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Benzyltrimethylammonium Chloride, NTP TOX 57

APPENDIX A
SUMMARY OF NONNEOPLASTIC LESIONS
IN RATS AND MICE

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TABLE A1
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 13-Week Gavage Study of Benzyltrimethylammonium Chloride^a

	Vehicle Control	12.5 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg
Disposition Summary					
Animals initially in study	10	10	10	10	10
Survivors					
Terminal sacrifice	10	10	10	10	10
Animals examined microscopically	10	2	1	10	10
Alimentary System					
Liver	(10)	(2)			(10)
Inflammation, focal Hepatocyte, centrilobular, vacuolization cytoplasmic	4 (40%)				5 (50%) 1 (10%)
Cardiovascular System					
Heart	(10)				(10)
Inflammation, focal	8 (80%)				5 (50%)
Endocrine System					
Pituitary gland	(10)				(10)
Cyst	1 (10%)				1 (10%)
Thyroid gland	(10)				(10)
Follicle, cyst	2 (20%)				1 (10%)
General Body System					
None					
Genital System					
Epididymis	(10)		(1)		(10)
Inflammation, focal, granulomatous			1 (100%)		
Prostate	(10)				(10)
Infiltration cellular, focal, lymphocyte Inflammation	1 (10%)				1 (10%)
Testes	(10)		(1)		(10)
Atrophy			1 (100%)		
Hematopoietic System					
Spleen	(10)				(10)
Hematopoietic cell proliferation	3 (30%)				4 (40%)
Integumentary System					
None					

TABLE A1
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 13-Week Gavage Study of Benzyltrimethylammonium Chloride

	Vehicle Control	12.5 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg
Musculoskeletal System					
None					
Nervous System					
None					
Respiratory System					
Lung	(10)			(10)	(10)
Inflammation, focal	6 (60%)			1 (10%)	5 (50%)
Nose	(10)				(10)
Inflammation	2 (20%)				
Special Senses System					
None					
Urinary System					
Kidney	(10)		(1)		(10)
Renal tubule, hemorrhage, focal	1 (10%)				

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

TABLE A2
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 13-Week Gavage Study of Benzyltrimethylammonium Chloride^a

	Vehicle Control	12.5 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg
Disposition Summary					
Animals initially in study	10	10	10	10	10
Early death					
Accidental death			1		
Natural deaths					2
Survivors					
Died last week of study				1	
Terminal sacrifice	10	10	9	9	8
Animals examined microscopically	10	3	2	10	10
Alimentary System					
Liver	(10)	(1)	(1)		(10)
Inflammation, focal	5 (50%)				4 (40%)
Hepatocyte, centrilobular, vacuolization cytoplasmic			1 (100%)		
Mesentery	(1)		(1)		
Fat, necrosis	1 (100%)		1 (100%)		
Pancreas	(10)		(1)		(10)
Acinus, atrophy					1 (10%)
Acinus, degeneration, focal	1 (10%)				
Cardiovascular System					
Heart	(10)		(1)		(10)
Inflammation, focal	5 (50%)		1 (100%)		4 (40%)
Endocrine System					
Pituitary gland	(10)				(10)
Pars distalis, cyst					1 (10%)
Thyroid gland	(10)		(1)		(10)
Follicle, cyst	1 (10%)				
General Body System					
None					
Genital System					
Uterus	(10)	(2)	(1)	(1)	(10)
Bilateral, cyst		2 (100%)		1 (100%)	
Bilateral, dilatation	2 (20%)				2 (20%)
Hematopoietic System					
Spleen	(10)		(1)		(10)
Hematopoietic cell proliferation	1 (10%)		1 (100%)		

TABLE A2
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 13-Week Gavage Study of Benzyltrimethylammonium Chloride

	Vehicle Control	12.5 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg
Integumentary System					
None					
Musculoskeletal System					
None					
Nervous System					
None					
Respiratory System					
Lung	(10)		(1)	(10)	(10)
Congestion					1 (10%)
Inflammation, focal	3 (30%)		1 (100%)	3 (30%)	6 (60%)
Nose	(10)				(10)
Inflammation, chronic active	1 (10%)				
Special Senses System					
None					
Urinary System					
None					

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

TABLE A3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 13-Week Gavage Study of Benzyltrimethylammonium Chloride^a

	Vehicle Control	12.5 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg
Disposition Summary					
Animals initially in study	10	10	10	10	10
Early death					
Natural death					1
Survivors					
Died last week of study				1	
Terminal sacrifice	10	10	10	9	9
Animals examined microscopically	10				10
Alimentary System					
Liver	(10)				(10)
Inflammation, chronic, focal Hepatocyte, centrilobular, hypertrophy	3 (30%)				3 (30%)
Salivary glands	(10)				(10)
Infiltration cellular, focal, lymphocyte	1 (10%)				
Cardiovascular System					
None					
Endocrine System					
Adrenal cortex	(10)				(10)
Capsule, hyperplasia, focal					1 (10%)
General Body System					
None					
Genital System					
Prostate	(10)				(10)
Infiltration cellular, lymphocyte	1 (10%)				
Hematopoietic System					
Spleen	(10)				(10)
Hematopoietic cell proliferation	1 (10%)				1 (10%)
Lymphoid follicle, hyperplasia					2 (20%)
Integumentary System					
None					
Musculoskeletal System					
None					

TABLE A3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 13-Week Gavage Study of Benzyltrimethylammonium Chloride

	Vehicle Control	12.5 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg
Nervous System None					
Respiratory System None					
Special Senses System None					
Urinary System None					

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

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 13-Week Gavage Study of Benzyltrimethylammonium Chloride^a

	Vehicle Control	12.5 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg
Disposition Summary					
Animals initially in study	10	10	10	10	10
Early death					
Natural death					1
Survivors					
Terminal sacrifice	10	10	10	10	9
Animals examined microscopically	10				10
Alimentary System					
Liver	(10)				(10)
Inflammation, chronic, focal	1 (10%)				
Necrosis, focal	2 (20%)				1 (10%)
Hepatocyte, centrilobular, hypertrophy	3 (30%)				3 (30%)
Cardiovascular System					
None					
Endocrine System					
Adrenal cortex	(10)				(10)
Bilateral, capsule, hyperplasia, focal	5 (50%)				5 (50%)
Capsule, hyperplasia, focal	1 (10%)				
Thyroid gland	(10)				(10)
Ultimobranchial cyst					1 (10%)
General Body System					
None					
Genital System					
Ovary	(10)				(10)
Hemorrhage					1 (10%)
Uterus	(10)				(10)
Endometrium, hyperplasia, cystic	3 (30%)				
Hematopoietic System					
Lymph node, mandibular	(10)				(10)
Hemorrhage					1 (10%)
Hyperplasia, lymphoid	1 (10%)				
Lymph node, mesenteric	(10)				(10)
Hyperplasia, lymphoid	1 (10%)				
Spleen	(10)				(10)
Hematopoietic cell proliferation	1 (10%)				3 (30%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 13-Week Gavage Study of Benzyltrimethylammonium Chloride

	Vehicle Control	12.5 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg
Integumentary System					
None					
Musculoskeletal System					
None					
Nervous System					
None					
Respiratory System					
Lung	(10)				(10)
Interstitial, inflammation, chronic		1 (10%)			2 (20%)
Nose	(10)				(10)
Olfactory epithelium, cytoplasmic alteration					1 (10%)
Special Senses System					
None					
Urinary System					
Urinary bladder	(10)				(10)
Infiltration cellular, lymphocyte					1 (10%)

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

APPENDIX C

HEMATOLOGY AND CLINICAL CHEMISTRY RESULTS

TABLE C1	Hematology and Clinical Chemistry Data for Rats in the 16-Day Gavage Study of Benzyltrimethylammonium Chloride	C-2
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TABLE C1
Hematology and Clinical Chemistry Data for Rats in the 16-Day Gavage Study
of Benzyltrimethylammonium Chloride^a

	Vehicle Control	16 mg/kg	32 mg/kg	63 mg/kg
Male				
n	5	5	5	5
Hematology				
Automated hematocrit (%)	40.4 ± 0.6	40.3 ± 0.6	40.7 ± 1.0	40.3 ± 0.4
Manual hematocrit (%)	45.4 ± 0.7	45.8 ± 0.7	45.8 ± 1.2	45.4 ± 0.5
Hemoglobin (g/dL)	15.0 ± 0.3	15.1 ± 0.1	15.1 ± 0.3	14.8 ± 0.1
Erythrocytes (10 ⁶ /μL)	7.06 ± 0.10	7.08 ± 0.12	7.13 ± 0.20	6.99 ± 0.11
Reticulocytes (10 ⁶ /μL)	0.29 ± 0.02	0.24 ± 0.06	0.25 ± 0.04	0.46 ± 0.13
Nucleated erythrocytes/100 leukocytes	0.40 ± 0.25	0.40 ± 0.25	0.20 ± 0.20	0.40 ± 0.25
Mean cell volume (fL)	57.1 ± 0.2	56.9 ± 0.3	57.1 ± 0.3	57.6 ± 0.5
Mean cell hemoglobin (pg)	21.2 ± 0.1	21.3 ± 0.3	21.3 ± 0.2	21.3 ± 0.2
Mean cell hemoglobin concentration (g/dL)	37.1 ± 0.2	37.4 ± 0.5	37.3 ± 0.3	36.8 ± 0.2
Platelets (10 ³ /μL)	838.4 ± 15.1	820.0 ± 34.2	857.4 ± 21.1	774.0 ± 9.4
Leukocytes (10 ³ /μL)	9.10 ± 0.32	8.42 ± 0.18	8.88 ± 0.55	9.06 ± 0.40
Segmented neutrophils (10 ³ /μL)	0.86 ± 0.16	0.82 ± 0.14	0.82 ± 0.14	1.00 ± 0.14
Lymphocytes (10 ³ /μL)	8.06 ± 0.31	7.38 ± 0.26	7.91 ± 0.35	7.63 ± 0.26
Monocytes (10 ³ /μL)	0.07 ± 0.05	0.20 ± 0.09	0.10 ± 0.06	0.37 ± 0.12
Eosinophils (10 ³ /μL)	0.12 ± 0.06	0.02 ± 0.02	0.06 ± 0.04	0.06 ± 0.04
Clinical Chemistry				
Urea nitrogen (mg/dL)	24.0 ± 0.5	25.8 ± 0.4	23.0 ± 0.7	25.0 ± 0.5
Creatinine (mg/dL)	0.70 ± 0.00	0.70 ± 0.00	0.70 ± 0.00	0.70 ± 0.00
Total protein (g/dL)	6.6 ± 0.2	6.3 ± 0.1	6.6 ± 0.1	6.2 ± 0.1
Albumin (g/dL)	4.8 ± 0.1	4.7 ± 0.1	4.7 ± 0.1	4.6 ± 0.1
Alanine aminotransferase (IU/L)	48 ± 1	56 ± 4	43 ± 1	43 ± 4
Alkaline phosphatase (IU/L)	545 ± 15	553 ± 13	566 ± 16	559 ± 13
Creatine kinase (IU/L)	440 ± 81	542 ± 147	505 ± 81	444 ± 79
Sorbitol dehydrogenase (IU/L)	33 ± 2	32 ± 3	31 ± 2	32 ± 2
Serum cholinesterase (IU/L)	676.8 ± 28.8	753.2 ± 13.5	738.4 ± 23.4	789.0 ± 39.7*
Erythrocyte cholinesterase (IU/L)	530.2 ± 143.6	726.4 ± 113.2	694.4 ± 121.9	726.6 ± 71.4
Bile acids (μmol/L)	28.3 ± 4.5	28.6 ± 4.0	39.9 ± 7.2	34.5 ± 5.1

TABLE CI
Hematology and Clinical Chemistry Data for Rats in the 16-Day Gavage Study
of Benzyltrimethylammonium Chloride

	Vehicle Control	16 mg/kg	32 mg/kg	63 mg/kg
Female				
n	5	5	5	5
Hematology				
Automated hematocrit (%)	44.5 ± 0.4	42.6 ± 0.8	42.5 ± 0.4	44.2 ± 1.1
Manual hematocrit (%)	46.4 ± 0.4	45.0 ± 0.5	44.8 ± 0.4	46.2 ± 0.9
Hemoglobin (g/dL)	15.6 ± 0.1	15.2 ± 0.2	15.0 ± 0.1	15.7 ± 0.3
Erythrocytes (10 ⁶ /μL)	7.59 ± 0.08	7.24 ± 0.13	7.20 ± 0.06	7.58 ± 0.20
Reticulocytes (10 ⁶ /μL)	0.20 ± 0.03	0.22 ± 0.03	0.18 ± 0.02	0.23 ± 0.03
Nucleated erythrocytes/100 leukocytes	0.00 ± 0.00	0.80 ± 0.37	0.20 ± 0.20	0.00 ± 0.00
Mean cell volume (fL)	58.6 ± 0.2	58.9 ± 0.1	59.1 ± 0.2	58.3 ± 0.3
Mean cell hemoglobin (pg)	20.6 ± 0.2	21.0 ± 0.2	20.8 ± 0.1	20.7 ± 0.2
Mean cell hemoglobin concentration (g/dL)	35.2 ± 0.3	35.7 ± 0.4	35.2 ± 0.3	35.5 ± 0.2
Platelets (10 ³ /μL)	714.8 ± 13.5	755.2 ± 23.9	763.2 ± 14.2	710.0 ± 23.9
Leukocytes (10 ³ /μL)	9.28 ± 0.50	9.46 ± 0.19	9.38 ± 0.93	8.24 ± 0.30
Segmented neutrophils (10 ³ /μL)	1.30 ± 0.26	1.21 ± 0.22	1.17 ± 0.23	0.77 ± 0.18
Lymphocytes (10 ³ /μL)	7.72 ± 0.37	7.89 ± 0.27	8.05 ± 0.84	7.32 ± 0.44
Monocytes (10 ³ /μL)	0.19 ± 0.05	0.27 ± 0.05	0.13 ± 0.04	0.09 ± 0.05
Eosinophils (10 ³ /μL)	0.07 ± 0.03	0.10 ± 0.03	0.04 ± 0.02	0.06 ± 0.02
Clinical Chemistry				
Urea nitrogen (mg/dL)	23.8 ± 0.4	23.6 ± 0.2	22.6 ± 1.3	22.4 ± 0.8
Creatinine (mg/dL)	0.70 ± 0.00	0.68 ± 0.02	0.66 ± 0.02	0.66 ± 0.04
Total protein (g/dL)	6.0 ± 0.1	6.0 ± 0.1	5.8 ± 0.1	6.0 ± 0.1
Albumin (g/dL)	4.5 ± 0.1	4.5 ± 0.1	4.3 ± 0.1	4.4 ± 0.1
Alanine aminotransferase (IU/L)	40 ± 2	37 ± 1	37 ± 2	37 ± 1
Alkaline phosphatase (IU/L)	505 ± 8	490 ± 18	501 ± 31	518 ± 9
Creatine kinase (IU/L)	432 ± 61	272 ± 32	421 ± 70	378 ± 86
Sorbitol dehydrogenase (IU/L)	30 ± 1	28 ± 0	27 ± 2	26 ± 1
Serum cholinesterase (IU/L)	2,364.0 ± 120.6	2,577.8 ± 189.9	2,061.0 ± 123.8	2,138.4 ± 223.7
Erythrocyte cholinesterase (IU/L)	673.8 ± 175.9	400.6 ± 164.4	1,185.8 ± 193.3	819.2 ± 204.7
Bile acids (μmol/L)	29.2 ± 2.9	31.4 ± 5.2	28.5 ± 5.0	28.9 ± 6.2

* Significantly different (P<0.05) from the vehicle control group by Dunnett's test

^a Mean ± standard error. Statistical tests were performed on unrounded data. No data are available for the 125 and 250 mg/kg groups due to 100% mortality.

TABLE C2
Hematology and Clinical Chemistry Data for Rats in the 13-Week Gavage Study
of Benzyltrimethylammonium Chloride^a

	Vehicle Control	12.5 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg
Male					
n					
Day 3	10	10	10	10	10
Day 21	10	10	10	10	10
Week 13	10	9	10	10	10
Hematology					
Automated hematocrit (%)					
Day 3	38.4 ± 0.5	39.0 ± 0.6	37.9 ± 0.4	38.7 ± 0.4	39.1 ± 0.7
Day 21	44.3 ± 0.4	44.3 ± 0.4	44.1 ± 0.3	44.8 ± 0.5	43.5 ± 0.7
Week 13	46.8 ± 0.4	48.5 ± 0.3*	47.9 ± 0.5	46.5 ± 0.5	46.5 ± 0.4
Manual hematocrit (%)					
Day 3	42.2 ± 0.7	41.5 ± 0.7	41.2 ± 0.4	43.1 ± 0.4	42.5 ± 0.8
Day 21	47.7 ± 0.5	47.5 ± 0.7	47.0 ± 0.5	48.0 ± 0.6	47.6 ± 0.6
Week 13	48.9 ± 0.4	50.0 ± 0.4	49.5 ± 0.4	48.7 ± 0.5	48.9 ± 0.4
Hemoglobin (g/dL)					
Day 3	13.7 ± 0.2	13.8 ± 0.2	13.5 ± 0.1	13.8 ± 0.1	13.8 ± 0.2
Day 21	15.4 ± 0.1	15.6 ± 0.1	15.5 ± 0.1	15.6 ± 0.1	15.4 ± 0.2
Week 13	15.8 ± 0.1	15.9 ± 0.1	16.0 ± 0.1	15.8 ± 0.2	15.8 ± 0.1
Erythrocytes (10⁶/μL)					
Day 3	6.27 ± 0.07	6.33 ± 0.09	6.18 ± 0.06	6.28 ± 0.05	6.36 ± 0.12
Day 21	7.25 ± 0.08	7.31 ± 0.06	7.34 ± 0.05	7.28 ± 0.08	7.09 ± 0.10
Week 13	8.96 ± 0.07	9.08 ± 0.06	9.03 ± 0.09	8.71 ± 0.09	8.67 ± 0.06*
Reticulocytes (10⁶/μL)					
Day 3	0.53 ± 0.03	0.58 ± 0.02	0.54 ± 0.04	0.50 ± 0.02	0.55 ± 0.03
Day 21	0.24 ± 0.01	0.23 ± 0.01	0.20 ± 0.02*	0.20 ± 0.01**	0.21 ± 0.01**
Week 13	0.21 ± 0.01	0.24 ± 0.02	0.24 ± 0.01	0.22 ± 0.01	0.22 ± 0.01
Nucleated erythrocytes (10³/μL)					
Day 3	0.17 ± 0.05	0.13 ± 0.06	0.12 ± 0.05	0.16 ± 0.02	0.13 ± 0.03
Day 21	0.05 ± 0.03	0.04 ± 0.03	0.01 ± 0.01	0.06 ± 0.03	0.07 ± 0.03
Week 13	0.02 ± 0.02	0.04 ± 0.03	0.00 ± 0.00 ^b	0.02 ± 0.02 ^b	0.00 ± 0.00
Mean cell volume (fL)					
Day 3	61.2 ± 0.3	61.5 ± 0.3	61.3 ± 0.3	61.6 ± 0.2	61.4 ± 0.2
Day 21	61.0 ± 0.4	60.7 ± 0.4	60.0 ± 0.3	61.6 ± 0.4	61.3 ± 0.3
Week 13	52.2 ± 0.2	53.4 ± 0.1**	53.0 ± 0.2**	53.4 ± 0.2**	53.6 ± 0.1**
Mean cell hemoglobin (pg)					
Day 3	21.8 ± 0.1	21.8 ± 0.2	21.9 ± 0.1	22.0 ± 0.1	21.7 ± 0.1
Day 21	21.2 ± 0.2	21.3 ± 0.1	21.1 ± 0.1	21.4 ± 0.1	21.7 ± 0.1
Week 13	17.6 ± 0.1	17.5 ± 0.1	17.7 ± 0.1	18.1 ± 0.1**	18.2 ± 0.1**
Mean cell hemoglobin concentration (g/dL)					
Day 3	35.6 ± 0.1	35.5 ± 0.2	35.7 ± 0.2	35.7 ± 0.2	35.4 ± 0.2
Day 21	34.8 ± 0.3	35.1 ± 0.2	35.2 ± 0.2	34.8 ± 0.3	35.4 ± 0.2
Week 13	33.7 ± 0.2	32.8 ± 0.2*	33.4 ± 0.3	33.9 ± 0.2	34.0 ± 0.2
Platelets (10³/μL)					
Day 3	1,091.1 ± 30.5	1,086.9 ± 25.3	1,080.6 ± 14.8	1,025.7 ± 11.2	1,069.5 ± 26.3
Day 21	793.1 ± 19.9	807.4 ± 8.6	820.8 ± 10.4	824.7 ± 20.0	838.7 ± 28.7
Week 13	649.8 ± 10.3	640.6 ± 9.7	646.3 ± 10.8	641.4 ± 6.6	653.7 ± 13.7
Leukocytes (10³/μL)					
Day 3	8.09 ± 0.28	8.49 ± 0.24	7.70 ± 0.24	7.89 ± 0.22	8.91 ± 0.54
Day 21	11.03 ± 0.41	12.07 ± 0.30	10.78 ± 0.45	10.78 ± 0.25	10.90 ± 0.59
Week 13	11.96 ± 0.53	12.60 ± 0.61	11.90 ± 0.38	12.86 ± 0.60	11.67 ± 0.36

TABLE C2
Hematology and Clinical Chemistry Data for Rats in the 13-Week Gavage Study
of Benzyltrimethylammonium Chloride

	Vehicle Control	12.5 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg
Male (continued)					
^a					
Day 3	10	10	10	10	10
Day 21	10	10	10	10	10
Week 13	10	9	10	10	10
Hematology (continued)					
Segmented neutrophils (10³/μL)					
Day 3	1.28 ± 0.21	1.14 ± 0.07	0.96 ± 0.11	0.10 ± 0.11	1.14 ± 0.08
Day 21	1.17 ± 0.07	1.37 ± 0.19	1.18 ± 0.14	1.35 ± 0.12	1.15 ± 0.14
Week 13	2.13 ± 0.17	1.59 ± 0.11*	1.56 ± 0.16 ^{a,b}	1.54 ± 0.20 ^{a,b}	1.25 ± 0.18**
Lymphocytes (10³/μL)					
Day 3	6.69 ± 0.32	7.18 ± 0.19	6.64 ± 0.27	6.72 ± 0.18	7.57 ± 0.49
Day 21	9.55 ± 0.43	10.16 ± 0.25	9.17 ± 0.41	9.01 ± 0.27	9.49 ± 0.47
Week 13	9.06 ± 0.43	10.35 ± 0.65	9.82 ± 0.42 ^b	10.29 ± 0.61 ^b	9.97 ± 0.50
Atypical lymphocytes (10³/μL)					
Day 21	0.04 ± 0.03	0.06 ± 0.05	0.00 ± 0.00	0.03 ± 0.02	0.00 ± 0.00
Week 13	0.22 ± 0.09	0.12 ± 0.05	0.18 ± 0.06 ^b	0.19 ± 0.09 ^b	0.16 ± 0.07
Monocytes (10³/μL)					
Day 3	0.09 ± 0.04	0.14 ± 0.06	0.08 ± 0.02	0.14 ± 0.05	0.19 ± 0.04
Day 21	0.22 ± 0.07	0.44 ± 0.09	0.37 ± 0.09	0.36 ± 0.07	0.24 ± 0.10
Week 13	0.46 ± 0.12	0.35 ± 0.07	0.18 ± 0.05 ^b	0.53 ± 0.10 ^b	0.21 ± 0.04
Eosinophils (10³/μL)					
Day 3	0.02 ± 0.01	0.02 ± 0.01	0.03 ± 0.02	0.02 ± 0.02	0.01 ± 0.01
Day 21	0.05 ± 0.04	0.02 ± 0.02	0.04 ± 0.02	0.04 ± 0.02	0.01 ± 0.01
Week 13	0.08 ± 0.03	0.16 ± 0.04	0.12 ± 0.04 ^b	0.11 ± 0.04 ^b	0.07 ± 0.03
Clinical Chemistry					
Urea nitrogen (mg/dL)					
Day 3	20.1 ± 0.6	19.3 ± 0.4	19.4 ± 0.3	19.8 ± 0.3	19.2 ± 0.3
Day 21	22.4 ± 1.5	21.4 ± 0.5	20.9 ± 0.3	23.4 ± 1.8	21.8 ± 0.5
Week 13	23.5 ± 0.5	24.2 ± 1.3	23.6 ± 0.6	22.6 ± 0.3	22.3 ± 0.6
Creatinine (mg/dL)					
Day 3	0.58 ± 0.01	0.59 ± 0.01	0.58 ± 0.01	0.56 ± 0.02	0.57 ± 0.02
Day 21	0.68 ± 0.01	0.67 ± 0.02	0.68 ± 0.01	0.67 ± 0.02	0.67 ± 0.02
Week 13	0.66 ± 0.02	0.69 ± 0.01	0.70 ± 0.02	0.68 ± 0.01	0.67 ± 0.02
Total protein (g/dL)					
Day 3	5.7 ± 0.1	5.8 ± 0.1	5.7 ± 0.1	5.6 ± 0.1	5.7 ± 0.1
Day 21	6.2 ± 0.1	6.2 ± 0.1	6.2 ± 0.1	6.2 ± 0.1	6.2 ± 0.0
Week 13	6.8 ± 0.1	6.8 ± 0.1	7.0 ± 0.1	6.7 ± 0.1	6.7 ± 0.1
Albumin (g/dL)					
Day 3	4.3 ± 0.0	4.4 ± 0.0	4.3 ± 0.1	4.2 ± 0.1	4.3 ± 0.1
Day 21	4.6 ± 0.1	4.5 ± 0.0	4.5 ± 0.0	4.6 ± 0.1	4.6 ± 0.1
Week 13	5.0 ± 0.0	5.0 ± 0.1	5.0 ± 0.0	4.9 ± 0.0	4.9 ± 0.0
Alanine aminotransferase (IU/L)					
Day 3	42 ± 1	41 ± 2	41 ± 2	43 ± 2	42 ± 1
Day 21	47 ± 1	50 ± 1	46 ± 1	47 ± 1	46 ± 1
Week 13	67 ± 4	60 ± 4	69 ± 5	67 ± 5	56 ± 2

TABLE C2
Hematology and Clinical Chemistry Data for Rats in the 13-Week Gavage Study
of Benzyltrimethylammonium Chloride

	Vehicle Control	12.5 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg
Male (continued)					
n					
Day 3	10	10	10	10	10
Day 21	10	10	10	10	10
Week 13	10	9	10	10	10
Clinical Chemistry (continued)					
Alkaline phosphatase (IU/L)					
Day 3	708 ± 12	737 ± 17	730 ± 12	722 ± 15	700 ± 17
Day 21	533 ± 9	562 ± 17	543 ± 8	532 ± 10	544 ± 10
Week 13	270 ± 6	271 ± 8	276 ± 5	245 ± 5*	227 ± 7**
Creatine kinase (IU/L)					
Day 3	443 ± 47	577 ± 64	529 ± 38	429 ± 35	463 ± 31
Day 21	432 ± 31	457 ± 34	399 ± 20	467 ± 47	443 ± 47
Week 13	226 ± 23	255 ± 20	244 ± 14	256 ± 21	256 ± 30
Sorbitol dehydrogenase (IU/L)					
Day 3	16 ± 1	14 ± 2	15 ± 1	16 ± 1	16 ± 1
Day 21	19 ± 1	19 ± 1	20 ± 1	17 ± 1	20 ± 1
Week 13	25 ± 2	22 ± 2	24 ± 1	22 ± 1	19 ± 1**
Serum cholinesterase (IU/L)					
Day 3	859.6 ± 15.2	851.2 ± 17.9	853.5 ± 15.0	846.4 ± 14.4	904.1 ± 19.4
Day 21	692.9 ± 13.4	719.5 ± 11.1	712.4 ± 11.8	745.0 ± 32.0	777.3 ± 18.7**
Week 13	741.9 ± 20.7	760.0 ± 13.4	792.0 ± 25.2	792.5 ± 23.7	753.6 ± 16.3
Bile acids (μmol/L)					
Day 3	28.1 ± 4.2	18.0 ± 1.3	17.6 ± 1.3	23.3 ± 2.3	20.9 ± 1.6
Day 21	28.4 ± 2.9	15.6 ± 1.1*	18.6 ± 2.3	22.0 ± 2.5	26.8 ± 3.6
Week 13	19.4 ± 5.6	16.3 ± 2.7	17.3 ± 3.7	13.7 ± 0.8	17.6 ± 1.7
Female					
n					
Day 3	10	10	10	10	10
Day 21	10	10	10	10	10
Week 13	10	10	9	10	8
Hematology					
Automated hematocrit (%)					
Day 3	42.9 ± 0.4	41.7 ± 0.5	41.9 ± 0.5	40.9 ± 0.5*	42.7 ± 0.4
Day 21	45.0 ± 0.4	45.2 ± 0.6	46.1 ± 0.3	45.0 ± 0.3	45.7 ± 0.4
Week 13	45.2 ± 0.4	46.8 ± 0.3*	46.2 ± 0.4	46.4 ± 0.3	44.8 ± 0.3
Manual hematocrit (%)					
Day 3	43.9 ± 0.4	42.5 ± 0.4	43.0 ± 0.4	42.9 ± 0.4	43.9 ± 0.5
Day 21	48.6 ± 0.4	48.1 ± 0.9	49.4 ± 0.5	48.1 ± 0.6	49.7 ± 0.4
Week 13	46.1 ± 0.3	47.2 ± 0.4	46.7 ± 0.3	47.0 ± 0.4	45.8 ± 0.4
Hemoglobin (g/dL)					
Day 3	14.7 ± 0.1	14.2 ± 0.1	14.3 ± 0.2	14.1 ± 0.2*	14.7 ± 0.1
Day 21	15.7 ± 0.1	15.7 ± 0.2	16.0 ± 0.1	15.7 ± 0.1	16.0 ± 0.1
Week 13	15.3 ± 0.1	15.7 ± 0.1*	15.5 ± 0.1	15.5 ± 0.1	15.1 ± 0.1

TABLE C2
Hematology and Clinical Chemistry Data for Rats in the 13-Week Gavage Study
of Benzyltrimethylammonium Chloride

	Vehicle Control	12.5 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg
Female (continued)					
^a					
Day 3	10	10	10	10	10
Day 21	10	10	10	10	10
Week 13	10	10	9	10	8
Hematology (continued)					
Erythrocytes ($10^6/\mu\text{L}$)					
Day 3	6.97 ± 0.08	6.74 ± 0.06	6.78 ± 0.10	6.61 ± 0.10*	6.91 ± 0.07
Day 21	7.15 ± 0.07	7.19 ± 0.12	7.31 ± 0.05	7.10 ± 0.07	7.31 ± 0.06
Week 13	7.88 ± 0.07	8.11 ± 0.05	7.97 ± 0.07	8.00 ± 0.06	7.70 ± 0.05
Reticulocytes ($10^6/\mu\text{L}$)					
Day 3	0.28 ± 0.02	0.27 ± 0.02	0.25 ± 0.01	0.28 ± 0.01	0.30 ± 0.02
Day 21	0.14 ± 0.01	0.12 ± 0.01	0.14 ± 0.02	0.15 ± 0.01	0.14 ± 0.01
Week 13	0.18 ± 0.01	0.18 ± 0.01	0.18 ± 0.01	0.18 ± 0.01	0.19 ± 0.01
Nucleated erythrocytes ($10^3/\mu\text{L}$)					
Day 3	0.13 ± 0.04	0.05 ± 0.03	0.08 ± 0.04	0.12 ± 0.04	0.06 ± 0.02
Day 21	0.06 ± 0.02	0.00 ± 0.00*	0.01 ± 0.01	0.04 ± 0.02	0.01 ± 0.01
Week 13	0.04 ± 0.02	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01
Mean cell volume (fL)					
Day 3	61.6 ± 0.1	61.8 ± 0.2	61.8 ± 0.3	61.9 ± 0.3	61.8 ± 0.3
Day 21	63.0 ± 0.2	62.9 ± 0.3	63.0 ± 0.3	63.4 ± 0.3	62.6 ± 0.3
Week 13	57.4 ± 0.1	57.7 ± 0.1	57.9 ± 0.1**	57.9 ± 0.1**	58.2 ± 0.2**
Mean cell hemoglobin (pg)					
Day 3	21.1 ± 0.1	21.1 ± 0.1	21.1 ± 0.1	21.4 ± 0.2	21.3 ± 0.1
Day 21	21.9 ± 0.1	21.9 ± 0.2	21.9 ± 0.1	22.1 ± 0.2	21.9 ± 0.1
Week 13	19.4 ± 0.1	19.4 ± 0.1	19.4 ± 0.1	19.4 ± 0.1	19.6 ± 0.1
Mean cell hemoglobin concentration (g/dL)					
Day 3	34.2 ± 0.1	34.2 ± 0.3	34.1 ± 0.2	34.5 ± 0.2	34.4 ± 0.2
Day 21	34.9 ± 0.1	34.8 ± 0.2	34.8 ± 0.1	34.9 ± 0.3	35.1 ± 0.2
Week 13	33.9 ± 0.1	33.7 ± 0.2	33.5 ± 0.2	33.4 ± 0.2	33.6 ± 0.2
Platelets ($10^3/\mu\text{L}$)					
Day 3	1,010.4 ± 33.0	1,056.0 ± 14.6	1,045.4 ± 20.1	1,016.0 ± 20.9	980.5 ± 24.8
Day 21	693.6 ± 15.7	696.2 ± 17.9	709.2 ± 16.2	723.9 ± 20.5	665.5 ± 12.8
Week 13	649.3 ± 13.8	653.2 ± 11.5	648.7 ± 20.6	708.8 ± 35.8	641.0 ± 16.4
Leukocytes ($10^3/\mu\text{L}$)					
Day 3	9.52 ± 0.28	9.39 ± 0.28	9.18 ± 0.26	9.24 ± 0.41	9.77 ± 0.33
Day 21	10.73 ± 0.48	10.20 ± 0.71	10.72 ± 0.58	9.71 ± 0.48	10.51 ± 0.36
Week 13	10.38 ± 0.32	9.85 ± 0.60	9.84 ± 0.42	10.71 ± 0.52	10.51 ± 0.63
Segmented neutrophils ($10^3/\mu\text{L}$)					
Day 3	1.08 ± 0.04	1.21 ± 0.11	1.23 ± 0.12	1.21 ± 0.08	1.10 ± 0.15
Day 21	1.06 ± 0.09	1.19 ± 0.15	1.02 ± 0.07	0.98 ± 0.11	1.06 ± 0.09
Week 13	1.30 ± 0.17	0.85 ± 0.11	1.72 ± 0.23	1.13 ± 0.18	1.05 ± 0.20
Lymphocytes ($10^3/\mu\text{L}$)					
Day 3	8.11 ± 0.29	7.71 ± 0.24	7.51 ± 0.29	7.53 ± 0.41	8.26 ± 0.23
Day 21	9.42 ± 0.45	8.79 ± 0.58	9.46 ± 0.61	8.57 ± 0.48	9.33 ± 0.41
Week 13	8.53 ± 0.34	8.45 ± 0.50	7.48 ± 0.41	8.84 ± 0.38	8.93 ± 0.61
Atypical lymphocytes ($10^3/\mu\text{L}$)					
Day 3	0.01 ± 0.01	0.03 ± 0.02	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00
Week 13	0.02 ± 0.02	0.24 ± 0.20	0.08 ± 0.04	0.13 ± 0.05	0.11 ± 0.04

TABLE C2
Hematology and Clinical Chemistry Data for Rats in the 13-Week Gavage Study
of Benzyltrimethylammonium Chloride

	Vehicle Control	12.5 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg
Female (continued)					
n					
Day 3	10	10	10	10	10
Day 21	10	10	10	10	10
Week 13	10	10	9	10	8
Hematology (continued)					
Monocytes ($10^3/\mu\text{L}$)					
Day 3	0.29 ± 0.09	0.42 ± 0.09	0.36 ± 0.09	0.38 ± 0.10	0.35 ± 0.09
Day 21	0.09 ± 0.05	0.09 ± 0.05	0.11 ± 0.05	0.12 ± 0.06	0.05 ± 0.03
Week 13	0.35 ± 0.07	0.37 ± 0.08	0.40 ± 0.07	0.49 ± 0.05	0.39 ± 0.11
Eosinophils ($10^3/\mu\text{L}$)					
Day 3	0.02 ± 0.01	0.01 ± 0.01	0.05 ± 0.02	0.03 ± 0.01	0.04 ± 0.02
Day 21	0.07 ± 0.02	0.06 ± 0.03	0.06 ± 0.02	0.01 ± 0.01*	0.00 ± 0.00**
Week 13	0.17 ± 0.02	0.15 ± 0.05	0.14 ± 0.04	0.10 ± 0.02	0.01 ± 0.01**
Clinical Chemistry					
Urea nitrogen (mg/dL)					
Day 3	21.7 ± 0.6	20.8 ± 0.7	19.6 ± 0.5	21.5 ± 0.5	22.6 ± 0.9
Day 21	22.8 ± 0.7	22.7 ± 0.6	21.7 ± 0.7	24.8 ± 1.4	23.4 ± 0.7
Week 13	21.2 ± 0.6	24.2 ± 0.8*	21.4 ± 0.8	21.8 ± 1.3	22.8 ± 0.7
Creatinine (mg/dL)					
Day 3	0.57 ± 0.02	0.57 ± 0.02	0.57 ± 0.02	0.58 ± 0.01	0.58 ± 0.01
Day 21	0.60 ± 0.00	0.65 ± 0.02	0.65 ± 0.02	0.64 ± 0.02	0.62 ± 0.01
Week 13	0.69 ± 0.02	0.69 ± 0.01	0.68 ± 0.02	0.69 ± 0.02	0.65 ± 0.03
Total protein (g/dL)					
Day 3	5.9 ± 0.1	5.8 ± 0.1	5.6 ± 0.1*	5.6 ± 0.0*	5.7 ± 0.1
Day 21	5.8 ± 0.0	5.8 ± 0.0	5.8 ± 0.1	5.8 ± 0.1	5.7 ± 0.1
Week 13	6.8 ± 0.1	6.7 ± 0.1	6.5 ± 0.1*	6.4 ± 0.1**	6.4 ± 0.1**
Albumin (g/dL)					
Day 3	4.5 ± 0.0	4.4 ± 0.1	4.3 ± 0.1	4.3 ± 0.1*	4.3 ± 0.0**
Day 21	4.5 ± 0.0	4.4 ± 0.0	4.5 ± 0.1	4.4 ± 0.0	4.4 ± 0.1
Week 13	5.0 ± 0.1	5.0 ± 0.0	4.9 ± 0.1	4.7 ± 0.1**	4.6 ± 0.1**
Alanine aminotransferase (IU/L)					
Day 3	37 ± 1	36 ± 1	36 ± 1	36 ± 2	36 ± 1
Day 21	36 ± 1	34 ± 1	34 ± 1	39 ± 1	39 ± 1
Week 13	42 ± 3	51 ± 4	41 ± 2	43 ± 2	48 ± 3
Alkaline phosphatase (IU/L)					
Day 3	541 ± 13	540 ± 13	537 ± 9	544 ± 13	544 ± 15
Day 21	398 ± 9	382 ± 8	400 ± 8	405 ± 13	383 ± 12
Week 13	212 ± 7	237 ± 5	235 ± 9	208 ± 6	233 ± 8
Creatine kinase (IU/L)					
Day 3	517 ± 44	574 ± 60	488 ± 44	484 ± 41	474 ± 33
Day 21	493 ± 60	505 ± 48	502 ± 29	387 ± 42	405 ± 46
Week 13	366 ± 29	311 ± 33	395 ± 25	309 ± 47	392 ± 44
Sorbitol dehydrogenase (IU/L)					
Day 3	13 ± 1	14 ± 2	13 ± 1	14 ± 1	14 ± 1
Day 21	18 ± 1	18 ± 2	19 ± 1	21 ± 1	18 ± 1
Week 13	17 ± 1	20 ± 1	15 ± 1	16 ± 2	13 ± 1

TABLE C2
Hematology and Clinical Chemistry Data for Rats in the 13-Week Gavage Study
of Benzyltrimethylammonium Chloride

	Vehicle Control	12.5 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg
Female (continued)					
n					
Day 3	10	10	10	10	10
Day 21	10	10	10	10	10
Week 13	10	10	9	10	8
Clinical Chemistry (continued)					
Serum cholinesterase (IU/L)					
Day 3	1,748.3 ± 49.9	1,774.0 ± 72.4	1,701.2 ± 94.9	1,764.3 ± 95.6	1,895.4 ± 76.1
Day 21	2,525.4 ± 68.3	2,872.1 ± 127.7	2,865.9 ± 143.1	2,819.0 ± 167.2	2,781.5 ± 181.6
Week 13	4,297.5 ± 144.8	4,412.9 ± 154.0	4,034.1 ± 206.4	3,284.1 ± 134.2**	2,797.9 ± 246.9**
Bile acids (μmol/L)					
Day 3	24.1 ± 2.3	20.8 ± 2.8	17.1 ± 1.5	21.8 ± 3.2	18.1 ± 2.6
Day 21	25.9 ± 1.5	20.9 ± 1.6	18.1 ± 2.6*	28.9 ± 4.7	20.4 ± 3.4
Week 13	14.9 ± 0.9	21.8 ± 4.0	20.1 ± 2.8	35.0 ± 8.6**	27.8 ± 3.9*

* Significantly different ($P < 0.05$) from the vehicle control group by Dunn's or Shirley's test

** $P < 0.01$

^a Mean ± standard error. Statistical tests were performed on unrounded data.

^b n=9

TABLE C3
Hematology and Clinical Chemistry Data for Mice in the 16-Day Gavage Study
of Benzyltrimethylammonium Chloride^a

	Vehicle Control	63 mg/kg	125 mg/kg
Male			
n	5	5	5
Hematology			
Automated hematocrit (%)	45.0 ± 0.3	45.5 ± 0.5	45.5 ± 0.7
Manual hematocrit (%)	50.2 ± 0.4	51.4 ± 0.4	50.4 ± 0.5
Hemoglobin (g/dL)	15.8 ± 0.2	15.7 ± 0.2	15.9 ± 0.2
Erythrocytes (10 ⁶ /μL)	9.00 ± 0.08	9.09 ± 0.11	9.10 ± 0.12
Reticulocytes (10 ⁶ /μL)	0.19 ± 0.03	0.15 ± 0.02	0.18 ± 0.02
Nucleated erythrocytes/100 leukocytes	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	50.0 ± 0.2	50.0 ± 0.2	50.0 ± 0.1
Mean cell hemoglobin (pg)	17.5 ± 0.0	17.3 ± 0.1	17.5 ± 0.1
Mean cell hemoglobin concentration (g/dL)	35.0 ± 0.1	34.6 ± 0.4	34.9 ± 0.3
Platelets (10 ³ /μL)	760.0 ± 24.3	718.6 ± 36.0	763.2 ± 38.4
Leukocytes (10 ³ /μL)	4.84 ± 0.39	4.98 ± 0.56	4.98 ± 0.54
Segmented neutrophils (10 ³ /μL)	0.53 ± 0.13	0.42 ± 0.06	0.59 ± 0.09
Lymphocytes (10 ³ /μL)	4.20 ± 0.27	4.44 ± 0.53	4.26 ± 0.44
Monocytes (10 ³ /μL)	0.08 ± 0.04	0.09 ± 0.02	0.05 ± 0.02
Eosinophils (10 ³ /μL)	0.03 ± 0.02	0.04 ± 0.02	0.08 ± 0.03
Clinical Chemistry			
Serum cholinesterase (IU/L)	5,620.2 ± 192.7	5,900.0 ± 160.0	5,941.8 ± 199.0
Erythrocyte cholinesterase (IU/L)	2,016.0 ± 185.2	1,891.4 ± 247.4	1,812.5 ± 82.1 ^b

TABLE C3
Hematology and Clinical Chemistry Data for Mice in the 16-Day Gavage Study
of Benzyltrimethylammonium Chloride

	Vehicle Control	63 mg/kg	125 mg/kg
Female			
n	5	5	4
Hematology			
Automated hematocrit (%)	44.1 ± 0.5	43.4 ± 0.5	43.9 ± 0.5
Manual hematocrit (%)	50.0 ± 0.4	49.4 ± 0.6	50.0 ± 0.9
Hemoglobin (g/dL)	15.6 ± 0.3	15.5 ± 0.2	15.4 ± 0.2
Erythrocytes (10 ⁶ /μL)	8.92 ± 0.09	8.75 ± 0.09	8.81 ± 0.14
Reticulocytes (10 ⁶ /μL)	0.22 ± 0.04	0.20 ± 0.06	0.16 ± 0.03
Nucleated erythrocytes/100 leukocytes	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00 ^c
Mean cell volume (fL)	49.4 ± 0.1	49.6 ± 0.2	49.9 ± 0.3
Mean cell hemoglobin (pg)	17.5 ± 0.1	17.7 ± 0.1	17.5 ± 0.1
Mean cell hemoglobin concentration (g/dL)	35.3 ± 0.3	35.6 ± 0.2	35.0 ± 0.1
Platelets (10 ³ /μL)	708.2 ± 21.8	738.6 ± 12.6	722.3 ± 22.9
Leukocytes (10 ³ /μL)	4.58 ± 0.48	5.26 ± 0.38	5.93 ± 0.49
Segmented neutrophils (10 ³ /μL)	0.64 ± 0.16	0.58 ± 0.09	0.51 ± 0.12
Lymphocytes (10 ³ /μL)	3.86 ± 0.46	4.50 ± 0.34	5.36 ± 0.37
Monocytes (10 ³ /μL)	0.05 ± 0.02	0.10 ± 0.06	0.07 ± 0.03
Eosinophils (10 ³ /μL)	0.03 ± 0.02	0.07 ± 0.02	0.00 ± 0.00
Clinical Chemistry			
Serum cholinesterase (IU/L)	8,155.8 ± 24.2	8,328.6 ± 186.0	8,038.5 ± 247.4
Erythrocyte cholinesterase (IU/L)	2,044.8 ± 443.0	2,888.2 ± 300.2	2,384.8 ± 560.3

^a Mean ± standard error. Statistical tests were performed on unrounded data. No data are available for the 250, 500, and 1,000 mg/kg groups due to 100% mortality.

^b n=4

^c n=5

TABLE C4
Clinical Chemistry Data for Mice in the 13-Week Gavage Study of Benzyltrimethylammonium Chloride^a

	Vehicle Control	12.5 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg
Male					
n	8	10	10	10	9
Urea nitrogen (mg/dL)	27.0 ± 0.6 ^b	31.6 ± 1.6	30.3 ± 1.8	30.8 ± 1.1	30.1 ± 1.7 ^c
Creatinine (mg/dL)	0.43 ± 0.02	0.48 ± 0.02	0.46 ± 0.02	0.47 ± 0.02	0.44 ± 0.02 ^c
Total protein (g/dL)	6.1 ± 0.1 ^d	6.0 ± 0.1 ^b	5.8 ± 0.1 ^{**}	5.7 ± 0.1 ^{**b}	5.7 ± 0.1 ^{**c}
Albumin (g/dL)	4.3 ± 0.1	4.3 ± 0.1	4.1 ± 0.1	4.2 ± 0.1	4.1 ± 0.1 ^c
Alanine aminotransferase (IU/L)	40 ± 8	53 ± 20	84 ± 31	71 ± 22	37 ± 8
Alkaline phosphatase ((IU/L)	91 ± 2 ^b	86 ± 4	86 ± 2	86 ± 3	84 ± 3
Creatine kinase (IU/L)	276 ± 87 ^b	255 ± 57	461 ± 113 ^b	485 ± 135	310 ± 77
Sorbitol dehydrogenase (IU/L)	47 ± 2	46 ± 1	45 ± 2	45 ± 4	45 ± 1 ^c
Serum cholinesterase (IU/L)	8,963 ± 210	8,923 ± 376	8,404 ± 107	8,380 ± 353 ^b	8,893 ± 369 ^c
Bile acids (μmol/L)	14.0 ± 1.1	13.8 ± 0.6 ^b	14.9 ± 0.8	15.2 ± 0.8 ^b	13.3 ± 0.6 ^c
Female					
n	10	10	10	10	9
Urea nitrogen (mg/dL)	26.0 ± 2.0	26.9 ± 1.2	28.9 ± 1.3	25.0 ± 1.8	26.3 ± 1.3
Creatinine (mg/dL)	0.59 ± 0.02	0.58 ± 0.02	0.60 ± 0.02	0.54 ± 0.02	0.58 ± 0.02
Total protein (g/dL)	6.0 ± 0.1	5.9 ± 0.1	5.9 ± 0.1	5.8 ± 0.1	5.8 ± 0.1
Albumin (g/dL)	4.6 ± 0.1	4.6 ± 0.1	4.5 ± 0.1	4.4 ± 0.0	4.4 ± 0.1
Alanine aminotransferase (IU/L)	34 ± 6	40 ± 9	29 ± 2	26 ± 1	36 ± 9
Alkaline phosphatase ((IU/L)	139 ± 3	126 ± 6	124 ± 4	128 ± 6	125 ± 6
Creatine kinase (IU/L)	297 ± 69	615 ± 212	428 ± 55	474 ± 91	318 ± 76
Sorbitol dehydrogenase (IU/L)	47 ± 1	48 ± 3	48 ± 1	48 ± 1	46 ± 1
Serum cholinesterase (IU/L)	10,020 ± 235	10,147 ± 114	9,964 ± 179	10,080 ± 230	9,726 ± 146
Bile acids (μmol/L)	15.1 ± 0.6	15.5 ± 0.8	15.5 ± 0.5	15.2 ± 0.5	15.6 ± 0.2

* Significantly different ($P \leq 0.05$) from the vehicle control group by Dunn's test

** Significantly different ($P \leq 0.01$) from the vehicle control group by Shirley's test

^a Mean ± standard error. Statistical tests were performed on unrounded data.

^b n=9

^c n=8

^d n=5

^e n=7

APPENDIX D ORGAN WEIGHTS AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE D1	Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 16-Day Gavage Study of Benzyltrimethylammonium Chloride	D-2
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TABLE D1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 16-Day Gavage Study of Benzyltrimethylammonium Chloride^a

	Vehicle Control	16 mg/kg	32 mg/kg	63 mg/kg
n	5	5	5	5
Male				
Necropsy body wt	240 ± 4	231 ± 5	233 ± 12	226 ± 8
Heart				
Absolute	0.833 ± 0.013	0.810 ± 0.016	0.828 ± 0.046	0.829 ± 0.038
Relative	3.46 ± 0.05	3.51 ± 0.06	3.55 ± 0.04	3.67 ± 0.11
R. Kidney				
Absolute	1.078 ± 0.024	1.061 ± 0.029	1.058 ± 0.081	1.011 ± 0.020
Relative	4.49 ± 0.10	4.59 ± 0.09	4.51 ± 0.14	4.48 ± 0.08
Liver				
Absolute	12.166 ± 0.302	11.288 ± 0.400	11.509 ± 0.970	10.997 ± 0.626
Relative	50.58 ± 0.70	48.82 ± 0.78	48.98 ± 1.68	48.47 ± 1.20
Lung				
Absolute	1.383 ± 0.058	1.355 ± 0.087	1.491 ± 0.104	1.314 ± 0.053
Relative	5.75 ± 0.20	5.85 ± 0.27	6.39 ± 0.30	5.82 ± 0.21
Spleen				
Absolute	0.626 ± 0.017	0.585 ± 0.020	0.605 ± 0.029	0.579 ± 0.024
Relative	2.60 ± 0.05	2.53 ± 0.05	2.60 ± 0.04	2.56 ± 0.04
R. Testis				
Absolute	1.266 ± 0.013	1.247 ± 0.026	1.231 ± 0.055	1.231 ± 0.019
Relative	5.27 ± 0.09	5.41 ± 0.14	5.28 ± 0.06	5.46 ± 0.11
Thymus				
Absolute	0.521 ± 0.010	0.501 ± 0.010	0.523 ± 0.029	0.502 ± 0.035
Relative	2.17 ± 0.06	2.17 ± 0.05	2.26 ± 0.13	2.21 ± 0.09
Female				
Necropsy body wt	137 ± 5	144 ± 5	142 ± 4	137 ± 4
Heart				
Absolute	0.548 ± 0.020	0.577 ± 0.024	0.596 ± 0.009	0.560 ± 0.021
Relative	4.01 ± 0.05	4.02 ± 0.05	4.21 ± 0.08	4.10 ± 0.12
R. Kidney				
Absolute	0.636 ± 0.031	0.655 ± 0.023	0.663 ± 0.020	0.619 ± 0.025
Relative	4.65 ± 0.12	4.57 ± 0.05	4.67 ± 0.11	4.53 ± 0.11
Liver				
Absolute	5.966 ± 0.333	6.233 ± 0.278	6.147 ± 0.219	5.771 ± 0.324
Relative	43.58 ± 1.29	43.37 ± 0.80	43.30 ± 1.00	42.09 ± 1.13
Lung				
Absolute	0.897 ± 0.041	0.985 ± 0.043	0.944 ± 0.034	0.884 ± 0.063
Relative	6.56 ± 0.13	6.88 ± 0.29	6.65 ± 0.18	6.44 ± 0.27
Spleen				
Absolute	0.401 ± 0.013	0.416 ± 0.017	0.426 ± 0.016	0.366 ± 0.021
Relative	2.93 ± 0.02	2.90 ± 0.08	3.00 ± 0.11	2.67 ± 0.07
Thymus				
Absolute	0.357 ± 0.022	0.367 ± 0.012	0.366 ± 0.008	0.353 ± 0.023
Relative	2.61 ± 0.13	2.56 ± 0.08	2.58 ± 0.09	2.58 ± 0.11

^a Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error). Differences from the vehicle control group were not significant by Dunnett's test. No data are available for the 125 and 250 mg/kg groups due to 100% mortality.

TABLE D2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Gavage Study
of Benzyltrimethylammonium Chloride^a

	Vehicle Control	12.5 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg
Male					
n	10	10	10	10	10
Necropsy body wt	338 ± 8	337 ± 8	336 ± 8	340 ± 5	311 ± 9
Heart					
Absolute	1.018 ± 0.030	1.010 ± 0.024	1.000 ± 0.024	1.016 ± 0.025	0.953 ± 0.028
Relative	3.02 ± 0.05	3.00 ± 0.04	2.98 ± 0.05	2.99 ± 0.06	3.07 ± 0.03
R. Kidney					
Absolute	1.266 ± 0.049	1.274 ± 0.044	1.307 ± 0.092	1.238 ± 0.036	1.208 ± 0.041
Relative	3.74 ± 0.07	3.78 ± 0.07	3.89 ± 0.24	3.64 ± 0.08	3.89 ± 0.05
Liver					
Absolute	12.136 ± 0.423	12.671 ± 0.412	11.893 ± 0.277	12.146 ± 0.262	11.409 ± 0.459
Relative	35.88 ± 0.50	37.58 ± 0.69	35.46 ± 0.34	35.78 ± 0.60	36.66 ± 0.73
Lung					
Absolute	1.540 ± 0.040	1.473 ± 0.045	1.503 ± 0.045	1.515 ± 0.042	1.388 ± 0.054
Relative	4.57 ± 0.08	4.37 ± 0.07	4.48 ± 0.09	4.46 ± 0.09	4.47 ± 0.10
R. Testis					
Absolute	1.459 ± 0.043	1.380 ± 0.036	1.385 ± 0.063	1.443 ± 0.029	1.423 ± 0.043
Relative	4.32 ± 0.07	4.11 ± 0.12	4.15 ± 0.21	4.25 ± 0.05	4.58 ± 0.02
Thymus					
Absolute	0.328 ± 0.016	0.343 ± 0.023	0.341 ± 0.022	0.360 ± 0.017	0.295 ± 0.012
Relative	0.97 ± 0.04	1.01 ± 0.05	1.02 ± 0.06	1.06 ± 0.05	0.96 ± 0.04
Female					
n	10	10	9	9	8
Necropsy body wt	190 ± 3	198 ± 4	193 ± 3	193 ± 4	187 ± 4
Heart					
Absolute	0.704 ± 0.011	0.679 ± 0.012	0.674 ± 0.016	0.693 ± 0.013	0.670 ± 0.014
Relative	3.71 ± 0.04	3.43 ± 0.05**	3.49 ± 0.05*	3.60 ± 0.07	3.59 ± 0.06
R. Kidney					
Absolute	0.716 ± 0.015	0.730 ± 0.020	0.710 ± 0.012	0.750 ± 0.014	0.730 ± 0.025
Relative	3.77 ± 0.07	3.68 ± 0.06	3.68 ± 0.05	3.90 ± 0.06	3.91 ± 0.10
Liver					
Absolute	6.435 ± 0.144	6.532 ± 0.221	6.449 ± 0.129	6.715 ± 0.204	6.731 ± 0.221
Relative	33.82 ± 0.32	32.92 ± 0.81	33.47 ± 0.54	34.79 ± 0.54	36.00 ± 0.68*
Lung					
Absolute	1.156 ± 0.048	1.184 ± 0.033	1.147 ± 0.037	1.195 ± 0.050	1.121 ± 0.045
Relative	6.06 ± 0.17	5.97 ± 0.13	5.97 ± 0.24	6.20 ± 0.24	6.00 ± 0.17
Thymus					
Absolute	0.263 ± 0.010	0.276 ± 0.014	0.263 ± 0.010	0.251 ± 0.013	0.257 ± 0.012
Relative	1.38 ± 0.04	1.39 ± 0.06	1.36 ± 0.04	1.30 ± 0.05	1.37 ± 0.06

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' or Dunnett's test

** Significantly different ($P \leq 0.01$) from the vehicle control group by Dunnett's test

^a Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE D3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 16-Day Gavage Study
of Benzyltrimethylammonium Chloride^a

	Vehicle Control	63 mg/kg	125 mg/kg
Male			
n	5	5	5
Necropsy body wt	26.4 ± 0.7	26.0 ± 0.5	26.1 ± 0.6
Heart			
Absolute	0.132 ± 0.005	0.130 ± 0.003	0.131 ± 0.003
Relative	5.00 ± 0.11	5.00 ± 0.06	5.01 ± 0.05
R. Kidney			
Absolute	0.249 ± 0.012	0.246 ± 0.007	0.255 ± 0.008
Relative	9.41 ± 0.22	9.43 ± 0.13	9.76 ± 0.11
Liver			
Absolute	1.456 ± 0.049	1.416 ± 0.044	1.437 ± 0.042
Relative	55.03 ± 0.66	54.35 ± 1.03	54.94 ± 0.64
Lung			
Absolute	0.180 ± 0.007	0.184 ± 0.007	0.194 ± 0.006
Relative	6.80 ± 0.20	7.08 ± 0.35	7.42 ± 0.18
Spleen			
Absolute	0.069 ± 0.003	0.067 ± 0.003	0.067 ± 0.003
Relative	2.61 ± 0.06	2.57 ± 0.08	2.57 ± 0.07
R. Testis			
Absolute	0.106 ± 0.002	0.103 ± 0.001	0.103 ± 0.004
Relative	4.03 ± 0.16	3.96 ± 0.07	3.94 ± 0.14
Thymus			
Absolute	0.054 ± 0.003	0.049 ± 0.004	0.051 ± 0.005
Relative	2.04 ± 0.13	1.87 ± 0.16	1.96 ± 0.20
Female			
n	5	5	4
Necropsy body wt	21.2 ± 0.4	21.9 ± 0.5	22.4 ± 0.1
Heart			
Absolute	0.120 ± 0.003	0.118 ± 0.005	0.118 ± 0.002
Relative	5.66 ± 0.11	5.40 ± 0.14	5.28 ± 0.09
R. Kidney			
Absolute	0.169 ± 0.007	0.173 ± 0.002	0.173 ± 0.007
Relative	7.96 ± 0.22	7.90 ± 0.12	7.75 ± 0.32
Liver			
Absolute	1.073 ± 0.043	1.136 ± 0.025	1.209 ± 0.017*
Relative	50.51 ± 1.35	51.88 ± 0.69	54.12 ± 1.04
Lung			
Absolute	0.171 ± 0.007	0.162 ± 0.008	0.150 ± 0.009
Relative	8.07 ± 0.23	7.38 ± 0.25	6.72 ± 0.36*
Spleen			
Absolute	0.078 ± 0.003	0.078 ± 0.004	0.076 ± 0.004
Relative	3.67 ± 0.12	3.56 ± 0.09	3.40 ± 0.20
Thymus			
Absolute	0.062 ± 0.003	0.064 ± 0.005	0.064 ± 0.007
Relative	2.94 ± 0.14	2.91 ± 0.21	2.84 ± 0.29

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' or Dunnett's test

^a Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error). No data are available for the 250, 500, and 1,000 mg/kg groups due to 100% mortality.

TABLE D4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Gavage Study of Benzyltrimethylammonium Chloride^a

	Vehicle Control	12.5 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg
Male					
n	10	10	10	8	9
Necropsy body wt	34.9 ± 0.7	34.9 ± 1.0	34.5 ± 0.6	34.8 ± 0.9	33.9 ± 0.9
Heart					
Absolute	0.142 ± 0.003	0.146 ± 0.003	0.146 ± 0.002	0.151 ± 0.003	0.145 ± 0.003
Relative	4.06 ± 0.06	4.19 ± 0.06	4.25 ± 0.05*	4.30 ± 0.10*	4.29 ± 0.06*
R. Kidney					
Absolute	0.284 ± 0.006	0.290 ± 0.008	0.285 ± 0.006	0.311 ± 0.008*	0.297 ± 0.009
Relative	8.13 ± 0.13	8.32 ± 0.17	8.28 ± 0.16	8.82 ± 0.15**	8.77 ± 0.16**
Liver					
Absolute	1.519 ± 0.042	1.553 ± 0.049	1.534 ± 0.049	1.599 ± 0.041	1.537 ± 0.036
Relative	43.44 ± 0.61	44.48 ± 0.57	44.47 ± 0.90	45.33 ± 0.50	45.39 ± 1.00
Lung					
Absolute	0.196 ± 0.011	0.199 ± 0.008	0.198 ± 0.014	0.188 ± 0.015	0.184 ± 0.006
Relative	5.63 ± 0.32	5.71 ± 0.17	5.78 ± 0.46	5.31 ± 0.34	5.43 ± 0.18
R. Testis					
Absolute	0.119 ± 0.005	0.113 ± 0.007	0.119 ± 0.003	0.120 ± 0.005	0.120 ± 0.004
Relative	3.39 ± 0.11	3.24 ± 0.21	3.46 ± 0.07	3.39 ± 0.12	3.54 ± 0.05
Thymus					
Absolute	0.063 ± 0.009	0.045 ± 0.006	0.044 ± 0.004	0.042 ± 0.005	0.044 ± 0.005
Relative	1.80 ± 0.25	1.31 ± 0.19	1.26 ± 0.11	1.19 ± 0.14	1.31 ± 0.14
Female					
n	10	10	10	10	9
Necropsy body wt	29.1 ± 1.0	29.9 ± 0.9	28.7 ± 0.9	29.2 ± 1.3	28.2 ± 0.9
Heart					
Absolute	0.125 ± 0.002	0.128 ± 0.003	0.122 ± 0.003	0.126 ± 0.003	0.124 ± 0.003
Relative	4.31 ± 0.12	4.31 ± 0.09	4.28 ± 0.11	4.37 ± 0.12	4.40 ± 0.08
R. Kidney					
Absolute	0.193 ± 0.003	0.190 ± 0.004	0.184 ± 0.004	0.192 ± 0.006	0.184 ± 0.006
Relative	6.70 ± 0.22	6.40 ± 0.18	6.44 ± 0.14	6.64 ± 0.17	6.52 ± 0.06
Liver					
Absolute	1.168 ± 0.022	1.223 ± 0.046	1.246 ± 0.034	1.249 ± 0.055	1.208 ± 0.039
Relative	40.47 ± 1.35	40.95 ± 0.81	43.57 ± 0.50	42.95 ± 1.21	42.81 ± 0.64
Lung					
Absolute	0.187 ± 0.004	0.196 ± 0.009	0.172 ± 0.005	0.176 ± 0.006	0.176 ± 0.006
Relative	6.48 ± 0.24	6.58 ± 0.27	6.02 ± 0.12	6.08 ± 0.16	6.25 ± 0.14
Thymus					
Absolute	0.051 ± 0.003	0.054 ± 0.003	0.048 ± 0.002	0.056 ± 0.005	0.050 ± 0.004
Relative	1.77 ± 0.09	1.79 ± 0.09	1.69 ± 0.10	1.90 ± 0.12	1.78 ± 0.16

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' or Dunnett's test

** Significantly different ($P \leq 0.01$) from the vehicle control group by Williams' test

^a Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).