APPENDIX D
SUMMARY OF LESIONS IN REGIMEN D FEMALE MICE IN THE 2-YEAR GAVAGE STUDY OF CHLORAL HYDRATE
(Single Dose on Postnatal Day 15)

TABLE D1

Summary of the Incidence of Neoplasms in Regimen D Female Mice in the 2-Year Gavage Study of Chloral Hydrate[a]

	Vehicle Control	10 mg/kg	25 mg/kg	50 mg/kg
Disposition Summary				
Animals initially in study	48	48	48	48
Early deaths				
Accidental deaths	2			
Moribund	4	1	6	4
Natural deaths	6	6	3	4
Survivors				
Died last week of study		1	1	
Terminal sacrifice	36	40	38	40
Animals examined microscopically	48	48	48	48
Alimentary System				
Gallbladder	(41)	(6)	(9)	(46)
Hepatocholangiocarcinoma, metastatic, liver		1 (17%)		
Lymphoma malignant	3 (7%)			
Intestine small, duodenum	(43)	(5)	(9)	(44)
Lymphoma malignant		1 (20%)		
Intestine small, jejunum	(41)	(7)	(8)	(45)
Lymphoma malignant		2 (29%)		1 (2%)
Liver	(48)	(48)	(48)	(48)
Hemangiosarcoma			1 (2%)	
Hepatocellular adenoma	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Hepatocellular carcinoma		2 (4%)	1 (2%)	1 (2%)
Hepatocholangiocarcinoma		1 (2%)		
Histiocytic sarcoma	1 (2%)	2 (4%)	2 (4%)	
Ito cell tumor NOS			1 (2%)	
Lymphoma malignant	9 (19%)	4 (8%)	3 (6%)	6 (13%)
Pancreas	(46)	(5)	(10)	(47)
Carcinoma, metastatic, uncertain primary site			1 (10%)	
Histiocytic sarcoma		1 (20%)		
Lymphoma malignant	5 (11%)			1 (2%)
Salivary glands	(47)	(7)	(10)	(48)
Lymphoma malignant	5 (11%)			
Cardiovascular System				
Heart	(48)	(8)	(10)	(48)
Hepatocholangiocarcinoma, metastatic, liver		1 (13%)		
Endocrine System				
Adrenal gland, medulla	(47)	(6)	(10)	(47)
Lymphoma malignant				1 (2%)
Pheochromocytoma benign		1 (17%)		
Islets, pancreatic	(46)	(4)	(11)	(47)
Adenoma			1 (9%)	
Histiocytic sarcoma		1 (25%)		
Parathyroid gland	(44)	(3)	(5)	(43)
Lymphoma malignant	2 (5%)			
Pituitary gland	(45)	(4)	(9)	(43)
Adenoma, pars distalis	1 (2%)		1 (11%)	1 (2%)
Adenoma, pars intermedia	1 (2%)			
Carcinoma, pars distalis				1 (2%)

TABLE D1
Summary of the Incidence of Neoplasms in Regimen D Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control	10 mg/kg	25 mg/kg	50 mg/kg
Endocrine System (continued)				
Thyroid gland	(46)	(5)	(9)	(47)
Adenoma, follicular cell	1 (2%)			
Lymphoma malignant	1 (2%)			
General Body System				
None				
Genital System				
Ovary	(46)	(22)	(30)	(46)
Granulosa cell tumor benign	1 (2%)			
Hepatocholangiocarcinoma, metastatic, liver		1 (5%)		
Histiocytic sarcoma		2 (9%)	2 (7%)	
Luteoma	1 (2%)			
Lymphoma malignant	2 (4%)		1 (3%)	
Lymphoma malignant, periovarian tissue	2 (4%)			
Uterus	(47)	(30)	(35)	(48)
Fibroma			1 (3%)	
Hemangiosarcoma		1 (3%)	1 (3%)	2 (4%)
Histiocytic sarcoma	1 (2%)	2 (7%)	3 (9%)	
Leiomyoma	1 (2%)			
Lymphoma malignant	1 (2%)			
Polyp				1 (2%)
Vagina	(44)	(7)	(10)	(46)
Fibrosarcoma	1 (2%)			1 (2%)
Histiocytic sarcoma		2 (29%)	3 (30%)	
Lymphoma malignant			1 (10%)	
Polyp				1 (2%)
Hematopoietic System				
Bone marrow	(47)	(8)	(10)	(48)
Histiocytic sarcoma		1 (13%)		
Lymphoma malignant	4 (9%)			1 (2%)
Lymph node	(47)	(13)	(11)	(48)
Alveolar/bronchiolar carcinoma, metastatic, mediastinal, lung				1 (2%)
Lymphoma malignant		1 (8%)		
Lymphoma malignant, inguinal	1 (2%)			
Lymphoma malignant, lumbar			1 (9%)	1 (2%)
Lymphoma malignant, mediastinal		2 (15%)		1 (2%)
Lymphoma malignant, pancreatic	1 (2%)			
Lymphoma malignant, renal		1 (8%)	1 (9%)	
Lymphoma malignant, thoracic		1 (8%)		
Lymph node, mandibular	(47)	(8)	(9)	(48)
Histiocytic sarcoma		1 (13%)		
Lymphoma malignant	7 (15%)	1 (13%)		
Squamous cell carcinoma, metastatic, nose			1 (11%)	
Lymph node, mesenteric	(46)	(10)	(8)	(45)
Carcinoma, metastatic, uncertain primary site			1 (13%)	
Histiocytic sarcoma		1 (10%)		
Lymphoma malignant	8 (17%)	5 (50%)	1 (13%)	1 (2%)

TABLE D1
Summary of the Incidence of Neoplasms in Regimen D Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control	10 mg/kg	25 mg/kg	50 mg/kg
Hematopoietic System (continued)				
Spleen	(47)	(18)	(17)	(47)
Hemangiosarcoma			1 (6%)	2 (4%)
Histiocytic sarcoma		1 (6%)		
Lymphoma malignant	11 (23%)	8 (44%)	2 (12%)	5 (11%)
Thymus	(36)	(4)	(7)	(40)
Hepatocholangiocarcinoma, metastatic, liver		1 (25%)		
Lymphoma malignant	8 (22%)		3 (43%)	
Integumentary System				
Mammary gland	(43)	(6)	(11)	(46)
Adenocarcinoma	1 (2%)	1 (17%)	2 (18%)	5 (11%)
Histiocytic sarcoma			1 (9%)	
Skin	(46)	(7)	(10)	(48)
Hemangioma	1 (2%)			
Hemangiosarcoma, metastatic, spleen				1 (2%)
Lymphoma malignant	1 (2%)			
Musculoskeletal System				
Bone	(47)	(8)	(10)	(48)
Hepatocholangiocarcinoma, metastatic, mandible, liver		1 (13%)		
Osteosarcoma, pelvis				1 (2%)
Bone, sternum	(45)	(8)	(10)	(48)
Alveolar/bronchiolar carcinoma, metastatic, adventitia, lung				1 (2%)
Nervous System				
Brain, cerebrum	(48)	(8)	(10)	(48)
Carcinoma, metastatic, pituitary gland				1 (2%)
Respiratory System				
Lung	(47)	(8)	(11)	(48)
Alveolar/bronchiolar adenoma	2 (4%)	1 (13%)	1 (9%)	1 (2%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)			
Alveolar/bronchiolar carcinoma		1 (13%)		2 (4%)
Alveolar/bronchiolar carcinoma, multiple			1 (9%)	
Carcinoma, metastatic, harderian gland				1 (2%)
Carcinoma, metastatic, uncertain primary site			1 (9%)	
Hepatocellular carcinoma, metastatic, liver		1 (13%)	1 (9%)	
Hepatocholangiocarcinoma, metastatic, liver		1 (13%)		
Histiocytic sarcoma		1 (13%)	2 (18%)	
Lymphoma malignant	6 (13%)			1 (2%)
Osteosarcoma, metastatic, bone				1 (2%)
Nose	(48)	(8)	(10)	(48)
Histiocytic sarcoma		1 (13%)		
Squamous cell carcinoma			1 (10%)	

TABLE D1
Summary of the Incidence of Neoplasms in Regimen D Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control	10 mg/kg	25 mg/kg	50 mg/kg
Special Senses System				
Harderian gland	(44)	(7)	(10)	(48)
Adenoma	1 (2%)			3 (6%)
Carcinoma				1 (2%)
Histiocytic sarcoma			1 (10%)	
Lymphoma malignant	2 (5%)			
Lacrimal gland	(37)	(6)	(7)	(47)
Lymphoma malignant	2 (5%)			
Zymbal's gland	(41)	(6)	(8)	(46)
Squamous cell carcinoma			1 (13%)	
Urinary System				
Kidney	(47)	(8)	(10)	(48)
Carcinoma, metastatic, uncertain primary site			1 (10%)	
Hepatocholangiocarcinoma, metastatic, liver		1 (13%)		
Histiocytic sarcoma		1 (13%)		
Lymphoma malignant	6 (13%)		1 (10%)	2 (4%)
Urinary bladder	(46)	(5)	(10)	(48)
Histiocytic sarcoma	1 (2%)			
Lymphoma malignant	3 (7%)		1 (10%)	
Neoplasm Summary				
Total animals with primary neoplasms[b]	24	20	19	25
Total primary neoplasms	107	52	45	45
Total animals with benign neoplasms	11	3	6	7
Total benign neoplasms	12	3	6	8
Total animals with malignant neoplasms	16	18	14	20
Total malignant neoplasms	95	49	38	37
Total animals with metastatic neoplasms		1	2	5
Total metastatic neoplasms		8	6	6
Total animals with uncertain neoplasms-benign or malignant			1	
Total uncertain neoplasms			1	

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

[b] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D2
Statistical Analysis of Primary Neoplasms at 2 Years in Regimen D Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control	10 mg/kg	25 mg/kg	50 mg/kg
Harderian Gland: Adenoma				
Overall rate[a]	1/44 (2%)	0/7 (0%)	0/10 (0%)	3/48 (6%)
Adjusted rate[b]	2.5%	0.0%	0.0%	6.7%
Terminal rate[c]	0/35 (0%)	0/1 (0%)	0/1 (0%)	2/40 (5%)
First incidence (days)	741	—[e]	—	738
Poly-3 test[d]	(NA)	—[f]	—	P=0.3373
Harderian Gland: Adenoma or Carcinoma				
Overall rate	1/44 (2%)	0/7 (0%)	0/10 (0%)	4/48 (8%)
Adjusted rate	2.5%	0.0%	0.0%	8.9%
Terminal rate	0/35 (0%)	0/1 (0%)	0/1 (0%)	3/40 (8%)
First incidence (days)	741	—	—	738
Poly-3 test	(NA)	—	—	P=0.2061
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	1/48 (2%)	3/48 (6%)	2/48 (4%)	2/48 (4%)
Adjusted rate	2.3%	6.7%	4.4%	4.5%
Terminal rate	1/36 (3%)	2/41 (5%)	1/39 (3%)	2/40 (5%)
First incidence (days)	757 (T)	667	678	757 (T)
Poly-3 test	P=0.5367	P=0.3200	P=0.5141	P=0.5129
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	3/47 (6%)	1/8 (13%)	1/11 (9%)	1/48 (2%)
Adjusted rate	7.1%	19.0%	12.8%	2.2%
Terminal rate	3/36 (8%)	1/2 (50%)	1/2 (50%)	1/40 (3%)
First incidence (days)	757 (T)	757 (T)	757 (T)	757 (T)
Poly-3 test	(NA)	—	—	P=0.2899N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	3/47 (6%)	2/8 (25%)	2/11 (18%)	3/48 (6%)
Adjusted rate	7.1%	38.0%	25.6%	6.6%
Terminal rate	3/36 (8%)	2/2 (100%)	2/2 (100%)	1/40 (2%)
First incidence (days)	757 (T)	757 (T)	757 (T)	618
Poly-3 test	(NA)	—	—	P=0.6361N
All Organs: Hemangiosarcoma				
Overall rate	0/48 (0%)	1/48 (2%)	2/48 (4%)	4/48 (8%)
Adjusted rate	0.0%	2.2%	4.4%	8.7%
Terminal rate	0/36 (0%)	1/41 (2%)	0/39 (0%)	2/40 (5%)
First incidence (days)	—	757 (T)	661	485
Poly-3 test	P=0.0246	P=0.5067N	P=0.2480	P=0.0681
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	1/48 (2%)	1/48 (2%)	2/48 (4%)	4/48 (8%)
Adjusted rate	2.3%	2.2%	4.4%	8.7%
Terminal rate	1/36 (3%)	1/41 (2%)	0/39 (0%)	2/40 (5%)
First incidence (days)	757 (T)	757 (T)	661	485
Poly-3 test	P=0.0765	P=0.7530N	P=0.5167	P=0.1973

TABLE D2
Statistical Analysis of Primary Neoplasms at 2 Years in Regimen D Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control	10 mg/kg	25 mg/kg	50 mg/kg
All Organs: Histiocytic Sarcoma				
Overall rate	1/48 (2%)	3/48 (6%)	4/48 (8%)	0/48 (0%)
Adjusted rate	2.3%	6.6%	8.9%	0.0%
Terminal rate	0/36 (0%)	1/41 (2%)	2/39 (5%)	0/40 (0%)
First incidence (days)	479	593	686	—
Poly-3 test	P=0.2903N	P=0.3193	P=0.1864	P=0.4960N
All Organs: Malignant Lymphoma				
Overall rate	14/48 (29%)	10/48 (21%)	5/48 (10%)	7/48 (15%)
Adjusted rate	32.4%	22.1%	11.0%	15.5%
Terminal rate	12/36 (33%)	9/41 (22%)	3/39 (8%)	6/40 (15%)
First incidence (days)	634	605	664	716
Poly-3 test	P=0.0352N	P=0.2114N	P=0.0140N	P=0.0567N
All Organs: Benign Neoplasms				
Overall rate	11/48 (23%)	3/48 (6%)	7/48 (15%)[g]	7/48 (15%)
Adjusted rate	25.6%	6.7%	15.5%	15.6%
Terminal rate	9/36 (25%)	3/41 (7%)	6/39 (15%)	6/40 (15%)
First incidence (days)	674	757 (T)	678	738
Poly-3 test	P=0.3694N	P=0.0162N	P=0.1923N	P=0.1937N
All Organs: Malignant Neoplasms				
Overall rate	16/48 (33%)	18/48 (38%)	14/48 (29%)	20/48 (42%)
Adjusted rate	36.0%	38.1%	30.0%	42.5%
Terminal rate	12/36 (33%)	13/41 (32%)	7/39 (18%)	14/40 (35%)
First incidence (days)	479	508	655	485
Poly-3 test	P=0.3166	P=0.4825	P=0.3700N	P=0.3169
All Organs: Benign or Malignant Neoplasms				
Overall rate	24/48 (50%)	20/48 (42%)	19/48 (40%)	25/48 (52%)
Adjusted rate	53.6%	42.3%	40.7%	53.0%
Terminal rate	18/36 (50%)	15/41 (37%)	12/39 (31%)	18/40 (45%)
First incidence (days)	479	508	655	485
Poly-3 test	P=0.4079	P=0.2116N	P=0.1708N	P=0.5720

(T)Terminal sacrifice
(NA)Not applicable

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

[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality

[c] Observed incidence at terminal kill

[d] 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

[f] Tissue was examined microscopically only when it was observed to be abnormal at necropsy; thus, statistical comparisons with the vehicle controls are not appropriate.

[g] Includes one animal with a neoplasm of uncertain malignancy

TABLE D3
Summary of the Incidence of Nonneoplastic Lesions in Regimen D Female Mice in the 2-Year Gavage Study of Chloral Hydrate[a]

	Vehicle Control	10 mg/kg	25 mg/kg	50 mg/kg
Disposition Summary				
Animals initially in study	48	48	48	48
Early deaths				
Accidental deaths	2			
Moribund	4	1	6	4
Natural deaths	6	6	3	4
Survivors				
Died last week of study		1	1	
Terminal sacrifice	36	40	38	40
Animals examined microscopically	48	48	48	48
Alimentary System				
Esophagus	(45)	(5)	(10)	(45)
Hyperkeratosis	2 (4%)	1 (20%)		
Gallbladder	(41)	(6)	(9)	(46)
Infiltration cellular, lymphocytic	4 (10%)			3 (7%)
Inflammation				2 (4%)
Intestine large, cecum	(43)	(4)	(8)	(45)
Hyperplasia, lymphoid	4 (9%)			
Intestine large, colon	(44)	(5)	(9)	(45)
Hyperplasia, lymphoid	1 (2%)			
Inflammation				1 (2%)
Intestine small, duodenum	(43)	(5)	(9)	(44)
Infiltration cellular, lymphocytic				1 (2%)
Inflammation			1 (11%)	
Intestine small, ileum	(40)	(4)	(7)	(45)
Hyperplasia, lymphoid				3 (7%)
Liver	(48)	(48)	(48)	(48)
Angiectasis		1 (2%)		3 (6%)
Basophilic focus	2 (4%)	2 (4%)	3 (6%)	3 (6%)
Clear cell focus			1 (2%)	
Ectasia, vein				1 (2%)
Eosinophilic focus	1 (2%)	1 (2%)	1 (2%)	
Fibrosis		1 (2%)		
Hematopoietic cell proliferation	4 (8%)	3 (6%)	9 (19%)	7 (15%)
Hyperplasia, bile duct		1 (2%)		
Hyperplasia, Kupffer cell		1 (2%)		
Infiltration cellular, lymphocytic	32 (67%)	36 (75%)	38 (79%)	37 (77%)
Inflammation	1 (2%)			
Mineralization				1 (2%)
Necrosis	34 (71%)	36 (75%)	31 (65%)	33 (69%)
Necrosis, coagulative			1 (2%)	
Regeneration				1 (2%)
Tension lipoidosis	17 (35%)	20 (42%)	10 (21%)	11 (23%)
Thrombus				1 (2%)
Vacuolization cytoplasmic	27 (56%)	36 (75%)	36 (75%)	23 (48%)
Mesentery	(1)			(1)
Necrosis, fat	1 (100%)			1 (100%)

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

TABLE D3
Summary of the Incidence of Nonneoplastic Lesions in Regimen D Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control	10 mg/kg	25 mg/kg	50 mg/kg
Alimentary System (continued)				
Pancreas	(46)	(5)	(10)	(47)
Atrophy			1 (10%)	2 (4%)
Ectasia, duct		1 (20%)		
Focal cellular change	2 (4%)			2 (4%)
Infiltration cellular, lymphocytic	31 (67%)		6 (60%)	30 (64%)
Inflammation	1 (2%)			
Salivary glands	(47)	(7)	(10)	(48)
Atrophy	4 (9%)		1 (10%)	
Infiltration cellular, lymphocytic	38 (81%)	7 (100%)	6 (60%)	45 (94%)
Stomach, forestomach	(45)	(5)	(9)	(46)
Hyperkeratosis	1 (2%)	1 (20%)	1 (11%)	
Hyperplasia		1 (20%)		
Infiltration cellular, lymphocytic				1 (2%)
Stomach, glandular	(45)	(5)	(9)	(46)
Cyst	2 (4%)		1 (11%)	1 (2%)
Infiltration cellular, lymphocytic				1 (2%)
Mineralization		1 (20%)		
Tongue	(46)	(8)	(10)	(48)
Inflammation	1 (2%)			
Cardiovascular System				
Heart	(48)	(8)	(10)	(48)
Degeneration, artery	1 (2%)			
Fibrosis				1 (2%)
Infiltration cellular, lymphocytic				1 (2%)
Endocrine System				
Adrenal gland	(47)	(7)	(10)	(48)
Accessory adrenal cortical nodule			1 (10%)	
Adrenal gland, cortex	(47)	(6)	(10)	(48)
Cyst	1 (2%)			
Focal cellular change	1 (2%)			
Hyperplasia				1 (2%)
Hyperplasia, spindle cell	44 (94%)	5 (83%)	9 (90%)	44 (92%)
Vacuolization cytoplasmic	1 (2%)			
Adrenal gland, medulla	(47)	(6)	(10)	(47)
Focal cellular change	1 (2%)			
Vacuolization cytoplasmic	1 (2%)			
Islets, pancreatic	(46)	(4)	(11)	(47)
Hyperplasia				1 (2%)
Infiltration cellular, lymphocytic	2 (4%)			
Parathyroid gland	(44)	(3)	(5)	(43)
Cyst	1 (2%)			
Ectopic thymus	1 (2%)			
Pituitary gland	(45)	(4)	(9)	(43)
Angiectasis		1 (25%)		1 (2%)
Cyst			1 (11%)	
Ectasia	1 (2%)			
Hyperplasia, pars distalis	4 (9%)	1 (25%)		3 (7%)

TABLE D3
Summary of the Incidence of Nonneoplastic Lesions in Regimen D Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control	10 mg/kg	25 mg/kg	50 mg/kg
Endocrine System (continued)				
Thyroid gland	(46)	(5)	(9)	(47)
Cyst, follicle	2 (4%)			2 (4%)
Depletion secretory			1 (11%)	
Goiter adenomatous				1 (2%)
Hyperplasia, follicular cell			1 (11%)	
Infiltration cellular, lymphocytic	4 (9%)			
Inflammation			1 (11%)	
Ultimobranchial cyst	11 (24%)	2 (40%)		14 (30%)
General Body System				
None				
Genital System				
Clitoral gland	(38)	(7)	(8)	(35)
Atrophy	38 (100%)	5 (71%)	7 (88%)	32 (91%)
Inflammation	1 (3%)			
Ovary	(46)	(22)	(30)	(46)
Amyloid deposition			1 (3%)	
Angiectasis				2 (4%)
Atrophy	32 (70%)	3 (14%)	4 (13%)	29 (63%)
Congestion				1 (2%)
Cyst	15 (33%)	9 (41%)	16 (53%)	11 (24%)
Cyst, periovarian tissue	10 (22%)	5 (23%)	9 (30%)	7 (15%)
Hematocyst	4 (9%)	1 (5%)		7 (15%)
Hemorrhage			1 (3%)	
Hyperplasia, adenomatous	1 (2%)			
Hyperplasia, tubular	1 (2%)			
Infiltration cellular, lymphocytic	2 (4%)			1 (2%)
Inflammation		1 (5%)		
Mineralization				1 (2%)
Ovotestis	1 (2%)			1 (2%)
Uterus	(47)	(30)	(35)	(48)
Adenomyosis				1 (2%)
Angiectasis			1 (3%)	
Atrophy	6 (13%)	2 (7%)	4 (11%)	3 (6%)
Dilatation	2 (4%)	2 (7%)	2 (6%)	3 (6%)
Ectasia, vein	1 (2%)			
Fibrosis		2 (7%)	1 (3%)	
Hemorrhage			1 (3%)	
Hyperplasia, atypical				1 (2%)
Hyperplasia, cystic, endometrium	35 (74%)	21 (70%)	24 (69%)	38 (79%)
Hypertrophy, myometrium				1 (2%)
Inflammation		1 (3%)		
Metaplasia, squamous	1 (2%)			
Thrombus	1 (2%)			
Vagina	(44)	(7)	(10)	(46)
Amyloid deposition			1 (10%)	
Atrophy	2 (5%)	2 (29%)	2 (20%)	2 (4%)
Dysplasia			1 (10%)	
Infiltration cellular, lymphocytic	2 (5%)			1 (2%)

TABLE D3
Summary of the Incidence of Nonneoplastic Lesions in Regimen D Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control	10 mg/kg	25 mg/kg	50 mg/kg
Hematopoietic System				
Bone marrow	(47)	(8)	(10)	(48)
Congestion			1 (10%)	
Hyperplasia	2 (4%)	2 (25%)	4 (40%)	2 (4%)
Hyperplasia, lymphoid	1 (2%)			
Myelofibrosis			1 (10%)	1 (2%)
Lymph node	(47)	(13)	(11)	(48)
Hyperplasia, lymphoid				1 (2%)
Hyperplasia, lymphoid, axillary	1 (2%)			
Hyperplasia, lymphoid, renal				1 (2%)
Lymph node, mandibular	(47)	(8)	(9)	(48)
Atrophy	4 (9%)		1 (11%)	
Hemorrhage	1 (2%)	1 (13%)	1 (11%)	1 (2%)
Hyperplasia, lymphoid	7 (15%)	3 (38%)	2 (22%)	10 (21%)
Infiltration cellular, histiocytic				1 (2%)
Polyarteritis			1 (11%)	
Lymph node, mesenteric	(46)	(10)	(8)	(45)
Atrophy	6 (13%)		2 (25%)	
Hematopoietic cell proliferation			1 (13%)	
Hemorrhage			1 (13%)	
Hyperplasia, lymphoid	3 (7%)			3 (7%)
Infiltration cellular, histiocytic				1 (2%)
Inflammation		1 (10%)		
Spleen	(47)	(18)	(17)	(47)
Amyloid deposition			1 (6%)	
Angiectasis		1 (6%)		
Atrophy		1 (6%)	5 (29%)	
Congestion	5 (11%)			
Hematocyst				1 (2%)
Hematopoietic cell proliferation	6 (13%)	2 (11%)	8 (47%)	7 (15%)
Hyperplasia, lymphoid	16 (34%)	4 (22%)	5 (29%)	18 (38%)
Infarct	1 (2%)			
Infiltration cellular, histiocytic		1 (6%)		
Necrosis	1 (2%)	1 (6%)	1 (6%)	1 (2%)
Polyarteritis			1 (6%)	
Thymus	(36)	(4)	(7)	(40)
Atrophy, cortex	25 (69%)	3 (75%)	4 (57%)	35 (88%)
Ectopic parathyroid gland		1 (25%)		
Hyperplasia, lymphoid, medulla	10 (28%)	1 (25%)	1 (14%)	14 (35%)
Integumentary System				
Mammary gland	(43)	(6)	(11)	(46)
Hyperplasia	2 (5%)	1 (17%)		1 (2%)
Infiltration cellular, lymphocytic	1 (2%)			1 (2%)
Lactation			1 (9%)	12 (26%)
Metaplasia, squamous		1 (17%)		
Musculoskeletal System				
Bone	(47)	(8)	(10)	(48)
Fibrous osteodystrophy, turbinate				10 (21%)
Bone, femur	(47)	(8)	(10)	(48)
Degeneration, cartilage	1 (2%)			
Fibrous osteodystrophy	22 (47%)			5 (10%)

TABLE D3
Summary of the Incidence of Nonneoplastic Lesions in Regimen D Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control	10 mg/kg	25 mg/kg	50 mg/kg
Musculoskeletal System (continued)				
Bone, sternum	(45)	(8)	(10)	(48)
Fibrous osteodystrophy, multifocal	35 (78%)	1 (13%)	3 (30%)	38 (79%)
Skeletal muscle	(45)	(8)	(10)	(47)
Infiltration cellular, lymphocytic	1 (2%)			
Nervous System				
Brain, cerebellum	(48)	(8)	(10)	(48)
Mineralization, thalamus	1 (2%)			
Brain, cerebrum	(48)	(8)	(10)	(48)
Hydrocephalus				1 (2%)
Mineralization, multifocal, thalamus	30 (63%)	2 (25%)	3 (30%)	26 (54%)
Peripheral nerve	(44)	(8)	(10)	(46)
Demyelination	1 (2%)			
Spinal cord, thoracic	(48)	(8)	(9)	(48)
Degeneration, axon	1 (2%)			
Infiltration cellular, lymphocytic	1 (2%)			
Respiratory System				
Lung	(47)	(8)	(11)	(48)
Congestion	1 (2%)			
Crystals				1 (2%) Edema
1	(2%)			
Hemorrhage	1 (2%)			
Hyperplasia, alveolar epithelium				2 (4%)
Infiltration cellular, histiocytic	4 (9%)			6 (13%)
Infiltration cellular, lymphocytic	28 (60%)	4 (50%)	4 (36%)	41 (85%)
Inflammation	4 (9%)			1 (2%)
Metaplasia, osseous			1 (9%)	
Pigmentation, hemosiderin	1 (2%)			
Thrombus				1 (2%)
Nose	(48)	(8)	(10)	(48)
Cytoplasmic alteration, respiratory epithelium	1 (2%)			
Inflammation		1 (13%)		
Special Senses System				
Eye	(42)	(3)	(5)	(45)
Cataract			1 (20%)	
Harderian gland	(44)	(7)	(10)	(48)
Atrophy			1 (10%)	
Ectasia	1 (2%)			
Hyperplasia		1 (14%)		2 (4%)
Infiltration cellular, lymphocytic	21 (48%)	1 (14%)	2 (20%)	19 (40%)
Lacrimal gland	(37)	(6)	(7)	(47)
Atrophy	5 (14%)			
Cytoplasmic alteration			1 (14%)	
Focal cellular change				1 (2%)
Infiltration cellular, lymphocytic	21 (57%)	4 (67%)	6 (86%)	34 (72%)

TABLE D3
Summary of the Incidence of Nonneoplastic Lesions in Regimen D Female Mice in the 2-Year Gavage Study of Chloral Hydrate

	Vehicle Control	10 mg/kg	25 mg/kg	50 mg/kg
Urinary System				
Kidney	(47)	(8)	(10)	(48)
Accumulation hyaline droplet		1 (13%)	2 (20%)	
Amyloid deposition, glomerulus	1 (2%)		1 (10%)	2 (4%)
Cyst, renal tubule	9 (19%)	3 (38%)	2 (20%)	4 (8%)
Edema				1 (2%)
Glomerulosclerosis	1 (2%)			3 (6%)
Hematopoietic cell proliferation			1 (10%)	
Hydronephrosis			1 (10%)	
Infarct				1 (2%)
Infiltration cellular, lymphocytic	37 (79%)	6 (75%)	9 (90%)	41 (85%)
Nephropathy	2 (4%)			
Pigmentation, renal tubule	2 (4%)			1 (2%)
Vacuolization cytoplasmic, renal tubule		1 (13%)	1 (10%)	
Urinary bladder	(46)	(5)	(10)	(48)
Infiltration cellular, lymphocytic	38 (83%)	4 (80%)	5 (50%)	39 (81%)