIS WAY
ON ORIGINAL

This information is in the Pharmacology review dated November 4, 1997

/S/ 5/22/98

Melodi McNeil, Regulatory Health Project Manager

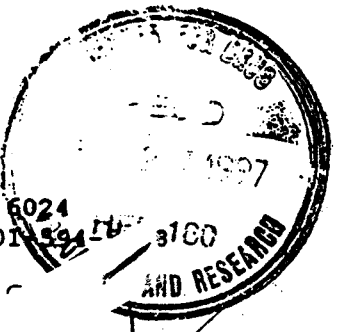
also see attached

APPEARS THIS WAY
ON ORIGINAL

Printed by Joseph DeGeorge

Electronic Mail Message

151



ivity: COMPANY CONFIDENTIAL

Date:
From: Joseph DeGeorge
Dept: HFD-024 WOC2 6024
Tel No: 301-594-6758 FAX 301-594-[illegible]3100

: Joseph DeGeorge (DEGEORGE)

bject: Re: Rat Carcinogenicity Study

C Executive Committee Report February 7, 1997

plication:
vision: HFD-180
te: February 4, 1996
viewer: Dr. Ahmad
air Person: Dr. Degeorge
mbers: Drs Contrera, Chen and Choudary
bject: Rat carcinogenicity study

104-week dietary carcinogenicity study in rats, doses of 120, 600 and 00 mg/kg/day were used. In this study, highest tested dose is the ximum tolerated dose since at this dose level body weight in males and les were 17% and 19% lower than the control body weights ectively. Treatment had no significant effect on food consumption. tment had no significant effect of intercurrent mortality rates. vival rates at the end of treatment period were comparable in all oups. Significant increase in the incidence of benign eochromocytoma in adrenal was seen in high dose treated male rats ontrol 1 = 13.3%, control 2 = 6.7%, low dose =13.3%, mid dose = 15% d high dose = 30%, $p < 0.001$ [trend test], pairwise: control 1 vs gh dose; $p = 0.003$ and control 2 vs high dose; $p = 0.001$). However, te of incidence of benign pheochromocytoma in adrenal of high dose eated males (30%)was "within laboratory historical control incidence nge (10-46%)". No other treatment related neoplastic findings were ident in this study. Hence, given the data currently available, it concluded that the study is negative for carcinogenic potential in rats. In this study dose selection was appropriate and study nduct was acceptable. All Exec. CAC members concurred with this nclusion.

::

FD-180/div file
FD-180/Dr. Ahmad
FD-180/Dr. Choudary

Executive CAC Final Report

/S/ V 4/21/97

April 8, 1997

Committee: Joseph DeGeorge, Ph.D, HFD-24, Chair
Albert Defelice, Ph.D, HFD-110, Acting Member
Ronald Steigerwalt, Ph.D, HFD-510, Acting Member
Jasti Choudary, B.V. Sc., Ph.D, HFD-180, Division Representative
Lillian Patrician, MS, MBA, HFD-024, Project Manager

(Ahmad/Choudary; HFD-180)

APR 24 1997

Colazide
Salix Pharmaceuticals, Inc.

Executive CAC meeting was convened, in part to assess protocols of 4-week dose ranging study in p53 +/- transgenic mice and 26-week oral carcinogenicity study in 6-8 weeks old p53+/- transgenic mice.

Protocol of 4-Week Dose Ranging Study in p53 +/- Transgenic Mice: To determine the maximum tolerated dose in p53 +/- transgenic mice, 6-8 weeks old p53 +/- transgenic mice (Knockout) of both sexes (5/sex/group) will be given 0 (vehicle), 375, 750, 1500 or 3000 mg/kg/day (10 ml/kg) of colazide orally (gavage) for 28 days. During the study period, clinical signs, body weights, food intakes, hematology and blood chemistry parameters will be monitored. Histopathological examinations will be limited to control and high dose treated mice and all gross lesions in all groups.

The protocol was acceptable to the Division. The Division also suggested that the sponsor monitor drug exposure (i.e. plasma AUC values for colazide [parent drug], 5-ASA [5-aminosalicylic acid: active moiety] and ABA [4-aminobenzoyl-beta alanine: carrier molecule]) at various dose levels and provide metabolism data in mice and human and protein binding data in mice and human. If the MTD could not be identified then these exposure data will be useful in selecting high dose in the planned carcinogenicity study in transgenic p 53 +/- mice.

The CAC Exec. members concluded:
1) The over all design of the protocol was acceptable with the following modifications and suggestions.

(a) The CAC accepted the dose ranging study in the mouse, but suggested the sponsor use the wild type strain from which the p53 strain is derived. The Reviewer will advise the sponsor that this is unnecessary to conduct dose ranging in the p53 transgenic animals. It is expensive, and findings can be realized in the parent line or wild type mouse of the same strain from which p 53 +/- is derived i.e. C57BL/6 mice.
(b) The sponsor should also be informed to use sufficient number of mice in the dose ranging study to obtain toxicokinetic data.

Protocol of 26-Week Oral Carcinogenicity Study in p53 +/- Transgenic Mice: According to the sponsor's proposed protocol, 6-8 weeks old p53 +/- transgenic mice (Knockout) of both sexes (20/sex/group) will be given 0 (vehicle), 500, 1000 or 2000 mg/kg/day of colazide orally (gavage) for 26 weeks. An additional group of p53 +/- mice (20/sex) will be included in this study which will be used as positive control (bromodichloromethane: 100 mg/kg/day for 26 weeks). During the study period, clinical signs, body weights, and food intakes will be monitored. At the end of treatment period all animals will be sacrificed and subjected to complete necropsy and histopathological examinations.

The Division indicated that the protocol is acceptable, except for the dose selection. The sponsor is to be informed that the dose selection in the 26-week carcinogenicity study should be based on the results of the 4-week dose ranging study in mice using ICH principals for dose selection. If the sponsor wants to select dose levels on the basis of exposure level, then they should provide necessary supporting data (see above). The Division also indicated that they should use p-cresidine (mutagen in Salmonella assay, and induces urinary bladder tumors in mice and rats and also gave a positive results in p53 +/- C57BL/6 mice) as a positive control instead of bromodichloromethane, since bromodichloromethane has not been tested in transgenic p53 +/- mice. The Division also recommended to use p-anisidine (mutagenic non-carcinogen as negative control in the proposed carcinogenicity protocol.

The CAC Exec. members concluded the sponsor should be informed that:

1) the overall study design/ protocol is acceptable
2) concurrence on the proposed doses could not be provided without supporting dose ranging study results
3) there is no need to include a negative control for regulatory evaluation purposes (i.e. p-anisidine: mutagenic and non-carcinogen) in the proposed carcinogenicity protocol but that a p53 confirmed positive control was important.

The above conclusions of the Executive CAC are to be conveyed to the sponsor as Center guidance on the evaluated protocols.

cc:

HFD-180/CSO
HFD-181/CSO
HFD-180 / Dr. Ahmad
HFD-180 / Dr. Chowdary