# APPENDIX B SUMMARY OF LESIONS IN REGIMEN B FEMALE MICE IN THE 2-YEAR GAVAGE STUDY OF CHLORAL HYDRATE

TABLE B1	Summary of the Incidence of Neoplasms in Regimen B 100 mg/kg Female Mice	
	in the 2-Year Gavage Study of Chloral Hydrate	B-2
TABLE B2	Statistical Analysis of Primary Neoplasms at 2 Years	
	in Regimen B 100 mg/kg Female Mice in the 2-Year Gavage Study	
	of Chloral Hydrate	В-8
TABLE B3	Summary of the Incidence of Nonneoplastic Lesions	
	in Regimen B 100 mg/kg Female Mice in the 2-Year Gavage Study	
	of Chloral Hydrate	B-11

# B-2 Chloral Hydrate, NTP TR 502

Table B1 Summary of the Incidence of Neoplasms in Regimen B 100 mg/kg Female Mice in the 2-Year Gavage Study of Chloral Hydrate  $^{\rm a}$ 

	Vehicle Control <sup>b</sup>	3 Months (Stop-Exposure)	6 Months (Stop-Exposure)	12 Months (Stop-Exposure)
Disposition Summary				
Animals initially in study	72	48	48	48
3-Month interim evaluation	8	8		
6-Month interim evaluation	8		8	
12-Month interim evaluation	8			8
Early deaths				
Moribund	2	2	3	
Natural deaths	9	4	6	7
Survivors				
Terminal sacrifice	37	34	31	33
Animals examined microscopically	72	48	48	48

#### Systems Examined at 3 Months with No Neoplasms Observed

Alimentary System
Cardiovascular System
Endocrine System
General Body System
Genital System
Hematopoietic System
Integumentary System
Musculoskeletal System
Nervous System
Respiratory System
Special Senses System

#### 6-Month Interim Evaluation

Respiratory System

**Urinary System** 

Lung (8)
Alveolar/bronchiolar adenoma 1 (13%)

#### Systems Examined with No Neoplasms Observed

Alimentary System
Cardiovascular System
Endocrine System
General Body System
Genital System
Hematopoietic System
Integumentary System
Musculoskeletal System
Nervous System
Special Senses System
Urinary System

TABLE B1

Summary of the Incidence of Neoplasms in Regimen B 100 mg/kg Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control	3 Months (Stop-Exposure)	6 Months (Stop-Exposure)	12 Months (Stop-Exposure)
12-Month Interim Evalua Alimentary System Mesentery Yolk sac carcinoma, metastatic, ovary	(1) 1 (100%)			
Genital System Ovary Yolk sac carcinoma	(8) 1 (13%)			(7)
Systems Examined with No Neop Cardiovascular System Endocrine System General Body System Hematopoietic System Integumentary System Musculoskeletal System Nervous System Respiratory System Special Senses System Urinary System	plasms Observed			
2-Year Study				
Alimentary System Esophagus	(47)	(36)	(40)	(38)
Lymphoma malignant Gallbladder	(46)	(37)	1 (3%) (36)	(36)
Lymphoma malignant	(40)	2 (5%)	(30)	(30)
Intestine large, cecum	(42)	(37)	(37)	(32)
Lymphoma malignant	1 (2%)	2 (5%)	(27)	(24)
Intestine large, colon Lymphoma malignant	(46) 2 (4%)	(37)	(37) 1 (3%)	(34)
Intestine small, jejunum	(41)	(37)	(37)	(32)
Lymphoma malignant	2 (5%)	1 (3%)	1 (3%)	
Liver Fibrosarcoma, metastatic, skin	(48)	(40)	(40)	(40)
Hepatocellular adenoma	1 (2%)	1 (3%)	1 (3%) 1 (3%)	2 (5%)
Hepatocellular carcinoma	1 (2%)	(,	1 (3%)	2 (5%)
Histiocytic sarcoma	1 (2%)	(150()	1 (3%)	1 (3%)
Lymphoma malignant Mesentery	6 (13%)	6 (15%) (1)	7 (18%)	8 (20%)
Fibrosarcoma, metastatic, skin	(1)	(1)	(2) 1 (50%)	
Lymphoma malignant	1 (100%)		(= =,=)	
Pancreas	(48)	(40)	(39)	(37)
Fibrosarcoma Fibrosarcoma, metastatic, skin	1 (2%)		2 (5%)	
Lymphoma malignant	2 (4%)	2 (5%)	5 (13%)	1 (3%)
, r g	. (.,)	(= ,= ,	- (,-)	(=,

B-4 Chloral Hydrate, NTP TR 502
TABLE B1
Summary of the Incidence of Neoplasms in Regimen B 100 mg/kg Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control	3 Months (Stop-Exposure)	6 Months (Stop-Exposure)	12 Months (Stop-Exposure)
2-Year Study (continued) Alimentary System (continued) Salivary glands Lymphoma malignant Tongue Lymphoma malignant Papilloma squamous	(48) 3 (6%) (48) 1 (2%)	(40) 3 (8%) (39)	(40) 3 (8%) (39) 1 (3%)	(39) 2 (5%) (40)
Cardiovascular System  Heart  Histiocytic sarcoma  Lymphoma malignant	(48) 1 (2%) 1 (2%)	(40)	(40) 1 (3%)	(39)
Endocrine System  Adrenal gland, cortex  Adenoma, spindle cell  Lymphoma malignant  Adrenal gland, medulla  Lymphoma malignant  Pheochromocytoma malignant  Islets, pancreatic  Lymphoma malignant  Parathyroid gland  Adenoma  Pituitary gland  Adenoma, pars distalis  Adenoma, pars intermedia  Thyroid gland  Adenoma, follicular cell  Lymphoma malignant	(46)  1 (2%) (46) 1 (2%) 1 (2%) (48) (38) (45) 2 (4%) (47)	(40) 1 (3%) (40) (40) 1 (3%) (31) (36) 3 (8%) (40) 1 (3%) 1 (3%)	(37) (37) (37) (38) (38) (36) (38) (40) (40) (38) (38)	(37)  1 (3%) (37) 1 (3%) (38) (36) (33) 1 (3%) (39)
General Body System Tissue NOS Fibrosarcoma, metastatic, skin Lymphoma malignant, fat	(1) 1 (100%)	(1)	1 (100%)	
Genital System Clitoral gland Lymphoma malignant Ovary Cystadenoma Fibrosarcoma, metastatic, periovarian tissue, skin Histiocytic sarcoma Luteoma Lymphoma malignant Lymphoma malignant Lymphoma benign	(43) (48) 1 (2%)  1 (2%) 1 (2%) 2 (4%) 1 (2%)	(37) (40) 4 (10%) 1 (3%)	(33) 1 (3%) (39) 2 (5%) 1 (3%)  2 (5%) 4 (10%)	(33) (38) 3 (8%) 1 (3%)

TABLE B1
Summary of the Incidence of Neoplasms in Regimen B 100 mg/kg Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control	3 Months (Stop-Exposure)	6 Months (Stop-Exposure)	12 Months (Stop-Exposure)
2-Year Study (continued)				
Genital System (continued)				
Uterus	(48)	(40)	(40)	(39)
Hemangiosarcoma	1 (2%)			
Histiocytic sarcoma	2 (4%)			1 (3%)
Lymphoma malignant			1 (3%)	1 (3%)
Polyp	1 (2%)	1 (3%)	1 (3%)	
Sarcoma stromal	(10)	(20)	(10)	1 (3%)
Vagina	(48)	(38)	(40)	(37)
Histiocytic sarcoma	2 (4%)	1 (3%)	1 (20/)	2 (5%)
Lymphoma malignant	2 (4%)	1 (3%)	1 (3%)	
Hematopoietic System				
Bone marrow	(47)	(39)	(40)	(38)
Hemangiosarcoma	1 (2%)	` ,	, ,	, ,
Lymphoma malignant	3 (6%)	3 (8%)	2 (5%)	
Lymph node	(48)	(40)	(40)	(40)
Histiocytic sarcoma, lumbar	1 (2%)			
Lymphoma malignant				1 (3%)
Lymphoma malignant, axillary	• (10()	1 (3%)	1 (3%)	
Lymphoma malignant, lumbar	2 (4%)	1 (3%)	1 (3%)	
Lymphoma malignant, mediastinal	1 (2%)		1 (3%)	
Lymphoma malignant, renal Lymphoma malignant, thoracic	1 (2%)		3 (8%)	1 (3%)
Squamous cell carcinoma, metastatic,			1 (3%)	1 (370)
lumbar, skin			1 (3%)	
Lymph node, mandibular	(47)	(40)	(39)	(39)
Lymphoma malignant	4 (9%)	4 (10%)	6 (15%)	7 (18%)
Lymph node, mesenteric	(46)	(40)	(38)	(39)
Fibrosarcoma, metastatic, skin			1 (3%)	
Histiocytic sarcoma	1 (2%)			1 (3%)
Lymphoma malignant	6 (13%)	6 (15%)	6 (16%)	8 (21%)
Spleen	(47)	(40)	(39)	(39)
Fibrosarcoma, metastatic, skin	4 (20)		1 (3%)	4 (20)
Hemangiosarcoma	1 (2%)			1 (3%)
Histiocytic sarcoma	9 (170/)	7 (190/)	11 (290/)	1 (3%)
Lymphoma malignant Thymus	8 (17%) (41)	7 (18%) (33)	11 (28%) (31)	8 (21%)
Fibrosarcoma, metastatic, skin	(41)	(33)	1 (3%)	(30)
Lymphoma malignant	3 (7%)	4 (12%)	5 (16%)	5 (17%)
Integumentary System	(44)	(2.6)	(20)	(2.6)
Mammary gland	(44)	(36)	(38)	(36)
Adenoacanthoma Adenocarcinoma		1 (20/)	1 (20/)	1 (3%)
Fibrosarcoma	1 (2%)	1 (3%)	1 (3%)	
Fibrosarcoma, metastatic, skin	1 (270)	1 (3%)		
Lymphoma malignant	1 (2%)	1 (370)	2 (5%)	
`L	- (=,0)		= (0,0)	

B-6 Chloral Hydrate, NTP TR 502
TABLE B1
Summary of the Incidence of Neoplasms in Regimen B 100 mg/kg Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control	3 Months (Stop-Exposure)	6 Months (Stop-Exposure)	12 Months (Stop-Exposure)
2-Year Study (continued) Integumentary System (continued) Skin Fibrosarcoma Hemangiosarcoma Lymphoma malignant Squamous cell carcinoma	(45) 1 (2%) 1 (2%)	(39) 2 (5%)	(39) 2 (5%) 2 (5%) 1 (3%)	(38)
Musculoskeletal System Skeletal muscle Fibrosarcoma, metastatic, skin Lymphoma malignant	(48)	(39) 1 (3%)	(40) 1 (3%) 2 (5%)	(39)
Nervous System Brain, cerebellum Lymphoma malignant Brain, cerebrum Lymphoma malignant Peripheral nerve Lymphoma malignant	(48) (48) (48)	(40) (40) (38) 1 (3%)	(40) 2 (5%) (40) 1 (3%) (39)	(40) (40) (38)
Respiratory System Lung Adenoacanthoma, metastatic, mammary glan Adenocarcinoma, metastatic, mammary glan Alveolar/bronchiolar adenoma Alveolar/bronchiolar carcinoma Fibrosarcoma, metastatic, skin Histiocytic sarcoma Lymphoma malignant Squamous cell carcinoma, metastatic, skin Nose Fibrosarcoma, metastatic, skin		(40)  2 (5%) 1 (3%)  3 (8%) (40) 1 (3%)	(40)  1 (3%) 4 (10%)  1 (3%)  4 (10%) 1 (3%) (40)	(40) 1 (3%) 7 (18%) 1 (3%) 8 (20%) (40)
Special Senses System Eye Histiocytic sarcoma, retrobulbar Harderian gland Adenoma Carcinoma Lymphoma malignant Lacrimal gland Lymphoma malignant Zymbal's gland Fibrosarcoma, metastatic, skin Lymphoma malignant	(41) (48) 2 (4%) 1 (2%) 2 (4%) (41) 1 (2%) (43)	(38) (38) 2 (5%) 2 (5%) (33) 2 (6%) (38) 1 (3%)	(34) (38) 2 (5%) 1 (3%) (33) 2 (6%) (36) 1 (3%)	(35) 1 (3%) (38) 3 (8%) (32) 2 (6%) (36)

TABLE B1
Summary of the Incidence of Neoplasms in Regimen B 100 mg/kg Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control	3 Months (Stop-Exposure)	6 Months (Stop-Exposure)	12 Months (Stop-Exposure)
2-Year Study (continued)				
Urinary System				
Kidney	(48)	(40)	(39)	(38)
Histiocytic sarcoma	1 (2%)	- 4		
Lymphoma malignant	6 (13%)	6 (15%)	7 (18%)	5 (13%)
Urinary bladder	(47)	(37)	(39) (36)	2 (00/)
Lymphoma malignant	3 (36%)	2 (5%)	2 (5%)	3 (8%)
Neoplasm Summary				
Total animals with primary neoplasms				
6-Month interim evaluation	1			
2-Year study	21	19	25	28
Total primary neoplasms	21	19	23	26
6-Month interim evaluation	1			
2-Year study	102	83	113	93
Total animals with benign neoplasms	102	03	113	75
6-Month interim evaluation	1			
2-Year study	8	11	13	13
Total benign neoplasms	O .		10	10
6-Month interim evaluation	1			
2-Year study	10	12	13	14
Total animals with malignant neoplasms				
12-Month interim evaluation	1			
2-Year study	16	13	19	21
Total malignant neoplasms				
12-Month interim evaluation	1			
2-Year study	92	71	100	79
Total animals with metastatic neoplasms				
12-Month interim evaluation	1			
2-Year study		2	4	1
Total metastatic neoplasms				
12-Month interim evaluation	1			
2-Year study		3	14	1

a Number of animals examined microscopically at the site and the number of animals with neoplasm

b Forty-eight mice served as vehicle controls for regimens A and B; the remaining 24 mice were designated for regimen B interim evaluations.

c Primary neoplasms: all neoplasms except metastatic neoplasms

B-8 Chloral Hydrate, NTP TR 502
TABLE B2
Statistical Analysis of Primary Neoplasms at 2 Years in Regimen B 100 mg/kg Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control (Regimen A)	3 Months (Stop-Exposure)	6 Months (Stop-Exposure)	12 Months (Stop-Exposure)	2 Years (Regimen A)
Harderian Gland: Adenoma	a				
Overall rate a	2/48 (4%)	2/38 (5%)	2/38 (5%)	3/38 (8%)	2/47 (4%)
Adjusted rate b	4.7%	5.6%	5.8%	8.3%	4.8%
Terminal rate		2/33 (6%)			
First incidence (days)	2/37 (5%) 757 (T)	2/33 (6%) 757 (T)	2/30 (7%) 757 (T)	3/33 (9%) 757 (T)	2/35 (6%) 757 (T)
Poly-3 test	P=0.5675	P=0.6275	P=0.6142	P=0.4216	P=0.6884
1 ory-3 test	1 =0.3073	1 =0.0273	1-0.0142	1-0.4210	1 -0.0004
Harderian Gland: Adenoma	a or Carcinoma				
Overall rate	3/48 (6%)	2/38 (5%)	2/38 (5%)	3/38 (8%)	2/47 (4%)
Adjusted rate	7.0%	5.6%	5.8%	8.3%	4.8%
Terminal rate	3/37 (8%)	2/33 (6%)	2/30 (7%)	3/33 (9%)	2/35 (6%)
First incidence (days)	757 (T)	757 (T)	757 (T)	757 (T)	757 (T)
Poly-3 test	P=0.4707N	P=0.5829N	P=0.5984N	P=0.5814	P=0.5072N
Liver: Hepatocellular Aden	oma				
Overall rate	1/48 (2%)	1/40 (3%)	1/40 (3%)	2/40 (5%)	2/48 (4%)
Adjusted rate	2.3%	2.7%	2.8%	5.3%	4.7%
Terminal rate	1/37 (3%)	1/34 (3%)	1/31 (3%)	2/33 (6%)	2/36 (6%)
First incidence (days)	757 (T)	757 (T)	757 (T)	757 (T)	757 (T)
Poly-3 test	P=0.3231	P=0.7287	P=0.7241	P=0.4553	P=0.5027
Liver: Hepatocellular Carci	inomo				
Overall rate	1/48 (2%)	0/40 (0%)	1/40 (3%)	2/40 (5%)	1/48 (2%)
Adjusted rate	2.3%	0.0%	2.8%	5.3%	2.3%
Terminal rate	1/37 (3%)	0/34 (0%)	1/31 (3%)	2/33 (6%)	1/36 (3%)
First incidence (days)	757 (T)	_e ` ´	757 (T)	757 (T)	757 (T)
Poly-3 test	P=0.4537	P=0.5288N	P=0.7241	P=0.4553	P=0.7589N
•					
Liver: Hepatocellular Aden		1/10/(00/)	2/10 (50)	1/40 (400)	240 (50)
Overall rate	2/48 (4%)	1/40 (3%)	2/40 (5%)	4/40 (10%)	3/48 (6%)
Adjusted rate	4.7%	2.7%	5.5%	10.6%	7.0%
Terminal rate	2/37 (5%)	1/34 (3%)	2/31 (7%)	4/33 (12%)	3/36 (8%)
First incidence (days)	757 (T)	757 (T)	757 (T)	757 (T)	757 (T)
Poly-3 test	P=0.2637	P=0.5502N	P=0.6343	P=0.2787	P=0.5035
Lung: Alveolar/bronchiolar	· Adenoma				
Overall rate	1/48 (2%)	2/40 (5%)	4/40 (10%)	7/40 (18%)	4/48 (8%)
Adjusted rate	2.3%	5.4%	11.0%	18.6%	9.4%
Terminal rate	1/37 (3%)	2/34 (6%)	4/31 (13%)	7/33 (21%)	4/36 (11%)
First incidence (days)	757 (T)	757 (T)	757 (T)	757 (T)	757 (T)
Poly-3 test	P=0.1385	P=0.4497	P=0.1309	P=0.0173	P=0.1805
Lung: Alveolar/bronchiolar	· Adenoma or Carcino	ma			
Overall rate	1/48 (2%)	3/40 (8%)	4/40 (10%)	7/40 (18%)	4/48 (8%)
Adjusted rate	2.3%	8.1%	11.0%	18.6%	9.4%
Terminal rate	1/37 (3%)	3/34 (9%)	4/31 (13%)	7/33 (21%)	4/36 (11%)
First incidence (days)	757 (T)	757 (T)	757 (T)	757 (T)	757 (T)
Poly-3 test	P=0.1887	P=0.2542	P=0.1309	P=0.0173	P=0.1805
•					

Chloral Hydrate, NTP TR 502 B-9
TABLE B2
Statistical Analysis of Primary Neoplasms at 2 Years in Regimen B 100 mg/kg Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control (Regimen A)	3 Months (Stop-Exposure)	6 Months (Stop-Exposure)	12 Months (Stop-Exposure)	2 Years (Regimen A)
Pituitary Gland (Pars Distalis)	: Adenoma				
Overall rate	0/45 (0%)	3/36 (8%)	1/36 (3%)	1/33 (3%)	5/41 (12%)
Adjusted rate	0.0%	8.9%	3.0%	3.2%	13.3%
Terminal rate	0/36 (0%)	3/32 (9%)	0/29 (0%)	1/28 (4%)	5/32 (16%)
First incidence (days)	— D. 0.0050	757 (T)	695	757 (T)	757 (T)
Poly-3 test	P=0.0278	P=0.0849	P=0.4620	P=0.4434	P=0.0237
Skin: Fibrosarcoma					
Overall rate	0/45 (0%)	2/39 (5%)	2/39 (5%)	0/38 (0%)	2/46 (4%)
Adjusted rate	0.0%	5.5%	5.5%	0.0%	4.8%
Terminal rate	0/37 (0%)	1/34 (3%)	0/31 (0%)	0/33 (0%)	2/36 (6%)
First incidence (days)	_ ` ′	699	682	_ ` ′	757 (T)
Poly-3 test	P=0.4175	P=0.2089	P=0.2078	f	P=0.2419
•					
Skin: Fibrosarcoma, Hemang					
Overall rate	1/45 (2%)	2/39 (5%)	3/39 (8%)	0/38 (0%)	4/46 (9%)
Adjusted rate	2.4%	5.5%	8.2%	0.0%	9.6%
Terminal rate	1/37 (3%)	1/34 (3%)	0/31 (0%)	0/33 (0%)	3/36 (8%)
First incidence (days) Poly-3 test	757 (T) P=0.2155	699 P=0.4561	631 P=0.2627	— P=0.5266N	692 P=0.1867
roly-3 test	F=0.2133	r=0.4301	F=0.2027	F=0.3200N	F=0.1607
All Organs: Histiocytic Sarcon	ma				
Overall rate	3/48 (6%)	1/40 (3%)	1/40 (3%)	3/40 (8%)	5/48 (10%)
Adjusted rate	7.0%	2.7%	2.8%	7.9%	11.4%
Terminal rate	2/37 (5%)	1/34 (3%)	1/31 (3%)	1/33 (3%)	2/36 (6%)
First incidence (days)	681	757 (T)	757 (T)	699	567
Poly-3 test	P=0.1054	P=0.3601N	P=0.3677N	P=0.6044	P=0.3698
All Organs: Malignant Lympl	homa				
Overall rate	9/48 (19%)	8/40 (20%)	13/40 (33%)	14/40 (35%)	15/48 (31%)
Adjusted rate	20.5%	21.6%	34.8%	37.0%	34.1%
Terminal rate	4/37 (11%)	7/34 (21%)	10/31 (32%)	13/33 (39%)	11/36 (31%)
First incidence (days)	605	747	471	694	555
Poly-3 test	P=0.0834	P=0.5614	P=0.1156	P=0.0780	P=0.1210
All Organs: Benign Neoplasm	c				
Overall rate	8/48 (17%)	11/40 (28%)	13/40 (33%)	13/40 (33%)	16/48 (33%)
Adjusted rate	18.3%	29.7%	35.6%	34.4%	37.5%
Terminal rate	6/37 (16%)	11/34 (32%)	12/31 (39%)	12/33 (36%)	15/36 (42%)
First incidence (days)	551	757 (T)	695	694	747
Poly-3 test	P=0.0672	P=0.1732	P=0.0646	P=0.0789	P=0.0404
All Organs: Malignant Neopla	asms				
Overall rate	16/48 (33%)	13/40 (33%)	19/40 (48%)	21/40 (53%)	23/48 (48%)
Adjusted rate	36.0%	34.9%	49.3%	54.5%	50.9%
Terminal rate	9/37 (24%)	11/34 (32%)	12/31 (39%)	17/33 (52%)	15/36 (42%)
First incidence (days)	605	699	471	670	555
Poly-3 test	P=0.0631	P=0.5518N	P=0.1587	P=0.0681	P=0.1194

#### B-10 Chloral Hydrate, NTP TR 502

in the 2-Year Gavage Study of Chloral Hydrate

TABLE B2
Statistical Analysis of Primary Neoplasms at 2 Years in Regimen B 100 mg/kg Female Mice

	Vehicle Control (Regimen A)	3 Months (Stop-Exposure)	6 Months (Stop-Exposure)	12 Months (Stop-Exposure)	2 Years (Regimen A)
All Organs: Benign or Ma	alignant Neoplasms				
Overall rate	21/48 (44%)	19/40 (48%)	25/40 (63%)	28/40 (70%)	33/48 (69%)
Adjusted rate	46.6%	51.0%	64.8%	72.7%	73.0%
Terminal rate	13/37 (35%)	17/34 (50%)	18/31 (58%)	24/33 (73%)	25/36 (69%)
First incidence (days)	551	699	471	670	555
Poly-3 test	P=0.0037	P=0.4292	P=0.0719	P=0.0119	P=0.0093

#### (T)Terminal sacrifice

a Number of neoplasm-bearing animals/number of animals with tissue examined microscopically

Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality

Observed incidence at terminal kill

Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in a dose group is indicated by **N**.

e Not applicable; no neoplasms in animal group

Value of statistic cannot be computed.

Table B3 Summary of the Incidence of Nonneoplastic Lesions in Regimen B 100 mg/kg Female Mice in the 2-Year Gavage Study of Chloral Hydrate $^{\rm a}$ 

	Vehicle Control <sup>b</sup>	3 Months (Stop-Exposure)	6 Months (Stop-Exposure)	12 Months (Stop-Exposure)
Disposition Summary Animals initially in study 3-Month interim evaluation 6-Month interim evaluation 12-Month interim evaluation	72 8 8 8	48 8	48 8	48
Early deaths Moribund Natural deaths Survivors	2 9	2 4	3 6	7
Terminal sacrifice  Animals examined microscopically	37 72	34 48	31 48	33 48
3-Month Interim Evaluation Alimentary System Esophagus Inflammation, mediastinum Liver Infiltration cellular, lymphocytic Necrosis Tension lipoidosis Salivary glands Infiltration cellular, lymphocytic	(8) 1 (13%) (8) 1 (13%) 6 (75%) (8) 5 (63%)	(8) (8) 3 (38%) 5 (63%) 4 (50%) (8)		
Endocrine System Adrenal gland, cortex Hyperplasia, spindle cell Islets, pancreatic Hyperplasia Thyroid gland Degeneration Ultimobranchial cyst	(8) 4 (50%) (8) (7)	(8) 3 (38%) (8) 1 (13%) (8) 1 (13%) 1 (13%)		
Genital System Ovary Congestion	(8) 1 (13%)	(8)		
Hematopoietic System Bone marrow Hyperplasia Lymph node, mandibular Hyperplasia, lymphoid Lymph node, mesenteric Hemorrhage Hyperplasia, lymphoid	(8) 1 (13%) (8) 1 (13%) (7) 1 (14%)	(8) (8) (8) 1 (13%)		

a Number of animals examined microscopically at the site and the number of animals with lesion

b Forty-eight mice served as vehicle controls for regimens A and B; the remaining 24 mice were designated for regimen B interim evaluations.

## B-12 Chloral Hydrate, NTP TR 502

TABLE B3

Summary of the Incidence of Nonneoplastic Lesions in Regimen B 100 mg/kg Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control	3 Months (Stop-Exposure)	6 Months (Stop-Exposure)	12 Months (Stop-Exposure)
3-Month Interim Evaluation Hematopoietic System (continued) Thymus Cyst Inflammation, mediastinum	(continued) (8) 1 (13%) 1 (13%)	(8) 1 (13%)		
Respiratory System Lung Congestion Hemorrhage Infiltration cellular, lymphocytic Inflammation Nose Mineralization, nasolacrimal duct	(8) 1 (13%) 1 (13%) 1 (13%) (8)	(8)  1 (13%) 1 (13%) (8) 1 (13%)		
Urinary System Urinary bladder Infiltration cellular, lymphocytic	(8) 1 (13%)	(8)		

#### Systems Examined with No Lesions Observed

Cardiovascular System
General Body System
Integumentary System
Musculoskeletal System
Nervous System
Special Senses System

#### 6-Month Interim Evaluation

Alimentary	System
------------	--------

1111110110111 5 5 5 5 5 5 5 5 5 5 5 5 5		
Liver	(8)	(8)
Infiltration cellular, lymphocytic	3 (38%)	4 (50%)
Necrosis	5 (63%)	6 (75%)
Tension lipoidosis	1 (13%)	5 (63%)
Vacuolization cytoplasmic	5 (63%)	7 (88%)
Salivary glands	(8)	(8)
Infiltration cellular, lymphocytic	4 (50%)	3 (38%)
Stomach, forestomach	(8)	(8)
Hyperkeratosis		1 (13%)
Stomach, glandular	(8)	(8)
Inflammation	1 (13%)	
Tongue	(8)	(8)
Infiltration cellular, histiocytic	1 (13%)	

TABLE B3

Summary of the Incidence of Nonneoplastic Lesions in Regimen B 100 mg/kg Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control	3 Months (Stop-Exposure)	6 Months (Stop-Exposure)	12 Months (Stop-Exposure)
6-Month Interim Evaluation Endocrine System Adrenal gland, cortex Degeneration, fatty Hyperplasia, spindle cell Parathyroid gland Ectopic thymus	(8) 4 (50%) (4) 1 (25%)		(8) 1 (13%) 7 (88%) (6)	
Genital System Ovary Cyst Hematocyst Uterus Infiltration cellular, lymphocytic Vagina Infiltration cellular, lymphocytic	(8) 1 (13%) 1 (13%) (8) (7) 1 (14%)		(8) (8) 1 (13%) (8)	
Hematopoietic System Bone marrow Hyperplasia Lymph node, mandibular Fibrosis Hyperplasia, lymphoid Spleen Congestion Hematopoietic cell proliferation Hyperplasia, lymphoid Thymus Atrophy, cortex Hemorrhage Hyperplasia, lymphoid, medulla	(8) 1 (13%) (8) 1 (13%) 2 (25%) (8) 1 (13%) 1 (13%) 1 (13%) (7) 2 (29%)		(8) 1 (13%) (8) 2 (25%) (8) 1 (13%) (7) 1 (14%) 1 (14%)	
Integumentary System Skin Hyperplasia	(8) 1 (13%)		(8)	
Respiratory System Lung Infiltration cellular, lymphocytic	(8) 5 (63%)		(8) 3 (38%)	
Special Senses System Lacrimal gland Infiltration cellular, lymphocytic	(6) 2 (33%)		(7) 3 (43%)	

## B-14 Chloral Hydrate, NTP TR 502

TABLE B3

Summary of the Incidence of Nonneoplastic Lesions in Regimen B 100 mg/kg Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control	3 Months (Stop-Exposure)	6 Months (Stop-Exposure)	12 Months (Stop-Exposure)
6-Month Interim Evaluation Urinary System Kidney Infiltration cellular, lymphocytic Urinary bladder Infiltration cellular, lymphocytic	(continued) (8) 2 (25%)		(8) 4 (50%) (8) 1 (13%)	
Systems Examined with No Lesion Cardiovascular System General Body System Musculoskeletal System Nervous System	ns Observed			
I2-Month Interim Evaluatio Alimentary System Esophagus Hyperkeratosis Gallbladder Infiltration cellular, lymphocytic Intestine large, cecum Hyperplasia, lymphoid Intestine large, rectum Cyst Liver Infiltration cellular, lymphocytic Necrosis Tension lipoidosis Vacuolization cytoplasmic Pancreas Infiltration cellular, lymphocytic Salivary glands Atrophy Infiltration cellular, lymphocytic Stomach, forestomach Hyperkeratosis	(8) 1 (13%) (8) 1 (13%) (8) 1 (13%) (8) 1 (13%) (8) 5 (63%) 2 (25%) 5 (63%) (8) 2 (25%) (8) 7 (88%) (8)			(8) (6) (8) 1 (13%) (6) (8) 6 (75%) 3 (38%) 1 (13%) 3 (38%) (8) 2 (25%) (8) 1 (13%) 7 (88%) (8) 1 (13%)
Cardiovascular System Heart Cardiomyopathy	(8) 1 (13%)			(8)
Endocrine System Adrenal gland, cortex Congestion Hyperplasia, spindle cell Vacuolization cytoplasmic	(7) 6 (86%)			(8) 1 (13%) 6 (75%) 2 (25%)

TABLE B3

Summary of the Incidence of Nonneoplastic Lesions in Regimen B 100 mg/kg Female Mice in the 2-Year Gavage Study of Chloral Hydrate

n (continued) (5)			
(6)			(5) 1 (20%) (6) 1 (17%)
(6) 5 (83%) (8) 2 (25%) (8) 2 (25%) 1 (13%) (8) 3 (38%)			(6) 3 (50%) (7) 1 (14%) 2 (29%) 1 (14%) 1 (14%) (8) 3 (38%)
(8) 1 (13%) (8) 3 (38%) (8) (8) 1 (13%) (7) 3 (43%)			(8) (8) 2 (25%) 1 (13%) (8) 4 (50%) 1 (13%) (8)  1 (13%) (8)  1 (13%) 1 (13%) 6 (75%)
(8)			(8) 2 (25%) (8) 2 (25%)
	(6) (6) (6) (8) (8) (2 (25%) (1 (13%) (8) (3 (38%) (8) (1 (13%) (8) (8) (1 (13%) (8) (7) (3 (43%) (8) (8)	(6)  (6)  5 (83%) (8)  2 (25%)  1 (13%) (8)  3 (38%)  (8)  1 (13%) (8)  3 (38%) (8)  (8)  (1 (13%) (7)  3 (43%)  (8)  (8)	(6) (6) (6) (5) (8) (8) (2) (25%) (1) (13%) (8) (3) (38%)  (8) (1) (13%) (8) (8) (8) (1) (13%) (8) (8) (7) (3) (43%)  (8) (8)

B-16 Chloral Hydrate, NTP TR 502

TABLE B3
Summary of the Incidence of Nonneoplastic Lesions in Regimen B 100 mg/kg Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control		6 Months (Stop-Exposure)	12 Months (Stop-Exposure)
12-Month Interim Evaluati Respiratory System Lung Infiltration cellular, lymphocytic Inflammation	(8) 7 (88%)			(8) 7 (88%) 1 (13%)
Special Senses System Harderian gland Infiltration cellular, lymphocytic Lacrimal gland Infiltration cellular, lymphocytic	(8) 1 (13%) (7) 3 (43%)			(8) (8) 5 (63%)
Urinary System Kidney Cyst, renal tubule Infiltration cellular, lymphocytic Nephropathy Urinary bladder Infiltration cellular, lymphocytic	(8)  7 (88%) 1 (13%) (8) 6 (75%)  ons Observed			(8) 1 (13%) 6 (75%) (8) 6 (75%)
General Body System Integumentary System	ns observed			
2-Year Study Alimentary System Esophagus Dilatation	(47)	(36)	(40) 1 (3%)	(38)
Hyperkeratosis Infiltration cellular, lymphocytic Ulcer Gallbladder Infiltration cellular, lymphocytic Inflammation Intestine large, cecum	1 (2%) 1 (2%) (46) 4 (9%)	(37) 2 (5%) (37)	1 (3%) (36) 4 (11%) 1 (3%) (37)	(36) 6 (17%) (32)
Hyperplasia, lymphoid Intestine large, colon Hyperplasia, goblet cell Hyperplasia, lymphoid Intestine large, rectum Erosion	(42) (44) (2 (5%)	(37)	(37) 2 (5%) (37)	(32) 4 (13%) (34) 1 (3%) 1 (3%) (32)
Inflammation Intestine small, duodenum Hyperplasia, lymphoid Infiltration cellular, lymphocytic Intestine small, ileum	(40)	1 (3%) (37)	(37) 1 (3%) (37)	(33) 1 (3%) (31)
Hyperplasia, lymphoid	2 (5%)	2 (6%)	3 (8%)	2 (6%)

# Chloral Hydrate, NTP TR 502 B-17 TABLE B3 Summary of the Incidence of Nonneoplastic Lesions in Regimen B 100 mg/kg Female Mice in the 2-Year Gavage Study of Chloral Hydrate

Alimentary System (continued)		Vehicle	Control		Months Exposure)		Ionths Exposure)		Months Exposure)
Intestine small, jejnumm	2-Year Study (continued)								
Hyperplasia, goblet cell	Alimentary System (continued)								
Hyperplasia, lymphoid   (48)	Intestine small, jejunum	(41)		(37)		(37)		(32)	
Liver									
Apoptosis Airophy 1 (3%)					(5%)		(5%)		
Acrophy   1 (3%)   2 (5%)		(48)			(20/)	(40)		(40)	
Basophilic focus         1 (2%)         3 (8%)         2 (5%)           Clear cell focus         2 (5%)         2 (5%)           Degeneration, centrilobular         1 (3%)         1 (3%)           Degeneration, cystic         1 (3%)         1 (3%)         3 (8%)         3 (8%)         3 (8%)         3 (8%)         3 (8%)         3 (8%)         3 (8%)         3 (8%)         3 (8%)         3 (8%)         3 (8%)         1 (3%)									
Clear cell focus		1	(20/)	1	(3%)	2	(90/)	2	(50/)
Degeneration, centrilobular   1 (3%)   2 (5%)   3 (8%)   2 (5%)   3 (8%)   2 (5%)   3 (8%)		1	(2%)			3	(8%)		
Degeneration, cystic   1 (3%)   1 (3%						1	(3%)	2	(3%)
Degeneration, fatty   1 (3%)   2 (5%)   3 (8%)   1 (3%)						1	(370)	1	(3%)
Ensinophilic focus									
Hematopoietic cell proliferation   3 (6%)   3 (8%)   5 (13%)   1 (3%)   1				1	(3%)	2	(5%)		. ,
Infiltration cellular, lymphocytic Infiltration cellular, plasma cell Inflammation (allular, plasma cell Inflammaticell (allular, plasma cell Inflammaticell (allular, plasma cell Inflammaticell (allular,		3	(6%)						
Infiltration cellular, plasma cell   1 (3%)	Hyperplasia, Kupffer cell							1	(3%)
Inflammation		33	(69%)	27	(68%)	29	(73%)	27	(68%)
Leukocytosis         1 (3%)           Mixed cell focus         1 (3%)           Necrosis         32 (67%)         24 (60%)         21 (53%)         20 (50%)           Necrosis         32 (67%)         24 (60%)         21 (53%)         20 (50%)           Necrosis, coagulative         1 (2%)         3 (8%)         1 (3%)           Tension lipidosis         17 (35%)         10 (25%)         10 (25%)         28 (70%)         24 (60%)           Vacuolization cytoplasmic         26 (54%)         29 (73%)         28 (70%)         24 (60%)           Mesentery         (1)         (1)         (2         (2           Infilitation cellular, lymphocytic         1 (100%)         1 (50%)         24 (60%)         20 (73%)         28 (70%)         24 (60%)         20 (73%)         28 (70%)         24 (60%)         20 (73%)         28 (70%)         24 (60%)         20 (73%)         28 (70%)         24 (60%)         20 (73%)         28 (70%)         24 (60%)         20 (73%)         28 (70%)         24 (60%)         20 (73%)         28 (70%)         24 (60%)         20 (73%)         28 (70%)         20 (73%)         20 (73%)         20 (73%)         20 (73%)         20 (73%)         20 (73%)         20 (73%)         20 (73%)         20 (73%)         20 (73	-			1	(3%)				
Mixed cell focus         I (3%)         1 (3%)           Necrosis         32 (67%)         24 (60%)         21 (53%)         20 (50%)           Necrosis         32 (67%)         24 (60%)         21 (53%)         20 (50%)           Necrosis, coagulative         1 (2%)         3 (8%)         1 (3%)           Tension lipoidosis         17 (35%)         10 (25%)         28 (70%)         24 (60%)           Vacuolization cytoplasmic         (6 (54%)         29 (73%)         28 (70%)         24 (60%)           Mesentery         (1)         (1)         (1)         (2           Infiltration cellular, lymphocytic         1 (10%)         1 (50%)         2 (5%)         2 (5%)           Pancreas         (48)         (40)         (39)         (37)         3 (57)		2	(4%)						
Necrosis         32 (67%)         24 (60%)         21 (53%)         20 (50%)           Necrosis, coagulative         1 (2%)         3 (8%)         1 (3%)           Tension lipoidosis         17 (35%)         10 (25%)         28 (70%)         24 (60%)           Wacuolization cytoplasmic         26 (54%)         29 (73%)         28 (70%)         24 (60%)           Mesentery         (1)         (1)         (2)         (20%)				1	(3%)				(20)
Necrosis, coagulative         1 (2%)         3 (8%)         1 (3%)           Tension lipotosis         17 (35%)         10 (25%)         28 (70%)         24 (60%)           Vacuolization cytoplasmic         26 (54%)         29 (73%)         28 (70%)         24 (60%)           Mesentery         (1)         (1)         (2)           Infiltration cellular, lymphocytic         1 (100%)         1 (50%)         2           Necrosis, fat		22	(670/)	24	(600/)	21	(520/)		
Tension lipoidosis				24	(60%)				
Vacuolization cytoplasmic         26 (54%)         29 (73%)         28 (70%)         24 (60%)           Mesentery         (1)         (1)         (2)           Infiltration cellular, lymphocytic         1 (100%)         Topacres         1 (50%)         Topacres         (48)         (40)         (39)         (37)           Atrophy         1 (2%)         1 (3%)         1 (3%)         1 (3%)         1 (3%)         1 (3%)         1 (3%)         1 (3%)         1 (3%)         2 (5%)         <			. ,	10	(25%)				. ,
Mesentery Infiltration cellular, lymphocytic Necrosis, fat         1 (100%)           Necrosis, fat         1 (100%)           Pancreas         (48)         (40)         (39)         (37)           Atrophy         1 (2%)         1 (3%)         1 (3%)         1 (2%)         2 (5%)         2 (5%)         2 (5%)         2 (5%)         2 (5%)         2 (5%)         2 (5%)         2 (5%)         2 (5%)         2 (5%)         16 (43					` /		` /		
Infiltration cellular, lymphocytic   Necrosis, fat   1 (100%)   39%   (37)			(3470)		(7370)		(7070)	24	(0070)
Necrosis, fat         1 (50%)           Pancreas         (48)         (40)         (39)         (37)           Atrophy         1 (2%)         1 (3%)         1 (3%)           Ectasia, duct         1 (3%)         2 (5%)         2 (5%)           Focal cellular change         2 (4%)         2 (5%)         2 (5%)         2 (5%)           Infiltration cellular, lymphocytic         26 (54%)         21 (53%)         16 (41%)         16 (43%)           Infiltration cellular, lymphocytic         1 (3%)         3 (8%)         3 (8%)         3 (8%)           Atrophy         1 (2%)         3 (8%)         3 (8%)         3 (8%)           Hyperplasia, duct         1 (2%)         1 (3%)         1 (79%)           Infiltration cellular, lymphocytic         38 (79%)         33 (83%)         35 (88%)         31 (79%)           Infiltration cellular, forestomach         (47)         (37)         (38)         (35)           Hyperkeratosis         1 (3%)         1 (3%)         2 (6%)           Hyperplasia         1 (3%)         2 (6%)           Hyperplasia         (47)         (37)         (38)         (36)           Cyst         2 (4%)         1 (3%)         3 (8%)         2 (6%)		(-)			(100%)	(-)			
Atrophy Ectasia, duct         1 (2%)         1 (3%)         1 (3%)           Ectasia, duct         1 (3%)         2 (5%)         2 (5%)         2 (5%)         2 (5%)         2 (5%)         2 (5%)         2 (5%)         16 (41%)         16 (43%)         16 (43%)         16 (41%)         16 (43%)         16 (43%)         16 (41%)         16 (43%)         16 (43%)         16 (41%)         16 (43%)         18 (3%)         18 (3%)         18 (3%)         18 (3%)         18 (3%)         16 (43%)         16 (43%)         16 (3					(,	1	(50%)		
Ectasia, duct         1 (3%)         Coal cellular change         2 (4%)         2 (5%)         2 (5%)         2 (5%)           Infiltration cellular, lymphocytic         26 (54%)         21 (53%)         16 (41%)         16 (43%)           Inflarmation         1 (3%)         Transpart	Pancreas	(48)		(40)		(39)		(37)	
Focal cellular change         2 (4%)         2 (5%)         2 (5%)         2 (5%)           Infiltration cellular, lymphocytic         26 (54%)         21 (53%)         16 (41%)         16 (43%)           Inflammation         1 (3%)         3         3         3         3         3         8%)         3         8%)         3         8%)         3         8%)         3         8%)         3         8%)         3         8%)         3         8%)         3         8%)         3         8%)         3         8%)         3         8%)         3         8%)         3         8%)         3         8%)         3         8%)         3         8%)         3         1,0%)         3         8%)         3         1,0%)         3         1,0%)         3         1,0%)         3         1,0%)         3         1,0%)         3         1,0%)         3         1,0%)         3         1,0%)         3         1,0%)         3         1,0%)         3         1,0%)         3         1,0%)         3         1,0%)         3         1,0%)         3         1,0%)         3         1,0%)         3         1,0%)         3         1,0%         3         1,0%         3	Atrophy	1	(2%)	1	(3%)	1	(3%)		
Infiltration cellular, lymphocytic Inflammation         26 (54%)         21 (53%)         16 (41%)         16 (43%)           Salivary glands         (48)         (40)         (40)         (39)           Atrophy         3 (8%)         3 (8%)         3 (8%)           Hyperplasia, duct         1 (2%)         1 (3%)         35 (88%)         31 (79%)           Infiltration cellular, lymphocytic Inflammation         1 (3%)         35 (88%)         31 (79%)           Inflammation         1 (3%)         1 (3%)         1 (3%)           Mineralization         4(7)         (37)         (38)         (35)           Stomach, forestomach         (47)         (37)         (38)         (35)           Hyperkeratosis         1 (3%)         2 (6%)           Hyperplasia         1 (3%)         2 (6%)           Ulcer         1 (3%)         (36)           Stomach, glandular         (47)         (37)         (38)         (36)           Crystals         1 (2%)         2 (4%)         1 (3%)         3 (8%)         2 (6%)           Degeneration, hyaline         1 (2%)         1 (3%)         3 (8%)         2 (6%)           Hyperplasia         1 (3%)         3 (3%)         3 (3%)         3 (3%)	Ectasia, duct								
Inflammation         1 (3%)           Salivary glands         (48)         (40)         (40)         (39)           Atrophy         3 (8%)         3 (8%)         3 (8%)           Hyperplasia, duct         1 (2%)         1 (3%)         35 (88%)         31 (79%)           Infiltration cellular, lymphocytic         38 (79%)         33 (83%)         35 (88%)         31 (79%)           Inflammation         1 (3%)         1 (3%)         1 (3%)           Mineralization         4 (47)         (37)         (38)         (35)           Hyperkeratosis         1 (3%)         2 (6%)           Hyperplasia         1 (3%)         2 (6%)           Ulcer         1 (3%)         (38)         (36)           Stomach, glandular         (47)         (37)         (38)         (36)           Crystals         1 (2%)         (39)         (38)         (36)           Cyst         2 (4%)         1 (3%)         3 (8%)         2 (6%)           Degeneration, hyaline         1 (2%)         1 (3%)         1 (3%)           Inflammation         1 (3%)         1 (3%)         1 (3%)           Tongue         (48)         (39)         (39)         (40)           I			. ,						
Salivary glands       (48)       (40)       (40)       (39)         Atrophy       3 (8%)       3 (8%)       3 (8%)         Hyperplasia, duct       1 (2%)       Infiltration cellular, lymphocytic       38 (79%)       33 (83%)       35 (88%)       31 (79%)         Inflammation       1 (3%)       1 (3%)       1 (3%)       1 (3%)       1 (3%)       2 (6%)         Stomach, forestomach       (47)       (37)       (38)       (35)         Hyperplasia       1 (3%)       2 (6%)         Ulcer       1 (3%)       3 (8%)       2 (6%)         Stomach, glandular       (47)       (37)       (38)       (36)         Crystals       1 (2%)       (38)       3 (8%)       2 (6%)         Cyst       2 (4%)       1 (3%)       3 (8%)       2 (6%)         Degeneration, hyaline       1 (2%)       1 (3%)       1 (3%)       1 (3%)         Inflammation       1 (3%)       1 (3%)       1 (3%)       1 (3%)       1 (3%)       1 (3%)       1 (3%)       1 (3%)       1 (3%)       1 (3%)       1 (3%)       1 (3%)       1 (3%)       1 (3%)       1 (3%)       1 (3%)       1 (3%)       1 (3%)       1 (3%)		26	(54%)			16	(41%)	16	(43%)
Atrophy Hyperplasia, duct Infiltration cellular, lymphocytic Infiltration cellular, lymphocytic Infiltration Inflammation I (3%) Mineralization Stomach, forestomach Hyperkeratosis Hyperplasia Ulcer Stomach, glandular Crystals Cyst Cyst Degeneration, hyaline Hyperplasia Inflammation I (3%) Infiltration cellular, mast cell  (48) Infiltration cellular, mast cell  (1 (2%) Infiltration cellular, mast cell  (48) Infiltration cellular, mast cell  (38) Is (38%) Is (		(40)			(3%)	(40)		(20)	
Hyperplasia, duct 1 (2%) Infiltration cellular, lymphocytic 38 (79%) 33 (83%) 35 (88%) 31 (79%) Inflammation 1 (3%) Mineralization 1 (3%) Stomach, forestomach (47) (37) (38) (35) Hyperkeratosis Hyperplasia Ulcer 1 (3%) Stomach, glandular (47) (37) (38) (36) Crystals 1 (2%) Cyst 2 (4%) 1 (3%) 3 (8%) 2 (6%) Degeneration, hyaline 1 (2%) Hyperplasia Inflammation 1 (48) (39) (39) (40) Infiltration cellular, mast cell (48) (39) (39) (40)		(48)		(40)			(90/.)	, ,	(80%)
Infiltration cellular, lymphocytic     38 (79%)     33 (83%)     35 (88%)     31 (79%)       Inflammation     1 (3%)     1 (3%)     1 (3%)       Mineralization     1 (3%)     38     (35)       Stomach, forestomach     (47)     (37)     (38)     (35)       Hyperkeratosis     1 (3%)     2 (6%)       Hyperplasia     1 (3%)     1 (3%)       Ulcer     (47)     (37)     (38)     (36)       Stomach, glandular     (47)     (37)     (38)     (36)       Crystals     1 (2%)     (3%)     3 (8%)     2 (6%)       Cyst     2 (4%)     1 (3%)     3 (8%)     2 (6%)       Degeneration, hyaline     1 (2%)     1 (3%)     1 (3%)       Inflammation     1 (3%)     1 (3%)     1 (3%)       Tongue     (48)     (39)     (39)     (39)     (40)       Infiltration cellular, mast cell     2 (4%)     2 (5%)     2 (5%)		1	(2%)			3	(670)	3	(0%)
Inflammation       1 (3%)         Mineralization       1 (3%)         Stomach, forestomach       (47)       (37)       (38)       (35)         Hyperkeratosis       1 (3%)       2 (6%)         Hyperplasia       1 (3%)       1 (3%)         Ulcer       1 (3%)       38)       (36)         Stomach, glandular       (47)       (37)       (38)       (36)         Crystals       1 (2%)       (2 (4%)       1 (3%)       3 (8%)       2 (6%)         Cyst       2 (4%)       1 (3%)       3 (8%)       2 (6%)         Degeneration, hyaline       1 (2%)       1 (3%)       1 (3%)         Hyperplasia       1 (3%)       1 (3%)       1 (3%)         Inflammation       1 (3%)       (48)       (39)       (39)       (40)         Infiltration cellular, mast cell       2 (4%)       2 (5%)       2 (5%)       2 (4%)       3 (5%)       2 (5%)				33	(83%)	35	(88%)	31	(79%)
Mineralization       1 (3%)       1 (3%)         Stomach, forestomach       (47)       (37)       (38)       (35)         Hyperkeratosis       1 (3%)       2 (6%)         Hyperplasia       1 (3%)       1 (3%)         Ulcer       1 (3%)       38)       (36)         Stomach, glandular       (47)       (37)       (38)       (36)         Crystals       1 (2%)       2 (4%)       1 (3%)       3 (8%)       2 (6%)         Degeneration, hyaline       1 (2%)       1 (3%)       3 (8%)       2 (6%)         Hyperplasia       1 (3%)       1 (3%)       1 (3%)         Inflammation       1 (3%)       1 (3%)       1 (3%)         Tongue       (48)       (39)       (39)       (39)       (40)         Infiltration cellular, mast cell       2 (4%)       2 (5%)       2 (5%)       2 (5%)		30	(1770)		. ,	33	(0070)	31	(1770)
Stomach, forestomach       (47)       (37)       (38)       (35)         Hyperkeratosis       1 (3%)       2 (6%)         Hyperplasia       1 (3%)       1 (3%)         Ulcer								1	(3%)
Hyperkeratosis       1 (3%)       2 (6%)         Hyperplasia       1 (3%)       1 (3%)         Ulcer       1 (3%)       1 (3%)         Stomach, glandular       (47)       (37)       (38)       (36)         Crystals       1 (2%)       1 (3%)       3 (8%)       2 (6%)         Osyst       2 (4%)       1 (3%)       3 (8%)       2 (6%)         Degeneration, hyaline       1 (2%)       1 (3%)       1 (3%)         Hyperplasia       1 (3%)       1 (3%)       1 (3%)         Inflammation       1 (3%)       (40)       1 (3%)         Tongue       (48)       (39)       (39)       (40)         Infiltration cellular, mast cell       2 (4%)       2 (5%)       2 (5%)	Stomach, forestomach	(47)			` /	(38)			` /
Hyperplasia Ulcer Stomach, glandular Crystals Cyst Cyst Cyst Speneration, hyaline Hyperplasia Inflammation Tongue Infiltration cellular, mast cell  Hyperplasia  (48) (37) (38) (38) (38) (36)  (37) (38) (38) (38) (38) (39) (38) (39) (39) (39) (40) (40) (40) (40) (40) (40) (40) (40	Hyperkeratosis					1	(3%)	2	(6%)
Stomach, glandular     (47)     (37)     (38)     (36)       Crystals     1 (2%)     3 (8%)     2 (6%)       Cyst     2 (4%)     1 (3%)     3 (8%)     2 (6%)       Degeneration, hyaline     1 (2%)     1 (3%)     1 (3%)       Hyperplasia     1 (3%)     1 (3%)       Inflammation     1 (3%)     (39)     (39)     (40)       Tongue     (48)     (39)     (39)     (40)       Infiltration cellular, mast cell     2 (4%)     2 (5%)									
Crystals       1 (2%)         Cyst       2 (4%)       1 (3%)       3 (8%)       2 (6%)         Degeneration, hyaline       1 (2%)									(3%)
Cyst     2 (4%)     1 (3%)     3 (8%)     2 (6%)       Degeneration, hyaline     1 (2%)				(37)		(38)		(36)	
Degeneration, hyaline       1 (2%)         Hyperplasia       1 (3%)         Inflammation       1 (3%)         Tongue       (48)       (39)       (39)       (40)         Infiltration cellular, mast cell       2 (4%)       2 (5%)       (40)				_	(201)		(0.01)		(-0.1)
Hyperplasia     1 (3%)       Inflammation     1 (3%)       Tongue     (48)     (39)     (39)     (40)       Infiltration cellular, mast cell     2 (4%)     2 (5%)				1	(3%)	3	(8%)	2	(0%)
Inflammation     1 (3%)       Tongue     (48)     (39)     (39)     (40)       Infiltration cellular, mast cell     2 (4%)     2 (5%)		1	(270)					1	(3%)
Tongue (48) (39) (39) (40) Infiltration cellular, mast cell 2 (4%) 2 (5%)	71 1					1	(3%)	1	(370)
Infiltration cellular, mast cell 2 (4%) 2 (5%)		(48)		(39)			(3/0)	(40)	
			(4%)			(37)		(40)	
				_					

B-18 Chloral Hydrate, NTP TR 502
TABLE B3
Summary of the Incidence of Nonneoplastic Lesions in Regimen B 100 mg/kg Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control			Months Exposure)		Ionths Exposure)		12 Months (Stop-Exposure)		
2-Year Study (continued) Cardiovascular System										
Heart	(48)		(40)		(40)		(39)			
Cardiomyopathy	(40)		(40)			(3%)	(37)			
Congestion						(2,3)	1	(3%)		
Degeneration	1	(2%)								
Dilatation								(3%)		
Hemorrhage, valve							1	(3%)		
Infiltration cellular, lymphocytic		(20/)		(3%)		(20/)				
Inflammation Polyarteritis		(2%) (2%)	1	(3%)	1	(3%)				
Thrombus		(2%)								
Tinonious	1	(270)								
<b>Endocrine System</b>										
Adrenal gland	(46)		(40)		(37)		(37)			
Accessory adrenal cortical nodule	1	(2%)								
Inflammation, extra adrenal tissue	(16)			(3%)	(27)		(25)			
Adrenal gland, cortex Congestion	(46)		(40)		(37)		(37)	(3%)		
Degeneration, fatty					1	(3%)		(3%)		
Ectopic tissue	1	(2%)				(3%)	1	(370)		
Focal cellular change		(270)				(5%)				
Hyperplasia, spindle cell	43	(93%)	37	(93%)		(92%)	32	(86%)		
Thrombus	1	(2%)		, ,		, ,				
Vacuolization cytoplasmic	2	(4%)	1	(3%)			1	(3%)		
Adrenal gland, medulla	(46)		(40)		(37)		(37)			
Congestion			1	(3%)		(20/)	1	(3%)		
Cytoplasmic alteration	1	(20/)	1	(20/)	1	(3%)				
Vacuolization cytoplasmic Islets, pancreatic	(48)	(2%)	(40)	(3%)	(37)		(38)			
Hyperplasia	(40)		(40)		(31)			(3%)		
Infiltration cellular, lymphocytic								(3%)		
Parathyroid gland	(38)		(31)		(33)		(36)	. ,		
Ectopic thymus	1	(3%)			1	(3%)	1	(3%)		
Infiltration cellular, lymphocytic		(3%)								
Vacuolization cytoplasmic		(3%)								
Pituitary gland	(45)		(36)	(20()	(36)		(33)			
Angiectasis				(3%)			1	(20/)		
Cyst Hyperplasia, pars distalis	4	(9%)		(3%) (8%)	1	(3%)		(3%) (3%)		
Thyroid gland	(47)	(970)	(40)	(870)	(40)	(370)	(39)	(370)		
Cyst, follicle	(17)			(3%)	(10)			(8%)		
Degeneration	1	(2%)		(=,=)	1	(3%)		(3%)		
Ectopic thymus								(3%)		
Goiter adenomatous					1	(3%)				
Hyperplasia, follicular cell			1	(3%)	1	(3%)		(3%)		
Hypertrophy, follicular cell		(00/)	_	(50/)	_	(50/)		(3%)		
Infiltration cellular, lymphocytic	4	(9%)		(5%)	2	(5%)	2	(5%)		
Inflammation Ultimobranchial cyst	11	(23%)		(3%) (23%)	0	(20%)	7	(18%)		
Omnobranchiai cyst	11	(2370)	9	(2370)	0	(2070)	,	(1070)		

TABLE B3
Summary of the Incidence of Nonneoplastic Lesions in Regimen B 100 mg/kg Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control	3 Months (Stop-Exposure)	6 Months (Stop-Exposure)	12 Months (Stop-Exposure)
2-Year Study (continued) General Body System None				
Genital System				
Clitoral gland	(43)	(37)	(33)	(33)
Atrophy	40 (93%)	35 (95%)	29 (88%)	31 (94%)
Infiltration cellular, lymphocytic				1 (3%)
Inflammation		1 (3%)	2 (6%)	
Ovary	(48)	(40)	(39)	(38)
Angiectasis	20 (010)	22 (224)	24 (05%)	1 (3%)
Atrophy	39 (81%)	33 (83%)	34 (87%)	32 (84%)
Congestion	1 (2%)	(150()	6 (150()	0 (040/)
Cyst	10 (21%)	6 (15%)	6 (15%) 6 (15%)	9 (24%)
Cyst, periovarian tissue Hematocyst	16 (33%) 7 (15%)	12 (30%) 2 (5%)	5 (13%)	8 (21%) 4 (11%)
Hyperplasia, adenomatous	2 (4%)	3 (8%)	3 (13%)	4 (1170)
Infiltration cellular, lymphocytic	5 (10%)	3 (8%)	1 (3%)	1 (3%)
Mineralization	3 (1070)	3 (0,0)	1 (370)	1 (3%)
Ovotestis			1 (3%)	- (070)
Uterus	(48)	(40)	(40)	(39)
Angiectasis	1 (2%)			
Atrophy	2 (4%)	2 (5%)	2 (5%)	1 (3%)
Dilatation	2 (4%)	1 (3%)	3 (8%)	1 (3%)
Ectasia, vein				1 (3%)
Fibrosis	1 (2%)	1 (3%)	1 (3%)	
Hyperplasia, cystic, endometrium	37 (77%)	32 (80%)	26 (65%)	29 (74%)
Infiltration cellular, lymphocytic				1 (3%)
Inflammation	1 (20/)			1 (3%)
Prolapse Thrombus	1 (2%)	1 (3%)		
Vagina	(48)	(38)	(40)	(37)
Atrophy	2 (4%)	2 (5%)	2 (5%)	(37)
Dysplasia	1 (2%)	1 (3%)	2 (370)	
Infiltration cellular, lymphocytic	3 (6%)	2 (5%)		
Inflammation	` '	2 (5%)		
Metaplasia				1 (3%)
Hematopoietic System				
Bone marrow	(47)	(39)	(40)	(38)
Depletion Depletion	(+1)	(37)	1 (3%)	(30)
Hyperplasia	3 (6%)	6 (15%)	4 (10%)	3 (8%)
Hypoplasia	= (0/0)	1 (3%)	. (10/0)	- (0,0)
Pigmentation		1 (3%)	1 (3%)	
Lymph node	(48)	(40)	(40)	(40)
Hyperplasia, plasma cell	. ,	• ,	1 (3%)	, ,
Hyperplasia, plasma cell, mediastinal		1 (3%)		
Inflammation			1 (3%)	

B-20 Chloral Hydrate, NTP TR 502
TABLE B3
Summary of the Incidence of Nonneoplastic Lesions in Regimen B 100 mg/kg Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control		Aonths Exposure)		Ionths Exposure)		Months Exposure)
2-Year Study (continued)							
Hematopoietic System (continued)							
Lymph node, mandibular	(47)	(40)		(39)		(39)	
Atrophy		1	(3%)	1	(3%)		
Hematopoietic cell proliferation		1	(3%)				
Hemorrhage	3 (6%)		(3%)		(3%)		
Hyperplasia, lymphoid	7 (15%)		(13%)	10	(26%)	4	(10%)
Hyperplasia, plasma cell			(3%)				
Inflammation			(3%)				
Lymph node, mesenteric	(46)	(40)		(38)		(39)	
Angiectasis	• (40)		(==:)	1	(3%)		(22)
Atrophy	2 (4%)	2	(5%)				(3%)
Congestion, sinus			(20/)			1	(3%)
Fibrosis	4 (00/)		(3%)	1	(20/)	1	(20/)
Hemorrhage	4 (9%)		(3%)		(3%)		(3%)
Hyperplasia, lymphoid Hyperplasia, plasma cell	2 (4%)		(5%) (3%)		(11%) (3%)	4	(10%)
Hyperplasia, piasina cen Hyperplasia, reticulum cell		1	(3%)		(3%)		
Inflammation					(3%)		
Spleen	(47)	(40)		(39)	(370)	(39)	
Amyloid deposition	(47)	(40)			(3%)	(37)	
Atrophy	2 (4%)	2	(5%)	1	(370)	1	(3%)
Congestion	2 (1/3)	-	(5,0)				(8%)
Erythrophagocytosis							(3%)
Hematopoietic cell proliferation	4 (9%)	4	(10%)	7	(18%)		(10%)
Hyperplasia, lymphoid	13 (28%)		(25%)		(28%)		(31%)
Hyperplasia, plasma cell, red pulp		1	(3%)				
Thymus	(41)	(33)		(31)		(30)	
Atrophy, cortex	30 (73%)	24	(73%)	20	(65%)	25	(83%)
Congestion	1 (2%)					1	(3%)
Cyst					(3%)		
Ectopic parathyroid gland	1 (2%)				(3%)		(3%)
Hyperplasia, lymphoid, medulla	14 (34%)	13	(39%)	12	(39%)	6	(20%)
Integumentary System							
Mammary gland	(44)	(36)		(38)		(36)	
Galactocele	(++)		(3%)	(30)		(30)	
Hyperplasia	1 (2%)	1	(5/0)	1	(3%)	3	(8%)
Infiltration cellular, lymphocytic	. (270)				(3%)	3	(5/0)
Inflammation	1 (2%)				()		
Lactation	4 (9%)	1	(3%)	1	(3%)		
Metaplasia, squamous	` '				(3%)		
Skin	(45)	(39)		(39)	*	(38)	
Alopecia						1	(3%)
Infiltration cellular, lymphocytic		1	(3%)	1	(3%)		

TABLE B3
Summary of the Incidence of Nonneoplastic Lesions in Regimen B 100 mg/kg Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle	Control		Months Exposure)		onths Exposure)		Months Exposure)
2-Year Study (continued) Musculoskeletal System Bone, femur	(47)		(40)		(40)		(40)	
Degeneration, cartilage Fibrous osteodystrophy		(38%)	, ,	(23%)	, ,	(13%)	1	(3%) (23%)
Bone, sternum	(47)	(3070)	(40)	(2370)	(40)	(1370)	(40)	(2370)
Fibrous osteodystrophy, multifocal		(77%)		(70%)		(63%)		(73%)
Skeletal muscle Infiltration cellular, lymphocytic	(48)	(4%)	(39)	(5%)	(40)		(39)	(3%)
Polyarteritis		(2%)	2	(370)			1	(370)
Nervous System								
Brain, cerebellum	(48)	(20)	(40)		(40)		(40)	
Degeneration Thrombus		(2%) (2%)						
Brain, cerebrum	(48)	(270)	(40)		(40)		(40)	
Degeneration	, ,	(2%)			. ,		, ,	
Infiltration cellular, lymphocytic	20	(5004)		(5%)	22	(500)	2.4	(5001)
Mineralization, multifocal, thalamus Thrombus		(58%) (2%)	21	(53%)	23	(58%)	24	(60%)
Peripheral nerve	(48)	(270)	(38)		(39)		(38)	
Infiltration cellular, lymphocytic	(.0)			(3%)	(5)		(20)	
Inflammation						(3%)		
Spinal cord, thoracic	(48)	(20/)	(40)		(40)		(39)	
Degeneration Infiltration cellular, lymphocytic	1	(2%)	1	(3%)				
Thrombus	1	(2%)		(272)				
Respiratory System								
Larynx	(44)		(40)		(34)		(34)	(20)
Concretion Crystals								(3%) (3%)
Infiltration cellular, lymphocytic	1	(2%)					1	(370)
Lung	(48)	· · ·	(40)		(40)		(40)	
Congestion		(20)	1	(3%)			1	(3%)
Foreign body Giant cell	1	(2%)					1	(3%)
Hemorrhage	2	(4%)	1	(3%)	1	(3%)		(5%)
Hyperplasia, alveolar epithelium		(1,1)		(5%)		(3%)		(5%)
Infiltration cellular, histiocytic	-	(550)		(3%)		(5%)		(5%)
Infiltration cellular, lymphocytic		(77%)		(75%)		(73%)		(68%)
Inflammation Thrombus		(8%) (2%)	4	(10%)	2	(5%)	3	(8%)
Thrombus, capillary	1	(270)					1	(3%)
Nose	(47)		(40)		(40)		(40)	•
Cyst, nasolacrimal duct	1	(2%)				(20()		
Dilatation, glands Inflammation	1	(2%)			1	(3%)		
IIII IIII III III III III III III III	1	(2/0)						

B-22 Chloral Hydrate, NTP TR 502
TABLE B3
Summary of the Incidence of Nonneoplastic Lesions in Regimen B 100 mg/kg Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control			Months Exposure)		6 Months Stop-Exposure)		12 Months (Stop-Exposure)	
2-Year Study (continued) Respiratory System (continued) Trachea Cyst	(47)		(40)		(39)			(3%)	
Foreign body Infiltration cellular, lymphocytic Inflammation	1	(2%)			1	(3%)	1	(3%)	
Special Senses System Eye	(41)		(38)		(34)		(35)		
Degeneration, retina Inflammation	1	(2%)	` ′	(3%)	(5.)		(55)		
Thrombus Harderian gland Atrophy Hyperplasia	(48)	(2%)		(3%) (5%)	(38)		(38)		
Infiltration cellular, lymphocytic Inflammation Thrombus		(38%) (2%)		(34%)	16	(42%)		(21%) (3%)	
Lacrimal gland Apoptosis	(41)			(3%)	(33)		(32)	(60()	
Atrophy Cytomegaly Ectasia, duct		(2%)		(3%)	1.5	(520()	1 1	(6%) (3%) (3%)	
Infiltration cellular, lymphocytic Necrosis Zymbal's gland	(43)	(61%)		(64%) (3%)	(36)	(52%)	(36)	(41%)	
Infiltration cellular, lymphocytic Inflammation	1	(2%)			1	(3%)			
Urinary System									
Kidney Amyloid deposition, glomerulus Congestion		(4%) (2%)	(40) 1	(3%)	(39)	(3%)	(38)	(5%)	
Cyst, renal tubule Glomerulosclerosis Hydronephrosis Hydronephrosis, bilateral	14	(29%)	9	(23%)	9	(23%)	1	(21%) (3%) (3%)	
Infarct Infiltration cellular, lymphocytic Infiltration cellular, plasma cell	39	(2%) (81%)	31	(3%) (78%) (3%)	31	(79%)	32	(84%)	
Inflammation Inflammation, adventitia Necrosis, coagulative Nephropathy		(2%)	1	(3%)		(3%) (5%)	А	(11%)	
Pigmentation, renal tubule Polyarteritis	1	(2%)	(25)			(370)	1	(3%)	
Urinary bladder Infiltration cellular, lymphocytic Polyarteritis		(81%) (2%)	(37)	(84%)	(39)	(85%)	(36) 28	(78%)	