

Table 16-1.

Summary of gross findings
(sacrificed, administration period)

Exp. No. 9933 (115-212)

Dose level (mg/kg)	No. of animals necropsied	Male animals				Female animals			
		0	20	100	500	0	20	100	500
Organ	Findings	5	5	5	5	5	5	5	3
CARDIOVASCULAR SYSTEM									
heart	hypertrophic	0	0	0	0	0	0	0	1
	nodule	0	0	0	0	0	0	0	1
	scarred	0	0	0	0	0	0	0	1
HEMATOPOIETIC SYSTEM									
spleen	dark	0	0	0	2	0	0	0	2
	white patch/zone	0	0	0	0	0	0	1	1
RESPIRATORY SYSTEM									
lung	brown patch/zone	0	0	0	0	0	0	0	1
DIGESTIVE SYSTEM									
stomach	black patch/zone	0	0	0	0	0	0	1	0
	red patch/zone	0	0	0	1	0	0	0	1
	white patch/zone	0	0	0	3	0	0	0	0
liver	dark	0	0	0	0	0	0	0	1
	white patch/zone	0	0	0	0	0	0	0	1
URINARY SYSTEM									
kidney	cyst	0	1	0	0	0	0	0	0
	dark	0	0	0	1	0	0	0	0
	scarred	0	0	1	0	0	0	0	0
REPRODUCTIVE SYSTEM									
testis	small	0	0	0	1	-	-	-	-
prostate	small	0	0	0	4*	-	-	-	-
seminal vesicle	small	0	0	0	4*	-	-	-	-
uterus	dilated lumen	-	-	-	-	0	1	1	0
ENDOCRINE SYSTEM									
adrenal gland	scarred	0	0	0	1	0	0	0	0

Significantly different from control group; * : $P \leq 0.05$ (Fisher)

Table 16-2.

Summary of gross findings
(dead, administration period)

Exp. No. 9933 (115-212)

Dose level (mg/kg)	No. of animals necropsied	Female animals			
		0	20	100	500
Organ	Findings				
HEMATOPOIETIC SYSTEM					
spleen	small	-	-	-	2
thymus	atrophic	-	-	-	1
DIGESTIVE SYSTEM					
stomach	autolysis	-	-	-	1
	black patch/zone	-	-	-	1
small intestine	autolysis	-	-	-	2
large intestine	autolysis	-	-	-	2
liver	autolysis	-	-	-	2
ENDOCRINE SYSTEM					
adrenal gland	hypertrophic	-	-	-	2
NERVOUS SYSTEM					
brain	autolysis	-	-	-	2

Table 16-3.

Summary of gross findings
(sacrificed, recovery period)

Exp. No. 9933 (115-212)

Dose level (mg/kg)	No. of animals necropsied	Male animals		Female animals	
		0	500	0	500
Organ	Findings	5	5	5	5
RESPIRATORY SYSTEM					
lung	black patch/zone	0	1	0	0
DIGESTIVE SYSTEM					
stomach	nodule	1	0	0	0
	white patch/zone	1	1	0	0
liver	hepatodiaphragmatic nodule	0	0	1	0
URINARY SYSTEM					
kidney	scarred	1	0	0	0
	white patch/zone	0	0	1	0
REPRODUCTIVE SYSTEM					
testis	small	0	1	-	-
prostate	small	0	1	-	-
seminal vesicle	small	0	1	-	-

Table 17-1.

Summary of histological findings
(sacrificed, administration period)

Exp. No. 9933 (115-212)

Sex: Male

Dose level (mg/kg)	0				20				100				500			
No. of animals necropsied	5				5				5				5			
No. of animals examined histologically	5				5				5				5			
Organ	Findings				Findings				Findings				Findings			
	1	2	3	T	1	2	3	T	1	2	3	T	1	2	3	T
CARDIOVASCULAR SYSTEM																
heart	(5)				(5)				(5)				(5)			
cellular infiltration, mononuclear	0	0	0	0	3	0	0	3	1	1	0	2	0	1	0	1
HEMATOPOIETIC SYSTEM																
spleen	(5)				(5)				(5)				(5)			
congestion	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
deposit, pigment	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	3
increase, extramedullary hematopoiesis	0	0	0	0	1	0	0	1	0	0	0	0	1	0	0	1
RESPIRATORY SYSTEM																
lung	(5)				(0)				(0)				(5)			
accumulation of foamy cells	1	0	0	1	-	-	-	-	-	-	-	-	1	0	0	1
cellular infiltration, mixed	0	0	0	0	-	-	-	-	-	-	-	-	1	0	0	1
osseous metaplasia	0	0	0	0	-	-	-	-	-	-	-	-	1	0	0	1
DIGESTIVE SYSTEM																
forestomach	(5)				(5)				(5)				(5)			
edema, intraepithelial	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0
hemorrhage	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
fibrosis	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
squamous hyperplasia	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	3
cecum	(5)				(5)				(5)				(5)			
basophilic change	0	0	0	0	0	0	0	0	0	0	0	0	1	2	0	3
cellular infiltration, eosinophile	0	0	0	0	0	0	0	0	1	0	0	1	1	0	0	1
cellular infiltration, mixed	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
increase in mitosis	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	5***
colon	(5)				(5)				(5)				(5)			
hemorrhage	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
basophilic change	0	0	0	0	0	0	0	0	0	0	0	0	3	1	0	4*#
cellular infiltration, eosinophile	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0
increase in mitosis	0	0	0	0	0	0	0	0	1	0	0	1	5	0	0	5***
rectum	(5)				(0)				(0)				(5)			
cellular infiltration, mixed	0	0	0	0	-	-	-	-	-	-	-	-	1	0	0	1
liver	(5)				(5)				(5)				(5)			
eosinophilic change, hepatocyte	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	4*#
microgranuloma	3	0	0	3	3	0	0	3	3	0	0	3	2	0	0	2
hypertrophy, hepatocyte, centrilobular	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	4*#

1: slight 2: moderate 3: marked T: total
 (): No. of animals examined microscopically at this site.
 Significantly different from control group; *: P≤0.05
 Significantly different from control group; #: P≤0.05

-: Not applicable.
 **: P≤0.01 (Fisher)
 ##: P≤0.01 (Mann-Whitney)

Table 17-1. -continued Summary of histological findings
(sacrificed, administration period)

Exp. No. 9933 (115-212)

Sex: Male

Dose level (mg/kg)	0				20				100				500			
No. of animals necropsied	5				5				5				5			
No. of animals examined histologically	5				5				5				5			
Organ	Findings				Findings				Findings				Findings			
	1	2	3	T	1	2	3	T	1	2	3	T	1	2	3	T
URINARY SYSTEM																
kidney	(5)				(1)				(1)				(5)			
basophilic tubule	1	0	0	1	0	0	0	0	1	0	0	1	0	0	0	0
degeneration, vacuolar, tubule	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
dilatation, tubule	0	0	0	0	1	0	0	1	1	0	0	1	0	0	0	0
cellular infiltration, lymphocyte	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
REPRODUCTIVE SYSTEM																
prostate	(5)				(5)				(5)				(5)			
atrophy	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	3
cellular infiltration, lymphocyte	0	0	0	0	1	0	0	1	1	0	0	1	1	0	0	1
seminal vesicle	(5)				(5)				(5)				(5)			
atrophy	0	0	0	0	0	0	0	0	0	0	0	0	3	1	0	4*#
ENDOCRINE SYSTEM																
adrenal gland	(5)				(5)				(5)				(5)			
angiectasis	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	2
degeneration, vacuolar	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	3
necrosis	0	0	0	0	0	0	0	0	0	0	0	0	2	1	0	3
accumulation of macrophage	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	3
hypertrophy, cortex	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	3

1: slight 2: moderate 3: marked T: total
 (): No. of animals examined microscopically at this site.
 Significantly different from control group; *: P≤0.05 (Fisher)
 Significantly different from control group; #: P≤0.05 (Mann-Whitney)

-: Not applicable.

(Fisher)
(Mann-Whitney)

Table 17-1. -continued Summary of histological findings
(sacrificed, administration period)

Exp. No. 9933 (115-212)

Sex: Female

Dose level (mg/kg)	0				20				100				500				
No. of animals necropsied	5				5				5				3				
No. of animals examined histologically	5				5				5				3				
Organ	Findings	1	2	3	T	1	2	3	T	1	2	3	T	1	2	3	T
CARDIOVASCULAR SYSTEM																	
heart		(5)				(5)				(5)				(3)			
	myxoid change	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
	cellular infiltration, mononuclear	2	0	0	2	0	0	0	0	0	0	0	0	1	0	0	1
	pericarditis	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
	fibrosis	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
	hypertrophy, myocardium	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
HEMATOPOIETIC SYSTEM																	
spleen		(5)				(5)				(5)				(3)			
	congestion	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	3*#
	atrophy	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
	deposit, pigment	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	3*#
	capsulitis	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
	increase, extramedullary hematopoiesis	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
RESPIRATORY SYSTEM																	
lung		(5)				(0)				(0)				(3)			
	accumulation of foamy cells	0	0	0	0	-	-	-	-	-	-	-	-	1	0	0	1
	accumulation of macrophage	1	0	0	1	-	-	-	-	-	-	-	-	0	0	0	0
DIGESTIVE SYSTEM																	
forestomach		(5)				(5)				(5)				(3)			
	edema	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
	ulcer	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
	squamous hyperplasia	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
glandular stomach		(5)				(5)				(5)				(3)			
	edema	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
colon		(5)				(5)				(5)				(3)			
	basophilic change	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
	hyperplasia, lymphoid tissue	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
	increase in mitosis	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	2
liver		(5)				(5)				(5)				(3)			
	congestion	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
	eosinophilic change, hepatocyte	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	3*#
	vacuolation in hepatocyte	4	0	0	4	1	0	0	1	0	0	0	0*#	1	0	0	1
	microgranuloma	5	0	0	5	5	0	0	5	3	0	0	3	2	0	0	2
	hypertrophy, hepatocyte, centrilobular	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1

1: slight 2: moderate 3: marked T: total
 (): No. of animals examined microscopically at this site.
 Significantly different from control group; *: P<0.05
 Significantly different from control group; #: P<0.05

-: Not applicable.
 (Fisher)
 (Mann-Whitney)

Table 17-1. -continued Summary of histological findings
(sacrificed, administration period)

Exp. No. 9933 (115-212)

Sex: Female

Dose level (mg/kg)	0				20				100				500			
No. of animals necropsied	5				5				5				3			
No. of animals examined histologically	5				5				5				3			
Organ	Findings				1 2 3 T				1 2 3 T				1 2 3 T			
URINARY SYSTEM																
kidney	(5)				(0)				(0)				(3)			
basophilic tubule dilatation, tubule mineralization	2	0	0	2	-	-	-	-	-	-	-	-	0	0	0	0
	2	0	0	2	-	-	-	-	-	-	-	-	0	0	0	0
	1	0	0	1	-	-	-	-	-	-	-	-	2	0	0	2
REPRODUCTIVE SYSTEM																
uterus	(5)				(1)				(1)				(3)			
dilatation, lumen	0	0	0	0	1	0	0	1	1	0	0	1	0	0	0	0
ENDOCRINE SYSTEM																
adrenal gland	(5)				(5)				(5)				(3)			
angiectasis	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	2
degeneration, vacuolar	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	3*#
necrosis	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	3*#
accumulation of macrophage	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	2
hypertrophy, cortex	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	2

1: slight 2: moderate 3: marked T: total
 (): No. of animals examined microscopically at this site.
 Significantly different from control group; *: P≤0.05 (Fisher)
 Significantly different from control group; #: P≤0.05 (Mann-Whitney)

-: Not applicable.

Table 17-2.

Summary of histological findings
(dead, administration period)

Exp. No. 9933 (115-212)

Sex: Female

Dose level (mg/kg)	0				20				100				500				
No. of animals necropsied	0				0				0				2				
No. of animals examined histologically	0				0				0				2				
Organ	Findings				1 2 3 T				1 2 3 T				1 2 3 T				
CARDIOVASCULAR SYSTEM																	
heart													(2)				
	cellular infiltration, mononuclear	-	-	-	-	-	-	-	-	-	-	-	-	1	0	0	1
HEMATOPOIETIC SYSTEM																	
spleen													(2)				
	atrophy	-	-	-	-	-	-	-	-	-	-	-	-	2	0	0	2
thymus													(2)				
	atrophy	-	-	-	-	-	-	-	-	-	-	-	-	1	0	0	1
RESPIRATORY SYSTEM																	
lung													(2)				
	accumulation of foamy cells	-	-	-	-	-	-	-	-	-	-	-	-	1	0	0	1
DIGESTIVE SYSTEM																	
glandular stomach													(2)				
	ulcer	-	-	-	-	-	-	-	-	-	-	-	-	1	0	0	1
mandibular gland													(2)				
	decrease, eosinophilic granule	-	-	-	-	-	-	-	-	-	-	-	-	2	0	0	2
ENDOCRINE SYSTEM																	
adrenal gland													(2)				
	congestion	-	-	-	-	-	-	-	-	-	-	-	-	1	0	0	1
	degeneration, vacuolar	-	-	-	-	-	-	-	-	-	-	-	-	1	0	0	1
	necrosis	-	-	-	-	-	-	-	-	-	-	-	-	0	1	0	1
	hypertrophy, cortex	-	-	-	-	-	-	-	-	-	-	-	-	1	0	0	1

1: slight 2: moderate 3: marked T: total
(): No. of animals examined microscopically at this site.

-: Not applicable.

Table 17-3.

Summary of histological findings
(sacrificed, recovery period)

Exp. No. 9933 (115-212)

Sex: Male

Dose level (mg/kg)	0				500					
No. of animals necropsied	5				5					
No. of animals examined histologically	5				5					
Organ	Findings	1	2	3	T	1	2	3	T	
CARDIOVASCULAR SYSTEM										
heart		(5)				(5)				
	necrosis	1	0	0	1	0	0	0	0	
	cellular infiltration, mononuclear	2	0	0	2	0	0	0	0	
	fibrosis	1	0	0	1	0	0	0	0	
HEMATOPOIETIC SYSTEM										
spleen		(5)				(5)				
	deposit, pigment	0	0	0	0	5	0	0	5***##	
RESPIRATORY SYSTEM										
lung		(5)				(5)				
	accumulation of foamy cells	2	0	0	2	1	0	0	1	
	cellular infiltration, mixed	0	0	0	0	1	0	0	1	
DIGESTIVE SYSTEM										
glandular stomach		(5)				(5)				
	ectopic tissue	1	0	0	1	0	0	0	0	
	epidermal cyst	1	0	0	1	0	0	0	0	
jejunum		(5)				(5)				
	mineralization	1	0	0	1	0	0	0	0	
colon		(5)				(5)				
	hyperplasia, lymphoid tissue	0	0	0	0	1	0	0	1	
liver		(5)				(5)				
	microgranuloma	4	0	0	4	5	0	0	5	
URINARY SYSTEM										
kidney		(5)				(5)				
	dilatation, tubule	1	0	0	1	0	0	0	0	
	mineralization	3	0	0	3	1	0	0	1	
	cellular infiltration, lymphocyte	1	0	0	1	1	0	0	1	
REPRODUCTIVE SYSTEM										
epididymis		(5)				(5)				
	decrease, sperm	0	0	0	0	1	0	0	1	
prostate		(5)				(5)				
	cellular infiltration, lymphocyte	1	1	0	2	1	0	0	1	

1: slight 2: moderate 3: marked T: total
 (): No. of animals examined microscopically at this site. -: Not applicable.
 Significantly different from control group; **: P≤0.01 (Fisher)
 Significantly different from control group; ##: P≤0.01 (Mann-Whitney)

Table 17-3. -continued Summary of histological findings
(sacrificed, recovery period)

Exp. No. 9933 (115-212)

Sex: Male

Dose level (mg/kg)	0				500				
No. of animals necropsied	5				5				
No. of animals examined histologically	5				5				
Organ	Findings	1	2	3	T	1	2	3	T
REPRODUCTIVE SYSTEM									
seminal vesicle		(5)				(5)			
atrophy		0	0	0	0	1	0	0	1
ENDOCRINE SYSTEM									
adrenal gland		(5)				(5)			
angiectasis		0	0	0	0	1	0	0	1
degeneration, vacuolar		0	0	0	0	3	0	0	3
necrosis		0	0	0	0	0	1	0	1
accumulation of macrophage		0	0	0	0	5	0	0	5***##
hypertrophy, cortex		0	0	0	0	1	0	0	1

1: slight 2: moderate 3: marked T: total
 (): No. of animals examined microscopically at this site. -: Not applicable.
 Significantly different from control group; **: P≤0.01 (Fisher)
 Significantly different from control group; ##: P≤0.01 (Mann-Whitney)

Table 17-3. -continued Summary of histological findings
(sacrificed, recovery period)

Exp. No. 9933 (115-212)

Sex: Female

Dose level (mg/kg)	0				500				
No. of animals necropsied	5				5				
No. of animals examined histologically	5				5				
Organ	Findings	1	2	3	T	1	2	3	T
HEMATOPOIETIC SYSTEM									
spleen		(5)				(5)			
	deposit, pigment	0	0	0	0	4	0	0	4*#
RESPIRATORY SYSTEM									
lung		(5)				(5)			
	accumulation of foamy cells	2	0	0	2	0	0	0	0
	osseous metaplasia	2	0	0	2	0	0	0	0
DIGESTIVE SYSTEM									
liver		(5)				(5)			
	vacuolation in hepatocyte	1	0	0	1	0	0	0	0
	microgranuloma	5	0	0	5	5	0	0	5
	hepatodiaphragmatic nodule	1	0	0	1	0	0	0	0
URINARY SYSTEM									
kidney		(5)				(5)			
	mineralization	2	0	0	2	0	0	0	0
	fibrosis	1	0	0	1	0	0	0	0
ENDOCRINE SYSTEM									
thyroid gland		(5)				(5)			
	ultimobranchial remnant	0	0	0	0	1	0	0	1
adrenal gland		(5)				(5)			
	angiectasis	0	0	0	0	3	2	0	5***##
	degeneration, vacuolar	0	0	0	0	3	0	0	3
	accumulation of macrophage	0	0	0	0	2	0	0	2

1: slight 2: moderate 3: marked T: total
 (): No. of animals examined microscopically at this site.
 Significantly different from control group; *: P<0.05
 Significantly different from control group; #: P<0.05

-: Not applicable.
 **: P<0.01 (Fisher)
 **#: P<0.01 (Mann-Whitney)