TABLE C2
Individual Animal Tumor Pathology of Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 312 ppm for 52 Weeks (continued)

Number of Days on Study	2 1 7	2 8 9	3 1 4	3 2 6	3 2 8	3 4 4	3 6 4	3 6 4	3 6 9	3 8 2	3 9 2	4 0 1	4 2 2	4 2 5	4 2 8	4 3 8	4 4 1	4 4 3	4 4 3	4 4 6	4 4 9	4 7 6	4 7 9	4 9 0	4 9 4
Carcass ID Number	2 0 9 3	2 0 7 4	2 1 1 5	2 1 1 4	2 0 9 1	2 1 4 4	2 0 8 2	2 0 8 3	2 1 5 2	2 1 0 2	2 1 2 2	2 1 5 4	2 1 2 4	2 0 7 5	2 1 2 5	2 1 0 4	2 1 1 1	2 0 1 5	2 1 8 5	2 1 6 5	2 1 4 3	2 1 3 2	2 1 4 5	2 0 9 5	2 1 6 3	2 1 0 1
Respiratory System (continued)																									
Lung (continued)																									
Hemangiosarcoma, metastatic, heart					X	X			X		X			X	X	X			X	X			X		X
Hemangiosarcoma, metastatic, liver																									
Hepatocellular carcinoma, metastatic, liver										X															
Histiocytic sarcoma			X					X				X													
Squamous cell carcinoma, metastatic, stomach																									
Mediastinum, hemangiosarcoma, metastatic, heart																								X	
Nose	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Special Senses System																									
Ear																									
Eye		+															+								
Adenocarcinoma, metastatic, harderian gland																	X								
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	M	+	+	+	+	+	+	+
Adenocarcinoma																	X								
Adenoma						X								X					X			X		X	X
Bilateral, adenocarcinoma																									
Bilateral, adenoma																							X		
Urinary System																									
Kidney	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, pancreas											X														
Adenoma																									
Hemangiosarcoma, metastatic, heart									X							X									X
Histiocytic sarcoma								X				X													
Renal tubule, adenoma																									
Urinary bladder	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X					X				X													X
Lymphoma malignant	X																								
Lymphoma malignant lymphocytic		X		X																					
Lymphoma malignant mixed																							X		

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 312 ppm for 52 Weeks (continued)

Number of Days on Study	4 9 5	5 0 6	5 1 0	5 1 6	5 3 9	5 3 9	5 4 6	5 4 6	5 5 4	5 5 9	5 6 3	5 7 3	5 9 3	6 0 4	6 0 7	6 1 6	6 2 5	6 3 5	6 3 7	6 3 9	6 4 9	6 6 4	6 6 6	7 2 0	7 2 9	
Carcass ID Number	2 1 3 1	2 0 9 2	2 1 2 3	2 1 4 1	2 0 9 4	2 1 3 5	2 1 3 3	2 1 6 1	2 0 8 4	2 1 3 4	2 1 5 3	2 1 5 5	2 1 5 1	2 1 6 2	2 1 2 1	2 1 1 2	2 1 1 3	2 1 0 5	2 1 0 3	2 0 7 3	2 0 7 1	2 0 7 2	2 1 6 4	2 0 8 1	2 1 4 2	Total Tissues/ Tumors
Respiratory System (continued)																										
Lung (continued)																										
Hemangiosarcoma, metastatic, heart	X	X		X			X				X			X					X							18
Hemangiosarcoma, metastatic, liver																				X						1
Hepatocellular carcinoma, metastatic, liver																										1
Histiocytic sarcoma									X							X										5
Squamous cell carcinoma, metastatic, stomach																		X								1
Mediastinum, hemangiosarcoma, metastatic, heart																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Special Senses System																										
Ear																	+									1
Eye									+							+										4
Adenocarcinoma, metastatic, harderian gland																										1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma																										1
Adenoma	X		X	X	X	X	X	X	X	X		X			X	X	X	X								20
Bilateral, adenocarcinoma																								X		1
Bilateral, adenoma													X						X	X	X	X	X		X	8
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, metastatic, pancreas																										1
Adenoma								X																		1
Hemangiosarcoma, metastatic, heart											X			X					X							6
Histiocytic sarcoma									X							X										4
Renal tubule, adenoma						X															X					2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma									X							X						X				7
Lymphoma malignant																										1
Lymphoma malignant lymphocytic								X																	X	4
Lymphoma malignant mixed																	X							X		3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 625 ppm for 13 Weeks

Number of Days on Study	1 6 9	1 8 5	1 9 4	2 0 8	2 2 4	2 3 1	2 4 7	2 5 1	2 7 0	2 7 1	2 8 4	2 8 5	2 9 6	3 0 3	3 1 2	3 2 7	3 4 2	3 5 2	3 7 0	4 1 0	4 7 1	5 0 6	5 2 0	5 3 9	5 5 3
Carcass ID Number	1 8 5 5	1 7 8 2	1 7 8 5	1 8 6 5	1 8 4 1	1 7 7 1	1 8 2 2	1 8 6 2	1 8 3 1	1 8 4 5	1 8 5 4	1 8 0 3	1 8 4 2	1 8 1 5	1 8 1 2	1 8 2 3	1 7 9 2	1 8 3 2	1 8 6 4	1 8 8 1	1 8 1 4	1 7 9 3	1 8 2 1	1 8 9 5	1 8 5 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	M	+
Gallbladder	A	A	A	A	A	+	+	+	A	+	A	A	A	A	A	+	+	+	A	+	A	+	+	+	+
Intestine large	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+
Intestine large, cecum	+	A	+	A	A	+	+	+	+	+	+	A	A	A	A	+	+	+	A	+	A	+	+	+	+
Intestine large, colon	+	+	+	A	+	+	+	+	+	+	+	+	+	A	A	+	+	+	A	+	+	+	+	+	+
Intestine large, rectum	+	A	+	A	+	M	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+
Intestine small	+	A	A	+	+	+	+	+	A	+	+	+	A	A	A	+	+	+	A	+	+	+	+	+	+
Intestine small, duodenum	M	A	A	A	A	+	+	+	A	+	A	A	A	A	M	+	+	+	A	+	+	+	+	+	M
Intestine small, ileum	+	A	A	+	A	+	+	+	A	+	A	A	A	A	A	+	+	+	A	+	A	+	+	+	+
Intestine small, jejunum	+	A	A	+	+	+	+	+	A	+	+	+	A	A	A	+	+	+	A	+	+	+	+	+	A
Carcinoma																									
Histiocytic sarcoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hemangiosarcoma, metastatic, heart																									
Hepatocellular carcinoma																							X	X	
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma																					X	X		X	
Hepatocellular adenoma, multiple																							X		X
Histiocytic sarcoma																									
Mesentery														+					+						
Fat, hemangioma																									
Fat, hemangiosarcoma																									
Fat, squamous cell carcinoma, metastatic, stomach																			X						
Pancreas	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+
Acinus, histiocytic sarcoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																			X						
Squamous cell papilloma																X	X								
Squamous cell papilloma, multiple																									
Stomach, glandular	+	+	+	+	A	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+
Squamous cell carcinoma, metastatic, stomach																			X						
Tooth																						+			
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Hemangiosarcoma																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 625 ppm for 13 Weeks (continued)

Number of Days on Study	5 5 8	5 6 6	5 6 7	5 6 7	5 8 0	5 9 5	5 9 5	6 1 1	6 1 7	6 2 3	6 3 1	6 3 8	6 3 8	6 5 0	6 6 6	6 7 7	6 9 2	6 9 3	7 0 7	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	1 8 4 4	1 7 8 3	1 7 7 5	1 8 0 2	1 7 7 3	1 8 0 1	1 8 5 3	1 8 6 3	1 8 3 3	1 8 0 5	1 8 2 5	1 8 1 1	1 8 3 4	1 8 0 4	1 8 2 4	1 7 7 4	1 7 9 4	1 8 5 1	1 7 8 4	1 8 6 1	1 7 7 2	1 7 9 1	1 8 1 3	1 8 3 5	1 8 4 3	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Gallbladder	+	A	+	+	+	+	+	+	A	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	32
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	39
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	41
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	35
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	37
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	40
Carcinoma																			X							1
Histiocytic sarcoma																	X									1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma				X							X															2
Hemangiosarcoma, metastatic, heart																		X			X					2
Hepatocellular carcinoma									X							X	X							X	X	7
Hepatocellular carcinoma, multiple							X			X		X		X					X		X	X				7
Hepatocellular adenoma	X	X	X		X			X					X	X		X						X		X	X	14
Hepatocellular adenoma, multiple						X			X												X					5
Histiocytic sarcoma																	X							X		2
Mesentery		+							+	+		+				+			+	+		+		+		11
Fat, hemangioma																						X		X		2
Fat, hemangiosarcoma																			X							1
Fat, squamous cell carcinoma, metastatic, stomach																				X						2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	46
Acinus, histiocytic sarcoma																								X		1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																				X	X	X				4
Squamous cell papilloma																					X					3
Squamous cell papilloma, multiple						X																				1
Stomach, glandular	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	44
Squamous cell carcinoma, metastatic, stomach																										1
Tooth																			+		+			+		4
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung												X														1
Hemangiosarcoma		X				X										X	X	X			X	X				7

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 625 ppm for 13 Weeks (continued)

Number of Days on Study	1 6 9 9	1 8 5 5	1 9 4 8	2 0 8 5	2 2 4 1	2 3 4 1	2 4 7 2	2 5 1 2	2 7 0 2	2 7 1 2	2 8 4 2	2 8 5 2	2 9 6 3	3 0 3 5	3 1 2 2	3 2 7 3	3 4 2 2	3 5 2 2	3 7 0 4	4 1 0 1	4 7 1 4	5 0 6 3	5 2 0 1	5 3 9 5	5 5 3 2
Carcass ID Number	1 8 5 5	1 7 8 2	1 7 8 5	1 8 6 5	1 8 4 1	1 7 7 1	1 8 2 2	1 8 6 2	1 8 3 1	1 8 4 5	1 8 5 4	1 8 0 3	1 8 4 2	1 8 1 5	1 8 1 2	1 8 2 3	1 7 9 2	1 8 3 2	1 8 6 4	1 7 8 1	1 8 1 4	1 7 9 3	1 8 2 1	1 8 9 5	1 8 5 2
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, adenoma																									
Adrenal gland, medulla	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	A	+	M	+	+	+	+	+	+	+	+	+	A	+	+	+	M	+	+	+	+	+	+	+
Parathyroid gland	M	M	M	M	+	M	M	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	+	M
Pituitary gland	+	+	+	+	+	+	I	+	+	I	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
Tissue NOS													+												
Genital System																									
Epididymis	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland																							+		
Adenoma																									
Carcinoma																							X		
Bilateral, carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	A	+	+	+	+	+	M	A	+	+	A	+	+	A	+	+	+	A	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hematopoietic System																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Renal, histiocytic sarcoma																									
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	M	+	A	M	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Histiocytic sarcoma																									
Lymph node, mandibular	+	+	+	+	M	+	+	+	I	+	+	M	+	+	A	+	+	+	+	+	+	M	M	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	M	M	+	+	M	+	+	M	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Histiocytic sarcoma																									
Squamous cell carcinoma, metastatic, stomach																		X							
Lymph node, mesenteric	+	A	M	+	+	+	+	+	+	+	+	I	+	+	A	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Squamous cell carcinoma, metastatic, stomach																		X							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	M	M	+	+	+	+	+	+
Histiocytic sarcoma																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 625 ppm for 13 Weeks (continued)

Number of Days on Study	5 5 5 5 5 5 5 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 5 6 6 6 8 9 9 1 1 2 3 3 3 5 6 7 9 9 0 2 2 2 2 2 2 8 6 7 7 0 5 5 1 7 3 1 8 8 0 6 7 2 3 7 3 9 9 9 9 9
Carcass ID Number	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 8 7 7 8 7 8 8 8 8 8 8 8 8 8 8 8 7 7 8 7 8 7 7 8 8 8 4 8 7 0 7 0 5 6 3 0 2 1 3 0 2 7 9 5 8 6 7 9 1 3 4 4 3 5 2 3 1 3 3 3 5 5 1 4 4 4 4 4 1 4 1 2 1 3 5 3
Endocrine System	
Adrenal gland	+ +
Adrenal gland, cortex	+ +
Bilateral, adenoma	X
Adrenal gland, medulla	+ +
Pheochromocytoma benign	X X
Islets, pancreatic	+ + + + + + + + + + + A + + + + + + + + + + + + +
Parathyroid gland	+ + + M + + + M M + + + + M + + M M M + + + + + +
Pituitary gland	+ + + + + + + + + + + + I + I + + M M + + + + +
Thyroid gland	+ +
Follicular cell, adenoma	X X
General Body System	
Tissue NOS	
Genital System	
Epididymis	+ +
Preputial gland	+ + + + + + + + + + + + +
Adenoma	X
Carcinoma	X X
Bilateral, carcinoma	X
Prostate	+ I +
Seminal vesicle	+ A + + + + + + + + + + A + + + + + + + + + + + +
Testes	+ +
Hemangioma	X
Hematopoietic System	
Blood	
Bone marrow	+ + + + + + + + + + + + A + + + + + + + + + + + +
Histiocytic sarcoma	X
Lymph node	+ +
Renal, histiocytic sarcoma	X
Lymph node, bronchial	+ + M + + + M M + + + + + + + M M + M M + + + + +
Alveolar/bronchiolar carcinoma, metastatic, lung	X
Histiocytic sarcoma	X
Lymph node, mandibular	+ M + + + + + + + + + M + M + + M + M + + + + + +
Lymph node, mediastinal	+ M + + + + + I + + + + M + M + + + + + M + + + M
Alveolar/bronchiolar carcinoma, metastatic, lung	X
Histiocytic sarcoma	X
Squamous cell carcinoma, metastatic, stomach	X
Lymph node, mesenteric	+ + + M + + + + + M + + M + + + + + + + + + + + +
Histiocytic sarcoma	X X
Squamous cell carcinoma, metastatic, stomach	
Spleen	+ +
Hemangiosarcoma	X
Histiocytic sarcoma	X X
Thymus	+ + + + + + + + + + I M A I M + M + + M + M I + M
Histiocytic sarcoma	X

Total Tissues/ Tumors
50
50
1
49
2
45
33
43
50
2
1
49
10
1
3
1
48
42
50
1
48
1
49
1
40
1
1
39
39
1
1
2
43
2
1
49
1
2
37
1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 625 ppm for 13 Weeks (continued)

Number of Days on Study	1 6 9	1 8 5	1 9 4	2 0 8	2 2 4	2 3 1	2 4 7	2 5 1	2 7 0	2 7 1	2 8 4	2 8 5	2 9 6	3 0 3	3 1 2	3 2 7	3 4 2	3 5 2	3 7 0	4 1 0	4 7 1	5 0 6	5 2 0	5 5 9	5 5 3
Carcass ID Number	1 8 5 5	1 7 8 2	1 7 8 5	1 8 6 5	1 8 4 1	1 7 7 1	1 8 2 2	1 8 6 2	1 8 3 1	1 8 4 5	1 8 5 4	1 8 0 3	1 8 4 2	1 8 1 5	1 8 1 2	1 8 2 3	1 8 9 2	1 8 3 2	1 8 6 4	1 7 8 1	1 8 1 4	1 7 9 3	1 8 2 1	1 7 9 5	1 8 5 2
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous gland, adenoma																									
Subcutaneous tissue, hemangiosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neuroblastoma malignant, metastatic, brain																	X								
Skeletal muscle																+			+						
Abdominal, squamous cell carcinoma, metastatic, stomach																			X						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, harderian gland																									
Histiocytic sarcoma																									
Olfactory lobe, glioma malignant																									X
Olfactory lobe, neuroblastoma malignant																	X								
Spinal cord						+																			
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, multiple																									
Adenocarcinoma, metastatic, harderian gland																									
Alveolar/bronchiolar adenoma																X		X				X	X		
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																			X		X	X			
Alveolar/bronchiolar carcinoma, multiple																									
Carcinoma, metastatic, preputial gland																									
Carcinoma, metastatic, Zymbal's gland																						X			
Hemangiosarcoma, metastatic, heart																									
Hemangiosarcoma, metastatic, liver																									
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Squamous cell carcinoma, metastatic, stomach																			X						
Mediastinum, adenocarcinoma, metastatic, lung																									
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																									
Mediastinum, histiocytic sarcoma																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 625 ppm for 13 Weeks (continued)

Number of Days on Study	5 5 5 5 5 5 5 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 5 6 6 6 8 9 9 1 1 2 3 3 3 5 6 7 9 9 0 2 2 2 2 2 2 8 6 7 7 0 5 5 1 7 3 1 8 8 0 6 7 2 3 7 3 9 9 9 9 9	
Carcass ID Number	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 8 7 7 8 7 8 8 8 8 8 8 8 8 8 8 8 7 7 8 7 8 7 7 8 8 8 4 8 7 0 7 0 5 6 3 0 2 1 3 0 2 7 9 5 8 6 7 9 1 3 4 4 3 5 2 3 1 3 3 3 5 5 1 4 4 4 4 4 1 4 1 2 1 3 5 3	Total Tissues/ Tumors
Integumentary System		
Mammary gland	M + M M M M M M M + M + M M M M M M M M M M + M	5
Skin	+ +	50
Sebaceous gland, adenoma	X X	2
Subcutaneous tissue, hemangiosarcoma	X	1
Musculoskeletal System		
Bone	+ +	50
Neuroblastoma malignant, metastatic, brain		1
Skeletal muscle		2
Abdominal, squamous cell carcinoma, metastatic, stomach		1
Nervous System		
Brain	+ +	50
Adenocarcinoma, metastatic, harderian gland	X	1
Histiocytic sarcoma	X	1
Olfactory lobe, glioma malignant	X	2
Olfactory lobe, neuroblastoma malignant	X	2
Spinal cord		1
Respiratory System		
Larynx	+ + + + + + + + + + + + A + + + + + + + + + + +	49
Lung	+ +	50
Adenocarcinoma, multiple	X	1
Adenocarcinoma, metastatic, harderian gland	X X X	3
Alveolar/bronchiolar adenoma	X X X X X X X X X	11
Alveolar/bronchiolar adenoma, multiple	X X X X X X X	6
Alveolar/bronchiolar carcinoma	X X X X X X X X X X X X	12
Alveolar/bronchiolar carcinoma, multiple	X X X X X X	5
Carcinoma, metastatic, preputial gland	X	1
Carcinoma, metastatic, Zymbal's gland		1
Hemangiosarcoma, metastatic, heart	X	1
Hemangiosarcoma, metastatic, liver	X	1
Hepatocellular carcinoma, metastatic, liver	X X X X X X	5
Histiocytic sarcoma	X X	2
Squamous cell carcinoma, metastatic, stomach		1
Mediastinum, adenocarcinoma, metastatic, lung	X	1
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung	X	1
Mediastinum, histiocytic sarcoma	X	1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 625 ppm for 13 Weeks (continued)

Number of Days on Study	1 6 9	1 8 5	1 9 4	2 0 8	2 2 4	2 3 1	2 4 7	2 5 1	2 7 0	2 7 1	2 8 4	2 8 5	2 9 6	3 0 3	3 1 2	3 2 7	3 4 2	3 5 2	3 7 0	4 1 0	4 7 1	5 0 6	5 2 0	5 3 9	5 5 3
Carcass ID Number	1 8 5 5	1 7 8 2	1 7 8 5	1 8 6 5	1 8 4 1	1 7 7 1	1 8 2 2	1 8 6 2	1 8 3 1	1 8 4 5	1 8 5 4	1 8 0 3	1 8 4 2	1 8 1 5	1 8 1 2	1 8 2 3	1 8 9 2	1 7 3 2	1 8 6 4	1 8 8 1	1 7 1 4	1 8 1 3	1 8 9 1	1 8 2 5	1 8 5 2
Respiratory System (continued)																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neuroblastoma malignant, metastatic, brain																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																						+			
Eye																									
Harderian gland	M	M	M	M	I	I	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Adenoma																				X	X				X
Bilateral, adenoma																									
Zymbal's gland																						+			
Carcinoma																						X			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, heart																									
Histiocytic sarcoma																									
Squamous cell carcinoma, metastatic, stomach																									
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	A	+	+	+	+	+	+
Hemangioma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant lymphocytic	X	X	X	X	X	X	X		X	X	X		X	X	X		X		X			X	X		X
Lymphoma malignant mixed								X				X													

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 625 ppm for 13 Weeks (continued)

Number of Days on Study	5 5 5 5 5 5 5 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 5 6 6 6 8 9 9 1 1 2 3 3 3 5 6 7 9 9 0 2 2 2 2 2 2 8 6 7 7 0 5 5 1 7 3 1 8 8 0 6 7 2 3 7 3 9 9 9 9 9
Carcass ID Number	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 8 7 7 8 7 8 8 8 8 8 8 8 8 8 8 8 7 7 8 7 8 7 7 8 8 8 4 8 7 0 7 0 5 6 3 0 2 1 3 0 2 7 9 5 8 6 7 9 1 3 4 4 3 5 2 3 1 3 3 3 5 5 1 4 4 4 4 4 1 4 1 2 1 3 5 3
Respiratory System (continued)	
Nose	+ +
Neuroblastoma malignant, metastatic, brain	X
Trachea	+ + + + + + + + + + + + A + + + + + + + + + + + +
Special Senses System	
Ear	
Eye	M + +
Harderian gland	+ +
Adenocarcinoma	X X X X X X
Adenoma	X X X X X X X X X X X
Bilateral, adenoma	X X X X X X X X X
Zymbal's gland	+ +
Carcinoma	X
Urinary System	
Kidney	+ +
Hemangiosarcoma, metastatic, heart	X
Histiocytic sarcoma	X X
Squamous cell carcinoma, metastatic, stomach	X
Renal tubule, adenoma	X
Urinary bladder	+ A +
Hemangioma	X
Systemic Lesions	
Multiple organs	+ +
Histiocytic sarcoma	X X
Lymphoma malignant lymphocytic	
Lymphoma malignant mixed	X X X

	Total Tissues/ Tumors
Number of Days on Study	
Carcass ID Number	
Respiratory System (continued)	
Nose	50
Neuroblastoma malignant, metastatic, brain	1
Trachea	48
Special Senses System	
Ear	1
Eye	4
Harderian gland	42
Adenocarcinoma	4
Adenoma	13
Bilateral, adenoma	7
Zymbal's gland	3
Carcinoma	2
Urinary System	
Kidney	50
Hemangiosarcoma, metastatic, heart	1
Histiocytic sarcoma	2
Squamous cell carcinoma, metastatic, stomach	1
Renal tubule, adenoma	1
Urinary bladder	46
Hemangioma	1
Systemic Lesions	
Multiple organs	50
Histiocytic sarcoma	2
Lymphoma malignant lymphocytic	17
Lymphoma malignant mixed	5

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 625 ppm for 26 Weeks

Number of Days on Study	1 5 9	1 7 8	1 9 4	2 0 3	2 0 9	2 1 5	2 2 2	2 2 3	2 3 1	2 3 5	2 4 0	2 4 1	2 4 5	2 5 0	2 5 1	2 5 5	2 6 2	2 6 8	2 6 8	2 7 0	2 8 8	2 8 8	3 0 1	3 0 6	3 1 3
Carcass ID Number	1 9 2 2	1 9 5 3	1 9 4 1	1 8 7 2	1 9 3 5	1 9 1 1	1 9 1 3	1 9 6 4	1 8 8 5	1 9 2 5	1 9 4 2	1 9 3 1	1 9 0 2	1 9 5 4	1 9 3 2	1 9 6 5	1 9 1 5	1 8 8 3	1 9 4 3	1 9 9 2	1 8 7 1	1 8 8 4	1 8 7 3	1 9 1 4	1 8 7 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	+	+	+	M	A	+	+	A	+	A	+	+	+	+	A	A	+	A	+	+	+	+	M +
Intestine large	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Intestine large, colon	+	+	+	+	+	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	A	+	+	+	A	+	A	+	+	+	+	A	+	A	+	A	+	+	A	A
Intestine small, ileum	A	A	+	+	+	A	+	+	+	A	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+
Histiocytic sarcoma																									
Intestine small, jejunum	+	A	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	M	+
Histiocytic sarcoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hemangiosarcoma, metastatic, heart																								X	
Hepatocellular carcinoma																									
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma																									X
Hepatocellular adenoma, multiple																									
Histiocytic sarcoma																									
Mast cell tumor NOS, metastatic, bone marrow																									
Squamous cell carcinoma, metastatic, stomach																									
Mesentery																									
Fat, histiocytic sarcoma																									
Fat, squamous cell carcinoma, metastatic, stomach																									
Pancreas	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, hemangiosarcoma, metastatic, liver																									
Acinus, histiocytic sarcoma																									
Acinus, squamous cell carcinoma, metastatic, stomach																									
Pharynx																									
Carcinoma, metastatic, Zymbal's gland																									
Squamous cell carcinoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor NOS, metastatic, bone marrow																									
Squamous cell carcinoma																						X			
Squamous cell papilloma																									
Stomach, glandular	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+
Histiocytic sarcoma																									
Squamous cell carcinoma, metastatic, stomach																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 625 ppm for 26 Weeks (continued)

Number of Days on Study	3 1 3	3 5 4	3 5 6	3 5 8	3 5 9	3 6 4	4 1 2	4 1 4	4 2 9	4 4 0	4 4 1	4 8 3	4 8 3	4 9 2	5 0 2	5 1 0	5 1 3	5 3 9	5 4 3	5 4 4	5 5 3	5 5 4	5 5 8	6 6 2	6 3 5	
Carcass ID Number	1 8 9 2	1 8 9 1	1 9 6 1	1 9 3 4	1 8 9 3	1 9 0 1	1 8 9 4	1 9 5 1	1 8 9 5	1 9 4 5	1 9 6 2	1 8 8 2	1 9 5 2	1 8 7 4	1 9 5 5	1 9 2 3	1 9 0 3	1 9 4 4	1 9 0 4	1 9 2 4	1 9 0 5	1 8 8 1	1 9 3 3	1 9 6 3	1 9 2 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	A	A	A	A	A	+	A	+	+	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	32
Intestine large	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	42
Histiocytic sarcoma						X																				1
Intestine large, colon	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	45
Intestine large, rectum	+	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	A	A	A	A	A	+	A	+	+	+	+	+	A	+	A	+	+	M	A	+	+	+	+	+	+	32
Intestine small, ileum	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	40
Histiocytic sarcoma						X																				1
Intestine small, jejunum	+	A	+	A	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	41
Histiocytic sarcoma						X																				1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																			X							1
Hemangiosarcoma, metastatic, heart					X								X		X	X										5
Hepatocellular carcinoma																X	X						X			3
Hepatocellular carcinoma, multiple													X													1
Hepatocellular adenoma							X	X										X		X				X	X	7
Hepatocellular adenoma, multiple										X			X								X		X			4
Histiocytic sarcoma						X											X									2
Mast cell tumor NOS, metastatic, bone marrow									X																	1
Squamous cell carcinoma, metastatic, stomach												X														1
Mesentery						+						+							+		+					4
Fat, histiocytic sarcoma						X																				1
Fat, squamous cell carcinoma, metastatic, stomach												X														1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinus, hemangiosarcoma, metastatic, liver																			X							1
Acinus, histiocytic sarcoma						X																				1
Acinus, squamous cell carcinoma, metastatic, stomach																						X				1
Pharynx									+												+					2
Carcinoma, metastatic, Zymbal's gland									X																	1
Squamous cell carcinoma																					X					1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor NOS, metastatic, bone marrow									X																	1
Squamous cell carcinoma	X		X	X								X										X				6
Squamous cell papilloma					X		X	X		X																4
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma						X																				1
Squamous cell carcinoma, metastatic, stomach																						X				1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 625 ppm for 26 Weeks (continued)

Number of Days on Study	1 5 9	1 7 8	1 9 4	2 0 3	2 0 9	2 1 5	2 2 2	2 2 3	2 3 1	2 3 5	2 4 0	2 4 1	2 4 5	2 5 0	2 5 1	2 5 5	2 6 2	2 6 8	2 6 8	2 7 0	2 8 8	2 8 8	3 0 1	3 0 6	3 1 3
Carcass ID Number	1 9 2 2	1 9 5 3	1 9 4 1	1 8 7 2	1 9 3 5	1 9 1 1	1 9 1 3	1 9 6 4	1 8 8 5	1 9 2 5	1 9 4 2	1 9 3 1	1 9 0 2	1 9 5 4	1 9 3 2	1 9 6 5	1 9 1 5	1 8 8 3	1 9 4 3	1 9 1 2	1 8 7 1	1 8 8 4	1 9 7 3	1 9 8 4	1 9 8 5
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland																									
Hemangiosarcoma																								X	
Histiocytic sarcoma																									
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Islets, pancreatic	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	M	+	+	+	+	+	+	+	M	M	M	+	+	+	M	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	I	+	+
Carcinoma, metastatic, Zymbal's gland																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland																									
Carcinoma																									
Bilateral, carcinoma																									
Prostate	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, liver																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Mast cell tumor NOS																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inguinal, squamous cell carcinoma, metastatic, stomach																									
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Hemangiosarcoma, metastatic, heart																									
Histiocytic sarcoma																									
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Mast cell tumor NOS, metastatic, bone marrow																									
Squamous cell carcinoma, metastatic, pharynx																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 625 ppm for 26 Weeks (continued)

Number of Days on Study	3 1 3 3	3 5 4	3 5 6	3 5 8	3 5 9	3 6 4	4 1 2	4 1 4	4 2 9	4 4 0	4 4 1	4 8 3	4 8 3	4 9 3	5 0 2	5 1 2	5 1 0	5 1 3	5 3 9	5 4 3	5 4 4	5 5 3	5 5 4	5 5 8	6 3 2	6 3 5	
Carcass ID Number	1 8 9 2	1 8 9 1	1 9 6 1	1 9 3 4	1 8 9 3	1 9 0 1	1 8 9 4	1 9 5 1	1 8 9 5	1 9 4 5	1 9 6 2	1 8 8 2	1 9 5 2	1 8 7 4	1 9 5 5	1 9 5 3	1 9 2 3	1 9 0 3	1 9 4 4	1 9 0 4	1 9 2 4	1 9 0 5	1 8 8 1	1 9 3 3	1 9 6 3	1 9 2 1	Total Tissues/ Tumors
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal's gland									X																		1
Hemangiosarcoma	X		X		X					X			X	X	X	X		X				X		X	X	13
Histiocytic sarcoma						X																					1
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma						X																					1
Islets, pancreatic	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	M	+	+	+	+	+	I	+	I	+	+	+	+	+	M	M	+	+	+	+	M	+	M	+	+		37
Pituitary gland	+	+	+	I	I	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M		43
Carcinoma, metastatic, Zymbal's gland									X																		1
Thyroid gland	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
General Body System																											
None																											
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland		+											+		+				+	+					+		6
Carcinoma																			X	X							2
Bilateral, carcinoma																									X		1
Prostate	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+		47
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Hemangiosarcoma, metastatic, liver																				X							1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hematopoietic System																											
Blood																											
Bone marrow	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Histiocytic sarcoma						X																					1
Mast cell tumor NOS									X																		1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Inguinal, squamous cell carcinoma, metastatic, stomach												X															1
Lymph node, bronchial	+	+	M	+	+	+	+	M	M	+	+	+	+	M	+	+	M	M	+	M	+	+	+	+	M		41
Alveolar/bronchiolar carcinoma, metastatic, lung																					X						1
Hemangiosarcoma, metastatic, heart													X														1
Histiocytic sarcoma						X																					1
Lymph node, mandibular	M	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+		43
Histiocytic sarcoma						X											X										2
Mast cell tumor NOS, metastatic, bone marrow									X																		1
Squamous cell carcinoma, metastatic, pharynx																					X						1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 625 ppm for 26 Weeks (continued)

Number of Days on Study	1 1 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 3 3 3 5 7 9 0 0 1 2 2 3 3 4 4 4 5 5 5 6 6 6 7 8 8 0 0 1 9 8 4 3 9 5 2 3 1 5 0 1 5 0 1 5 2 8 8 0 8 8 1 6 3
Carcass ID Number	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 9 9 9 8 9 9 9 9 8 9 9 9 9 9 9 9 9 8 9 9 8 8 8 9 8 2 5 4 7 3 1 1 6 8 2 4 3 0 5 3 6 1 8 4 1 7 8 7 1 7 2 3 1 2 5 1 3 4 5 5 2 1 2 4 2 5 5 3 3 2 1 4 3 4 5
Hematopoietic System (continued)	
Lymph node, mediastinal	+ + + + + + + + + M + + + + + + + + + + + + + +
Alveolar/bronchiolar carcinoma, metastatic, lung	
Histiocytic sarcoma	
Squamous cell carcinoma, metastatic, stomach	
Lymph node, mesenteric	+ +
Histiocytic sarcoma	
Spleen	+ +
Histiocytic sarcoma	
Mast cell tumor NOS, metastatic, bone marrow	
Osteosarcoma, metastatic, uncertain primary site	
Squamous cell carcinoma, metastatic, stomach	
Thymus	+ +
Integumentary System	
Mammary gland	M + M + + M M + M M M + M + M M M + + M M M M M M
Skin	+ +
Subcutaneous tissue, leiomyosarcoma	
Musculoskeletal System	
Bone	+ +
Skeletal muscle	
Diaphragm, hemangiosarcoma, metastatic, liver	
Diaphragm, squamous cell carcinoma, metastatic, stomach	
Nervous System	
Brain	+ +
Histiocytic sarcoma	
Olfactory lobe, glioma malignant	
Spinal cord	+ +
Respiratory System	
Larynx	+ +
Lung	+ +
Alveolar/bronchiolar adenoma	
Alveolar/bronchiolar adenoma, multiple	
Alveolar/bronchiolar carcinoma	X
Alveolar/bronchiolar carcinoma, multiple	
Carcinoma, metastatic, Zymbal's gland	
Hemangiosarcoma, metastatic, heart	
Hemangiosarcoma, metastatic, liver	
Histiocytic sarcoma	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 625 ppm for 26 Weeks (continued)

Number of Days on Study	3 1 3	3 5 4	3 5 6	3 5 8	3 5 9	3 6 4	4 1 2	4 1 4	4 2 9	4 4 0	4 4 1	4 8 3	4 8 3	4 9 2	5 0 2	5 1 0	5 1 3	5 3 9	5 3 3	5 4 4	5 4 4	5 5 3	5 5 4	5 5 8	6 2 2	6 3 5	
Carcass ID Number	1 8 9 2	1 8 9 1	1 9 6 1	1 9 3 4	1 8 9 3	1 9 0 1	1 8 9 4	1 9 5 1	1 8 9 5	1 9 4 5	1 9 6 2	1 8 8 2	1 9 5 2	1 8 7 4	1 9 5 5	1 9 2 3	1 9 0 3	1 9 4 4	1 9 0 4	1 9 2 4	1 9 0 4	1 9 8 5	1 9 3 1	1 8 3 3	1 9 6 3	1 9 2 1	Total Tissues/ Tumors
Hematopoietic System (continued)																											
Lymph node, mediastinal	+	+	M	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M	44
Alveolar/bronchiolar carcinoma, metastatic, lung																					X						1
Histiocytic sarcoma						X																					1
Squamous cell carcinoma, metastatic, stomach	X											X															2
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																	X										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma						X											X										2
Mast cell tumor NOS, metastatic, bone marrow									X																		1
Osteosarcoma, metastatic, uncertain primary site																				X							1
Squamous cell carcinoma, metastatic, stomach												X															1
Thymus	M	+	+	M	M	+	+	+	I	M	M	+	+	M	+	+	+	M	+	+	+	M	+	+	M		40
Integumentary System																											
Mammary gland	M	M	M	M	+	M	M	I	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	9
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, leiomyosarcoma																										X	1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+																		+								2
Diaphragm, hemangiosarcoma, metastatic, liver																			X								1
Diaphragm, squamous cell carcinoma, metastatic, stomach	X																										1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																	X										1
Olfactory lobe, glioma malignant																				X							1
Spinal cord																											2
Respiratory System																											
Larynx	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	47
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X		X						X			X						X	X			X		7
Alveolar/bronchiolar adenoma, multiple														X		X			X				X	X			5
Alveolar/bronchiolar carcinoma									X			X			X								X		X		6
Alveolar/bronchiolar carcinoma, multiple														X			X	X			X			X			5
Carcinoma, metastatic, Zymbal's gland									X																		1
Hemangiosarcoma, metastatic, heart	X		X										X														3
Hemangiosarcoma, metastatic, liver																				X							1
Histiocytic sarcoma						X											X										2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 625 ppm for 26 Weeks (continued)

Number of Days on Study	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3
	5	7	9	0	0	1	2	2	3	3	4	4	4	5	5	5	6	6	6	7	8	8	0	0	1
	9	8	4	3	9	5	2	3	1	5	0	1	5	0	1	5	2	8	8	0	8	8	1	6	3
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	9	9	9	8	9	9	9	9	8	9	9	9	9	9	9	9	9	8	9	9	8	8	8	9	8
	2	5	4	7	3	1	1	6	8	2	4	3	0	5	3	6	1	8	4	1	7	8	7	1	7
	2	3	1	2	5	1	3	4	5	5	2	1	2	4	2	5	5	3	3	2	1	4	3	4	5
Respiratory System (continued)																									
Lung (continued)																									
Osteosarcoma, metastatic, uncertain primary site																									
Squamous cell carcinoma, metastatic, stomach																									
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																									
Mediastinum, carcinoma, metastatic, Zymbal's gland																									
Mediastinum, hemangiosarcoma, metastatic, heart																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye											+														
Harderian gland	M	+	M	M	M	+	M	+	+	M	M	M	+	M	+	M	M	M	+	M	+	+	+	+	I
Adenoma																								X	
Bilateral, adenoma																									
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, heart																									
Histiocytic sarcoma																									
Mast cell tumor NOS, metastatic, bone marrow																									
Osteosarcoma, metastatic, uncertain primary site																									
Squamous cell carcinoma, metastatic, stomach																									
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	I	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant lymphocytic	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Lymphoma malignant mixed															X										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 625 ppm for 26 Weeks (continued)

Number of Days on Study	3 1 3	3 5 4	3 5 6	3 5 8	3 5 9	3 6 4	4 1 2	4 1 4	4 2 9	4 4 0	4 4 1	4 8 3	4 8 3	4 9 2	5 0 2	5 1 0	5 1 3	5 3 9	5 4 3	5 4 4	5 5 3	5 5 4	5 5 8	6 3 2	6 3 5	
Carcass ID Number	1 8 9 2	1 8 9 1	1 9 6 1	1 9 3 4	1 8 9 3	1 9 0 1	1 8 9 4	1 9 5 1	1 8 9 5	1 9 4 5	1 9 6 2	1 8 8 2	1 9 5 2	1 8 7 4	1 9 5 5	1 9 2 3	1 9 0 3	1 9 4 4	1 9 0 4	1 9 2 4	1 9 0 5	1 8 8 1	1 9 3 3	1 9 6 3	1 9 2 1	Total Tissues/ Tumors
Respiratory System (continued)																										
Lung (continued)																										
Osteosarcoma, metastatic, uncertain primary site																				X						1
Squamous cell carcinoma, metastatic, stomach												X														1
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																					X					1
Mediastinum, carcinoma, metastatic, Zymbal's gland									X																	1
Mediastinum, hemangiosarcoma, metastatic, heart															X											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Special Senses System																										
Eye								+						+												3
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	36
Adenoma				X		X						X		X		X	X		X	X					X	10
Bilateral, adenoma															X			X						X		3
Zymbal's gland									+														+			2
Carcinoma									X														X			2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, heart													X													1
Histiocytic sarcoma						X											X									2
Mast cell tumor NOS, metastatic, bone marrow									X																	1
Osteosarcoma, metastatic, uncertain primary site																				X						1
Squamous cell carcinoma, metastatic, stomach												X														1
Renal tubule, adenoma										X																1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma						X											X									2
Lymphoma malignant lymphocytic							X	X		X	X			X										X		30
Lymphoma malignant mixed																		X					X			3

TABLE C3a
Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: Stop-Exposure Group versus Controls

	0 ppm	200 ppm (40 weeks)	312 ppm (52 weeks)	625 ppm (13 weeks)	625 ppm (26 weeks)
Harderian Gland: Adenoma					
Overall rate[a]	6/50 (12%)	26/50 (52%)	28/50 (56%)	20/50 (40%)	13/50 (26%)
Adjusted rate[b]	14.8%	87.9%	100.0%	94.3%	100.0%
Terminal rate[c]	2/35 (6%)	6/9 (67%)	1/1 (100%)	4/5 (80%)	0/0
First incidence (days)	543	440	344	410	306
Life table test[d]		P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test[d]		P<0.001	P<0.001	P<0.001	P=0.046
Fisher exact test[d]		P<0.001	P<0.001	P=0.001	P=0.062
Harderian Gland: Carcinoma					
Overall rate	0/50 (0%)	2/50 (4%)	2/50 (4%)	4/50 (8%)	0/50 (0%)
Adjusted rate	0.0%	5.6%	51.5%	38.8%	0.0%
Terminal rate	0/35 (0%)	0/9 (0%)	0/1 (0%)	1/5 (20%)	0/0
First incidence (days)	–[e]	510	441	567	–
Life table test		P=0.182	P=0.028	P<0.001	–
Logistic regression test		P=0.397	P=0.190	P=0.006	–
Fisher exact test		P=0.247	P=0.247	P=0.059	–
Harderian Gland: Adenoma or Carcinoma					
Overall rate	6/50 (12%)	27/50 (54%)	30/50 (60%)	23/50 (46%)	13/50 (26%)
Adjusted rate	14.8%	88.3%	100.0%	100.0%	100.0%
Terminal rate	2/35 (6%)	6/9 (67%)	1/1 (100%)	5/5 (100%)	0/0
First incidence (days)	543	440	344	410	306
Life table test		P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test		P<0.001	P<0.001	P<0.001	P=0.046
Fisher exact test		P<0.001	P<0.001	P<0.001	P=0.062
Heart: Hemangiosarcoma					
Overall rate	0/50 (0%)	15/50 (30%)	33/50 (66%)	7/50 (14%)	13/50 (26%)
Adjusted rate	0.0%	76.2%	100.0%	61.8%	100.0%
Terminal rate	0/35 (0%)	5/9 (56%)	1/1 (100%)	2/5 (40%)	0/0
First incidence (days)	–	330	328	566	306
Life table test		P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test		P<0.001	P<0.001	P<0.001	P<0.001
Fisher exact test		P<0.001	P<0.001	P=0.006	P<0.001
Kidney (Renal Tubule): Adenoma					
Overall rate	0/50 (0%)	4/48 (8%)	3/49 (6%)	1/50 (2%)	1/50 (2%)
Adjusted rate	0.0%	17.4%	27.8%	14.3%	6.3%
Terminal rate	0/35 (0%)	0/9 (0%)	0/1 (0%)	0/5 (0%)	0/0
First incidence (days)	–	516	539	707	440
Life table test		P=0.016	P=0.007	P=0.181	P=0.278
Logistic regression test		P=0.073	P=0.075	P=0.273	P=0.731
Fisher exact test		P=0.054	P=0.117	P=0.500	P=0.500

TABLE C3a
Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: Stop-Exposure Group versus Controls (continued)

	0 ppm	200 ppm (40 weeks)	312 ppm (52 weeks)	625 ppm (13 weeks)	625 ppm (26 weeks)
Liver: Hepatocellular Adenoma					
Overall rate	13/50 (26%)	27/49 (55%)	19/50 (38%)	19/49 (39%)	11/50 (22%)
Adjusted rate	32.1%	91.1%	100.0%	91.0%	100.0%
Terminal rate	9/35 (26%)	7/9 (78%)	1/1 (100%)	4/5 (80%)	0/0
First incidence (days)	379	399	326	471	313
Life table test		P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test		P<0.001	P=0.045	P=0.042	P=0.284
Fisher exact test		P=0.003	P=0.142	P=0.126	P=0.408N
Liver: Hepatocellular Carcinoma					
Overall rate	11/50 (22%)	14/49 (29%)	10/50 (20%)	14/49 (29%)	4/50 (8%)
Adjusted rate	26.0%	50.3%	74.6%	90.9%	50.5%
Terminal rate	5/35 (14%)	1/9 (11%)	0/1 (0%)	4/5 (80%)	0/0
First incidence (days)	540	407	382	520	483
Life table test		P=0.010	P<0.001	P<0.001	P<0.001
Logistic regression test		P=0.530N	P=0.453N	P=0.142	P=0.393
Fisher exact test		P=0.301	P=0.500N	P=0.301	P=0.045N
Liver: Hepatocellular Adenoma or Carcinoma					
Overall rate	21/50 (42%)	33/49 (67%)	24/50 (48%)	24/49 (49%)	13/50 (26%)
Adjusted rate	47.9%	93.4%	100.0%	94.4%	100.0%
Terminal rate	13/35 (37%)	7/9 (78%)	1/1 (100%)	4/5 (80%)	0/0
First incidence (days)	379	399	326	471	313
Life table test		P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test		P=0.004	P=0.169	P=0.063	P=0.561
Fisher exact test		P=0.010	P=0.344	P=0.310	P=0.069N
Liver: Hepatoblastoma or Hepatocellular Carcinoma					
Overall rate	11/50 (22%)	14/49 (29%)	11/50 (22%)	14/49 (29%)	4/50 (8%)
Adjusted rate	26.0%	50.3%	77.1%	90.9%	50.5%
Terminal rate	5/35 (14%)	1/9 (11%)	0/1 (0%)	4/5 (80%)	0/0
First incidence (days)	540	407	382	520	483
Life table test		P=0.010	P<0.001	P<0.001	P<0.001
Logistic regression test		P=0.530N	P=0.559N	P=0.142	P=0.386N
Fisher exact test		P=0.301	P=0.595N	P=0.301	P=0.045N
Liver: Hepatoblastoma, Hepatocellular Adenoma, or Carcinoma					
Overall rate	21/50 (42%)	33/49 (67%)	25/50 (50%)	24/49 (49%)	13/50 (26%)
Adjusted rate	47.9%	93.4%	100.0%	94.4%	100.0%
Terminal rate	13/35 (37%)	7/9 (78%)	1/1 (100%)	4/5 (80%)	0/0
First incidence (days)	379	399	326	471	313
Life table test		P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test		P=0.004	P=0.103	P=0.063	P=0.561
Fisher exact test		P=0.010	P=0.274	P=0.310	P=0.069N

TABLE C3a
Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: Stop-Exposure Group versus Controls (continued)

	0 ppm	200 ppm (40 weeks)	312 ppm (52 weeks)	625 ppm (13 weeks)	625 ppm (26 weeks)
Lung: Alveolar/bronchiolar Adenoma					
Overall rate	18/50 (36%)	24/50 (48%)	26/50 (52%)	17/50 (34%)	12/50 (24%)
Adjusted rate	46.9%	94.3%	100.0%	85.3%	100.0%
Terminal rate	15/35 (43%)	8/9 (89%)	1/1 (100%)	3/5 (60%)	0/0
First incidence (days)	572	399	344	327	358
Life table test		P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test		P=0.015	P=0.001	P=0.044	P<0.001
Fisher exact test		P=0.156	P=0.079	P=0.500N	P=0.138N
Lung: Alveolar/bronchiolar Adenocarcinoma or Carcinoma					
Overall rate	5/50 (10%)	22/50 (44%)	16/50 (32%)	18/50 (36%)	11/50 (22%)
Adjusted rate	14.3%	89.5%	100.0%	87.7%	100.0%
Terminal rate	5/35 (14%)	7/9 (78%)	1/1 (100%)	3/5 (60%)	0/0
First incidence (days)	729 (T)	481	392	370	241
Life table test		P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test		P<0.001	P<0.001	P<0.001	P<0.001
Fisher exact test		P<0.001	P=0.006	P=0.002	P=0.086
Lung: Alveolar/bronchiolar Adenoma, Adenocarcinoma, or Carcinoma					
Overall rate	21/50 (42%)	36/50 (72%)	32/50 (64%)	28/50 (56%)	17/50 (34%)
Adjusted rate	54.9%	100.0%	100.0%	100.0%	100.0%
Terminal rate	18/35 (51%)	9/9 (100%)	1/1 (100%)	5/5 (100%)	0/0
First incidence (days)	572	399	344	327	241
Life table test		P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test		P<0.001	P<0.001	P<0.001	P<0.001
Fisher exact test		P=0.002	P=0.022	P=0.115	P=0.268N
Preputial Gland: Carcinoma					
Overall rate	0/50 (0%)	1/50 (2%)	4/50 (8%)	4/50 (8%)	3/50 (6%)
Adjusted rate	0.0%	10.0%	100.0%	16.9%	100.0%
Terminal rate	0/35 (0%)	0/9 (0%)	1/1 (100%)	0/5 (0%)	0/0
First incidence (days)	–	699	639	520	539
Life table test		P=0.247	P<0.001	P=0.012	P<0.001
Logistic regression test		P=0.368	P<0.001	P=0.039	P=0.002
Fisher exact test		P=0.500	P=0.059	P=0.059	P=0.121
Preputial Gland: Adenoma or Carcinoma					
Overall rate	0/50 (0%)	1/50 (2%)	4/50 (8%)	5/50 (10%)	3/50 (6%)
Adjusted rate	0.0%	10.0%	100.0%	22.9%	100.0%
Terminal rate	0/35 (0%)	0/9 (0%)	1/1 (100%)	0/5 (0%)	0/0
First incidence (days)	–	699	639	520	539
Life table test		P=0.247	P<0.001	P=0.003	P<0.001
Logistic regression test		P=0.368	P<0.001	P=0.013	P=0.002
Fisher exact test		P=0.500	P=0.059	P=0.028	P=0.121

TABLE C3a
Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: Stop-Exposure Group versus Controls (continued)

	0 ppm	200 ppm (40 weeks)	312 ppm (52 weeks)	625 ppm (13 weeks)	625 ppm (26 weeks)
Stomach (Forestomach): Squamous Cell Papilloma					
Overall rate	1/50 (2%)	3/50 (6%)	4/50 (8%)	4/50 (8%)	4/50 (8%)
Adjusted rate	2.5%	21.4%	100.0%	28.3%	20.1%
Terminal rate	0/35 (0%)	1/9 (11%)	1/1 (100%)	1/5 (20%)	0/0
First incidence (days)	652	584	401	327	359
Life table test		P=0.065	P=0.004	P=0.020	P=0.003
Logistic regression test		P=0.195	P=0.181	P=0.260	P=0.301
Fisher exact test		P=0.309	P=0.181	P=0.181	P=0.181
Stomach (Forestomach): Squamous Cell Carcinoma					
Overall rate	0/50 (0%)	0/50 (0%)	5/50 (10%)	4/50 (8%)	6/50 (12%)
Adjusted rate	0.0%	0.0%	33.1%	51.6%	40.9%
Terminal rate	0/35 (0%)	0/9 (0%)	0/1 (0%)	2/5 (40%)	0/0
First incidence (days)	–	–	422	370	288
Life table test		–	P<0.001	P<0.001	P<0.001
Logistic regression test		–	P=0.017	P=0.013	P=0.061
Fisher exact test		–	P=0.028	P=0.059	P=0.013
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma					
Overall rate	1/50 (2%)	3/50 (6%)	9/50 (18%)	7/50 (14%)	10/50 (20%)
Adjusted rate	2.5%	21.4%	100.0%	56.6%	52.8%
Terminal rate	0/35 (0%)	1/9 (11%)	1/1 (100%)	2/5 (40%)	0/0
First incidence (days)	652	584	401	327	288
Life table test		P=0.065	P<0.001	P<0.001	P<0.001
Logistic regression test		P=0.195	P=0.004	P=0.025	P=0.313
Fisher exact test		P=0.309	P=0.008	P=0.030	P=0.004
Zymbal's Gland: Adenoma or Carcinoma					
Overall rate	1/50 (2%)	1/50 (2%)	0/50 (0%)	2/50 (4%)	2/50 (4%)
Adjusted rate	2.9%	4.8%	0.0%	8.8%	37.3%
Terminal rate	1/35 (3%)	0/9 (0%)	0/1 (0%)	0/5 (0%)	0/0
First incidence (days)	729 (T)	650	–	506	429
Life table test		P=0.531	P=0.998N	P=0.178	P=0.009
Logistic regression test		P=0.661	P=0.998N	P=0.420	P=0.237
Fisher exact test		P=0.753N	P=0.500N	P=0.500	P=0.500
All Organs: Hemangioma					
Overall rate	1/50 (2%)	4/50 (8%)	0/50 (0%)	4/50 (8%)	0/50 (0%)
Adjusted rate	2.9%	28.8%	0.0%	51.1%	0.0%
Terminal rate	1/35 (3%)	2/9 (22%)	0/1 (0%)	2/5 (40%)	0/0
First incidence (days)	729 (T)	595	–	595	–
Life table test		P=0.012	P=0.998N	P<0.001	–
Logistic regression test		P=0.053	P=0.998N	P=0.010	–
Fisher exact test		P=0.181	P=0.500N	P=0.181	P=0.500N

TABLE C3a
Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: Stop-Exposure Group versus Controls (continued)

	0 ppm	200 ppm (40 weeks)	312 ppm (52 weeks)	625 ppm (13 weeks)	625 ppm (26 weeks)
All Organs: Hemangiosarcoma					
Overall rate	1/50 (2%)	17/50 (34%)	34/50 (68%)	12/50 (24%)	14/50 (28%)
Adjusted rate	2.9%	78.2%	100.0%	75.1%	100.0%
Terminal rate	1/35 (3%)	5/9 (56%)	1/1 (100%)	2/5 (40%)	0/0
First incidence (days)	729 (T)	330	328	566	306
Life table test		P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test		P<0.001	P<0.001	P<0.001	P<0.001
Fisher exact test		P<0.001	P<0.001	P<0.001	P<0.001
All Organs: Hemangioma or Hemangiosarcoma					
Overall rate	2/50 (4%)	20/50 (40%)	34/50 (68%)	14/50 (28%)	14/50 (28%)
Adjusted rate	5.7%	85.1%	100.0%	84.3%	100.0%
Terminal rate	2/35 (6%)	6/9 (67%)	1/1 (100%)	3/5 (60%)	0/0
First incidence (days)	729 (T)	330	328	566	306
Life table test		P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test		P<0.001	P<0.001	P<0.001	P<0.001
Fisher exact test		P<0.001	P<0.001	P<0.001	P<0.001
All Organs: Lymphocytic Malignant Lymphoma					
Overall rate	2/50 (4%)	6/50 (12%)	4/50 (8%)	17/50 (34%)	30/50 (60%)
Adjusted rate	4.7%	26.7%	100.0%	35.8%	81.5%
Terminal rate	0/35 (0%)	1/9 (11%)	1/1 (100%)	0/5 (0%)	0/0
First incidence (days)	511	208	289	169	159
Life table test		P=0.033	P=0.034	P<0.001	P<0.001
Logistic regression test		P=0.539	P=0.702N	P=0.658	P=0.573
Fisher exact test		P=0.134	P=0.339	P<0.001	P<0.001
All Organs: Lymphoma (Mixed or NOS)					
Overall rate	2/50 (4%)	2/50 (4%)	4/50 (8%)	5/50 (10%)	3/50 (6%)
Adjusted rate	5.3%	7.8%	58.0%	34.8%	43.3%
Terminal rate	1/35 (3%)	0/9 (0%)	0/1 (0%)	1/5 (20%)	0/0
First incidence (days)	666	514	217	251	251
Life table test		P=0.382	P=0.005	P=0.010	P=0.002
Logistic regression test		P=0.273	P=0.034	P=0.002	P<0.001
Fisher exact test		P=0.691N	P=0.339	P=0.218	P=0.500
All Organs: Malignant Lymphoma (Lymphocytic, Mixed, or NOS)					
Overall rate	4/50 (8%)	8/50 (16%)	8/50 (16%)	22/50 (44%)	33/50 (66%)
Adjusted rate	9.8%	32.4%	100.0%	58.2%	89.5%
Terminal rate	1/35 (3%)	1/9 (11%)	1/1 (100%)	1/5 (20%)	0/0
First incidence (days)	511	208	217	169	159
Life table test		P=0.023	P<0.001	P<0.001	P<0.001
Logistic regression test		P=0.544	P=0.447	P=0.322	P=0.458
Fisher exact test		P=0.178	P=0.178	P<0.001	P<0.001

TABLE C3a
Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: Stop-Exposure Group versus Controls (continued)

	0 ppm	200 ppm (40 weeks)	312 ppm (52 weeks)	625 ppm (13 weeks)	625 ppm (26 weeks)
All Organs: Histiocytic Sarcoma					
Overall rate	0/50 (0%)	5/50 (10%)	7/50 (14%)	2/50 (4%)	2/50 (4%)
Adjusted rate	0.0%	21.3%	43.0%	28.9%	15.6%
Terminal rate	0/35 (0%)	0/9 (0%)	0/1 (0%)	1/5 (20%)	0/0
First incidence (days)	–	576	314	692	364
Life table test		P=0.006	P<0.001	P=0.011	P=0.036
Logistic regression test		P=0.028	P=0.057	P=0.035	P=0.337
Fisher exact test		P=0.028	P=0.006	P=0.247	P=0.247
All Organs: Malignant Lymphoma or Histiocytic Sarcoma					
Overall rate	4/50 (8%)	13/50 (26%)	15/50 (30%)	24/50 (48%)	35/50 (70%)
Adjusted rate	9.8%	46.8%	100.0%	72.1%	91.2%
Terminal rate	1/35 (3%)	1/9 (11%)	1/1 (100%)	2/5 (40%)	0/0
First incidence (days)	511	208	217	169	159
Life table test		P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test		P=0.090	P=0.079	P=0.097	P=0.291
Fisher exact test		P=0.016	P=0.005	P<0.001	P<0.001
All Organs: Benign Neoplasms					
Overall rate	41/50 (82%)	41/50 (82%)	41/50 (82%)	34/50 (68%)	22/50 (44%)
Adjusted rate	87.2%	100.0%	100.0%	100.0%	100.0%
Terminal rate	29/35 (83%)	9/9 (100%)	1/1 (100%)	5/5 (100%)	0/0
First incidence (days)	379	399	326	327	306
Life table test		P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test		P=0.079	P=0.071	P=0.029	P=0.204
Fisher exact test		P=0.602N	P=0.602N	P=0.083N	P<0.001N
All Organs: Malignant Neoplasms					
Overall rate	20/50 (40%)	43/50 (86%)	50/50 (100%)	49/50 (98%)	49/50 (98%)
Adjusted rate	44.8%	95.3%	100.0%	100.0%	100.0%
Terminal rate	11/35 (31%)	7/9 (78%)	1/1 (100%)	5/5 (100%)	0/0
First incidence (days)	511	208	217	169	159
Life table test		P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test		P<0.001	P<0.001	P<0.001	P=0.007
Fisher exact test		P<0.001	P<0.001	P<0.001	P<0.001
All Organs: Benign or Malignant Neoplasms					
Overall rate	46/50 (92%)	49/50 (98%)	50/50 (100%)	49/50 (98%)	49/50 (98%)
Adjusted rate	93.9%	100.0%	100.0%	100.0%	100.0%
Terminal rate	30/35 (91%)	9/9 (100%)	1/1 (100%)	5/5 (100%)	0/0
First incidence (days)	379	208	217	169	159
Life table test		P<0.001	P<0.001	P<0.001	P<0.001
Logistic regression test		P=0.081	P=0.170	P=0.161	P=0.470
Fisher exact test		P=0.181	P=0.059	P=0.181	P=0.181

TABLE C3a
Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: Stop-Exposure Group versus Controls (continued)

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, epididymis, gallbladder, heart, kidney, larynx, liver, lung, nose, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE C3b
Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 200 ppm (40-Week) Exposure Group versus 625 ppm (13-Week) Exposure Group

	200 ppm (40 weeks)	625 ppm (13 weeks)
Adrenal Medulla: Benign Pheochromocytoma		
Overall rate[a]	0/45 (0%)	2/49 (4%)
Adjusted rate[b]	0.0%	23.5%
Terminal rate[c]	0/9 (0%)	1/5 (20%)
First incidence (days)	–[e]	567
Life table test[d]		P=0.149
Logistic regression test[d]		P=0.182
Fisher exact test[d]		P=0.269
Bone Marrow: Mast Cell Tumor NOS		
Overall rate	3/50 (6%)	0/48 (0%)
Adjusted rate	15.6%	0.0%
Terminal rate	0/9 (0%)	0/5 (0%)
First incidence (days)	555	–
Life table test		P=0.216N
Logistic regression test		P=0.178N
Fisher exact test		P=0.129N
Brain: Malignant Glioma		
Overall rate	0/50 (0%)	2/50 (4%)
Adjusted rate	0.0%	12.6%
Terminal rate	0/9 (0%)	0/5 (0%)
First incidence (days)	–	553
Life table test		P=0.192
Logistic regression test		P=0.187
Fisher exact test		P=0.247
Brain: Malignant Neuroblastoma		
Overall rate	0/50 (0%)	2/50 (4%)
Adjusted rate	0.0%	7.6%
Terminal rate	0/9 (0%)	0/5 (0%)
First incidence (days)	–	342
Life table test		P=0.178
Logistic regression test		P=0.283
Fisher exact test		P=0.247
Harderian Gland: Adenoma		
Overall rate	26/50 (52%)	20/50 (40%)
Adjusted rate	87.9%	94.3%
Terminal rate	6/9 (67%)	4/5 (80%)
First incidence (days)	440	410
Life table test		P=0.341
Logistic regression test		P=0.536
Fisher exact test		P=0.158N

TABLE C3b
Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 200 ppm (40-Week) Exposure Group versus 625 ppm (13-Week) Exposure Group (continued)

	200 ppm (40 weeks)	625 ppm (13 weeks)
Harderian Gland: Carcinoma		
Overall rate	2/50 (4%)	4/50 (8%)
Adjusted rate	5.6%	38.8%
Terminal rate	0/9 (0%)	1/5 (20%)
First incidence (days)	510	567
Life table test		P=0.206
Logistic regression test		P=0.231
Fisher exact test		P=0.339
Harderian Gland: Adenoma or Carcinoma		
Overall rate	27/50 (54%)	23/50 (46%)
Adjusted rate	88.3%	100.0%
Terminal rate	6/9 (67%)	5/5 (100%)
First incidence (days)	440	410
Life table test		P=0.204
Logistic regression test		P=0.284
Fisher exact test		P=0.274N
Heart: Hemangiosarcoma		
Overall rate	15/50 (30%)	7/50 (14%)
Adjusted rate	76.2%	61.8%
Terminal rate	5/9 (56%)	2/5 (40%)
First incidence (days)	330	566
Life table test		P=0.323N
Logistic regression test		P=0.174N
Fisher exact test		P=0.045N
Kidney (Renal Tubule): Adenoma		
Overall rate	4/48 (8%)	1/50 (2%)
Adjusted rate	17.4%	14.3%
Terminal rate	0/9 (0%)	0/5 (0%)
First incidence (days)	516	707
Life table test		P=0.290N
Logistic regression test		P=0.249N
Fisher exact test		P=0.168N
Liver: Hemangiosarcoma		
Overall rate	0/49 (0%)	2/49 (4%)
Adjusted rate	0.0%	10.7%
Terminal rate	0/9 (0%)	0/5 (0%)
First incidence (days)	–	567
Life table test		P=0.169
Logistic regression test		P=0.192
Fisher exact test		P=0.247

TABLE C3b
Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 200 ppm (40-Week) Exposure Group versus 625 ppm (13-Week) Exposure Group (continued)

	200 ppm (40 weeks)	625 ppm (13 weeks)
Liver: Hepatocellular Adenoma		
Overall rate	27/49 (55%)	19/49 (39%)
Adjusted rate	91.1%	91.0%
Terminal rate	7/9 (78%)	4/5 (80%)
First incidence (days)	399	471
Life table test		P=0.487
Logistic regression test		P=0.534N
Fisher exact test		P=0.078N
Liver: Hepatocellular Carcinoma		
Overall rate	14/49 (29%)	14/49 (29%)
Adjusted rate	50.3%	90.9%
Terminal rate	1/9 (11%)	4/5 (80%)
First incidence (days)	407	520
Life table test		P=0.176
Logistic regression test		P=0.246
Fisher exact test		P=0.588N
Liver: Hepatocellular Adenoma or Carcinoma		
Overall rate	33/49 (67%)	24/49 (49%)
Adjusted rate	93.4%	94.4%
Terminal rate	7/9 (78%)	4/5 (80%)
First incidence (days)	399	471
Life table test		P=0.427
Logistic regression test		P=0.561N
Fisher exact test		P=0.050N
Lung: Alveolar/bronchiolar Adenoma		
Overall rate	24/50 (48%)	17/50 (34%)
Adjusted rate	94.3%	85.3%
Terminal rate	8/9 (89%)	3/5 (60%)
First incidence (days)	399	327
Life table test		P=0.478
Logistic regression test		P=0.419N
Fisher exact test		P=0.111N
Lung: Alveolar/bronchiolar Adenocarcinoma or Carcinoma		
Overall rate	22/50 (44%)	18/50 (36%)
Adjusted rate	89.5%	87.7%
Terminal rate	7/9 (78%)	3/5 (60%)
First incidence (days)	481	370
Life table test		P=0.265
Logistic regression test		P=0.419
Fisher exact test		P=0.270N

TABLE C3b
Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 200 ppm (40-Week) Exposure Group versus 625 ppm (13-Week) Exposure Group (continued)

	200 ppm (40 weeks)	625 ppm (13 weeks)
Lung: Alveolar/bronchiolar Adenoma, Adenocarcinoma, or Carcinoma		
Overall rate	36/50 (72%)	28/50 (56%)
Adjusted rate	100.0%	100.0%
Terminal rate	9/9 (100%)	5/5 (100%)
First incidence (days)	399	327
Life table test		P=0.275
Logistic regression test		P=0.514
Fisher exact test		P=0.072N
Mesentery: Hemangioma		
Overall rate	3/50 (6%)	2/50 (4%)
Adjusted rate	26.1%	40.0%
Terminal rate	2/9 (22%)	2/5 (40%)
First incidence (days)	651	729 (T)
Life table test		P=0.615
Logistic regression test		P=0.692N
Fisher exact test		P=0.500N
Preputial Gland: Carcinoma		
Overall rate	1/50 (2%)	4/50 (8%)
Adjusted rate	10.0%	16.9%
Terminal rate	0/9 (0%)	0/5 (0%)
First incidence (days)	699	520
Life table test		P=0.115
Logistic regression test		P=0.123
Fisher exact test		P=0.138
Preputial Gland: Adenoma or Carcinoma		
Overall rate	1/50 (2%)	5/50 (10%)
Adjusted rate	10.0%	22.9%
Terminal rate	0/9 (0%)	0/5 (0%)
First incidence (days)	699	520
Life table test		P=0.054
Logistic regression test		P=0.059
Fisher exact test		P=0.070
Stomach (Forestomach): Squamous Cell Papilloma		
Overall rate	3/50 (6%)	4/50 (8%)
Adjusted rate	21.4%	28.3%
Terminal rate	1/9 (11%)	1/5 (20%)
First incidence (days)	584	327
Life table test		P=0.286
Logistic regression test		P=0.433
Fisher exact test		P=0.500

TABLE C3b
Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 200 ppm (40-Week) Exposure Group versus 625 ppm (13-Week) Exposure Group (continued)

	200 ppm (40 weeks)	625 ppm (13 weeks)
Stomach (Forestomach): Squamous Cell Carcinoma		
Overall rate	0/50 (0%)	4/50 (8%)
Adjusted rate	0.0%	51.6%
Terminal rate	0/9 (0%)	2/5 (40%)
First incidence (days)	–	370
Life table test		P=0.019
Logistic regression test		P=0.031
Fisher exact test		P=0.059
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma		
Overall rate	3/50 (6%)	7/50 (14%)
Adjusted rate	21.4%	56.6%
Terminal rate	1/9 (11%)	2/5 (40%)
First incidence (days)	584	327
Life table test		P=0.045
Logistic regression test		P=0.099
Fisher exact test		P=0.159
Thyroid Gland (Follicular Cell): Adenoma		
Overall rate	2/48 (4%)	2/50 (4%)
Adjusted rate	15.3%	40.0%
Terminal rate	1/9 (11%)	2/5 (40%)
First incidence (days)	650	729 (T)
Life table test		P=0.471
Logistic regression test		P=0.549
Fisher exact test		P=0.676N
Zymbal's Gland: Carcinoma		
Overall rate	1/50 (2%)	2/50 (4%)
Adjusted rate	4.8%	8.8%
Terminal rate	0/9 (0%)	0/5 (0%)
First incidence (days)	650	506
Life table test		P=0.369
Logistic regression test		P=0.440
Fisher exact test		P=0.500
All Organs: Hemangioma		
Overall rate	4/50 (8%)	4/50 (8%)
Adjusted rate	28.8%	51.1%
Terminal rate	2/9 (22%)	2/5 (40%)
First incidence (days)	595	595
Life table test		P=0.370
Logistic regression test		P=0.436
Fisher exact test		P=0.643N

TABLE C3b
Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 200 ppm (40-Week) Exposure Group versus 625 ppm (13-Week) Exposure Group (continued)

	200 ppm (40 weeks)	625 ppm (13 weeks)
All Organs: Hemangiosarcoma		
Overall rate	17/50 (34%)	12/50 (24%)
Adjusted rate	78.2%	75.1%
Terminal rate	5/9 (56%)	2/5 (40%)
First incidence (days)	330	566
Life table test		P=0.482
Logistic regression test		P=0.549N
Fisher exact test		P=0.189N
All Organs: Hemangioma or Hemangiosarcoma		
Overall rate	20/50 (40%)	14/50 (28%)
Adjusted rate	85.1%	84.3%
Terminal rate	6/9 (67%)	3/5 (60%)
First incidence (days)	330	566
Life table test		P=0.471
Logistic regression test		P=0.531N
Fisher exact test		P=0.146N
All Organs: Lymphocytic Malignant Lymphoma		
Overall rate	6/50 (12%)	17/50 (34%)
Adjusted rate	26.7%	35.8%
Terminal rate	1/9 (11%)	0/5 (0%)
First incidence (days)	208	169
Life table test		P=0.005
Logistic regression test		P=0.293
Fisher exact test		P=0.008
All Organs: Malignant Lymphoma (Mixed or NOS)		
Overall rate	2/50 (4%)	5/50 (10%)
Adjusted rate	7.8%	34.8%
Terminal rate	0/9 (0%)	1/5 (20%)
First incidence (days)	514	251
Life table test		P=0.117
Logistic regression test		P=0.031
Fisher exact test		P=0.218
All Organs: Malignant Lymphoma (Lymphocytic, Mixed, or NOS)		
Overall rate	8/50 (16%)	22/50 (44%)
Adjusted rate	32.4%	58.2%
Terminal rate	1/9 (11%)	1/5 (20%)
First incidence (days)	208	169
Life table test		P=0.001
Logistic regression test		P=0.135
Fisher exact test		P=0.002

TABLE C3b
Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 200 ppm (40-Week) Exposure Group versus 625 ppm (13-Week) Exposure Group (continued)

	200 ppm (40 weeks)	625 ppm (13 weeks)
All Organs: Histiocytic Sarcoma		
Overall rate	5/50 (10%)	2/50 (4%)
Adjusted rate	21.3%	28.9%
Terminal rate	0/9 (0%)	1/5 (20%)
First incidence (days)	576	692
Life table test		P=0.415N
Logistic regression test		P=0.347N
Fisher exact test		P=0.218N
All Organs: Malignant Lymphoma or Histiocytic Sarcoma		
Overall rate	13/50 (26%)	24/50 (48%)
Adjusted rate	46.8%	72.1%
Terminal rate	1/9 (11%)	2/5 (40%)
First incidence (days)	208	169
Life table test		P=0.007
Logistic regression test		P=0.297
Fisher exact test		P=0.019
All Organs: Benign Neoplasms		
Overall rate	41/50 (82%)	34/50 (68%)
Adjusted rate	100.0%	100.0%
Terminal rate	9/9 (100%)	5/5 (100%)
First incidence (days)	399	327
Life table test		P=0.191
Logistic regression test		P=0.119
Fisher exact test		P=0.083N
All Organs: Malignant Neoplasms		
Overall rate	43/50 (86%)	49/50 (98%)
Adjusted rate	95.3%	100.0%
Terminal rate	7/9 (78%)	5/5 (100%)
First incidence (days)	208	169
Life table test		P=0.010
Logistic regression test		P=0.020
Fisher exact test		P=0.030
All Organs: Benign or Malignant Neoplasms		
Overall rate	49/50 (98%)	49/50 (98%)
Adjusted rate	100.0%	100.0%
Terminal rate	9/9 (100%)	5/5 (100%)
First incidence (days)	208	169
Life table test		P=0.040
Logistic regression test		P=0.509
Fisher exact test		P=0.753N

TABLE C3b
Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 200 ppm (40-Week) Exposure Group versus 625 ppm (13-Week) Exposure Group (continued)

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, epididymis, gallbladder, heart, kidney, larynx, liver, lung, nose, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE C3c
Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 312 ppm (52-Week) Exposure Group versus 625 ppm (26-Week) Exposure Group

	312 ppm (52 weeks)	625 ppm (26 weeks)
Harderrian Gland: Adenoma		
Overall rate[a]	28/50 (56%)	13/50 (26%)
Adjusted rate[b]	100.0%	100.0%
Terminal rate[c]	1/1 (100%)	0/0
First incidence (days)	344	306
Life table test[d]		P=0.051
Logistic regression test[d]		P=0.533N
Fisher exact test[d]		P=0.002N
Harderrian Gland: Carcinoma		
Overall rate	2/50 (4%)	0/50 (0%)
Adjusted rate	51.5%	0.0%
Terminal rate	0/1 (0%)	0/0
First incidence (days)	441	-[e]
Life table test		P=0.663N
Logistic regression test		P=0.507N
Fisher exact test		P=0.247N
Harderrian Gland: Adenoma or Carcinoma		
Overall rate	30/50 (60%)	13/50 (26%)
Adjusted rate	100.0%	100.0%
Terminal rate	1/1 (100%)	0/0
First incidence (days)	344	306
Life table test		P=0.068
Logistic regression test		P=0.404N
Fisher exact test		P<0.001N
Heart: Hemangiosarcoma		
Overall rate	33/50 (66%)	13/50 (26%)
Adjusted rate	100.0%	100.0%
Terminal rate	1/1 (100%)	0/0
First incidence (days)	328	306
Life table test		P=0.032N
Logistic regression test		P=0.021N
Fisher exact test		P<0.001N
Kidney (Renal Tubule): Adenoma		
Overall rate	3/49 (6%)	1/50 (2%)
Adjusted rate	27.8%	6.3%
Terminal rate	0/1 (0%)	0/0
First incidence (days)	539	440
Life table test		P=0.655
Logistic regression test		P=0.627N
Fisher exact test		P=0.301N

TABLE C3c
Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 312 ppm (52-Week) Exposure Group versus 625 ppm (26-Week) Exposure Group (continued)

	312 ppm (52 weeks)	625 ppm (26 weeks)
Liver: Hepatocellular Adenoma		
Overall rate	19/50 (38%)	11/50 (22%)
Adjusted rate	100.0%	100.0%
Terminal rate	1/1 (100%)	0/0
First incidence (days)	326	313
Life table test		P=0.017
Logistic regression test		P=0.395
Fisher exact test		P=0.063N
Liver: Hepatocellular Carcinoma		
Overall rate	10/50 (20%)	4/50 (8%)
Adjusted rate	74.6%	50.5%
Terminal rate	0/1 (0%)	0/0
First incidence (days)	382	483
Life table test		P=0.328
Logistic regression test		P=0.520N
Fisher exact test		P=0.074N
Liver: Hepatocellular Adenoma or Carcinoma		
Overall rate	24/50 (48%)	13/50 (26%)
Adjusted rate	100.0%	100.0%
Terminal rate	1/1 (100%)	0/0
First incidence (days)	326	313
Life table test		P=0.023
Logistic regression test		P=0.536
Fisher exact test		P=0.019N
Liver: Hepatocellular Hepatoblastoma or Carcinoma		
Overall rate	11/50 (22%)	4/50 (8%)
Adjusted rate	77.1%	50.5%
Terminal rate	0/1 (0%)	0/0
First incidence (days)	382	483
Life table test		P=0.354
Logistic regression test		P=0.466N
Fisher exact test		P=0.045N
Liver: Hepatoblastoma, Hepatocellular Adenoma, or Carcinoma		
Overall rate	25/50 (50%)	13/50 (26%)
Adjusted rate	100.0%	100.0%
Terminal rate	1/1 (100%)	0/0
First incidence (days)	326	313
Life table test		P=0.026
Logistic regression test		P=0.580
Fisher exact test		P=0.011N

TABLE C3c
Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 312 ppm (52-Week) Exposure Group versus 625 ppm (26-Week) Exposure Group (continued)

	312 ppm (52 weeks)	625 ppm (26 weeks)
Lung: Alveolar/bronchiolar Adenoma		
Overall rate	26/50 (52%)	12/50 (24%)
Adjusted rate	100.0%	100.0%
Terminal rate	1/1 (100%)	0/0
First incidence (days)	344	358
Life table test		P=0.062
Logistic regression test		P=0.452N
Fisher exact test		P=0.004N
Lung: Alveolar/bronchiolar Adenocarcinoma or Carcinoma		
Overall rate	16/50 (32%)	11/50 (22%)
Adjusted rate	100.0%	100.0%
Terminal rate	1/1 (100%)	0/0
First incidence (days)	392	241
Life table test		P=0.005
Logistic regression test		P=0.124
Fisher exact test		P=0.184N
Lung: Alveolar/bronchiolar Adenoma, Adenocarcinoma, or Carcinoma		
Overall rate	32/50 (64%)	17/50 (34%)
Adjusted rate	100.0%	100.0%
Terminal rate	1/1 (100%)	0/0
First incidence (days)	344	241
Life table test		P=0.013
Logistic regression test		P=0.570
Fisher exact test		P=0.002N
Preputial Gland: Carcinoma		
Overall rate	4/50 (8%)	3/50 (6%)
Adjusted rate	100.0%	100.0%
Terminal rate	1/1 (100%)	0/0
First incidence (days)	639	539
Life table test		P=0.003
Logistic regression test		P=0.018
Fisher exact test		P=0.271N
Stomach (Forestomach): Squamous Cell Papilloma		
Overall rate	4/50 (8%)	4/50 (8%)
Adjusted rate	100.0%	20.1%
Terminal rate	1/1 (100%)	0/0
First incidence (days)	401	359
Life table test		P=0.097
Logistic regression test		P=0.440
Fisher exact test		P=0.643N

TABLE C3c
Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 312 ppm (52-Week) Exposure Group versus 625 ppm (26-Week) Exposure Group (continued)

	312 ppm (52 weeks)	625 ppm (26 weeks)
Stomach (Forestomach): Squamous Cell Carcinoma		
Overall rate	5/50 (10%)	6/50 (12%)
Adjusted rate	33.1%	40.9%
Terminal rate	0/1 (0%)	0/0
First incidence (days)	422	288
Life table test		P=0.015
Logistic regression test		P=0.271
Fisher exact test		P=0.500
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma		
Overall rate	9/50 (18%)	10/50 (20%)
Adjusted rate	100.0%	52.8%
Terminal rate	1/1 (100%)	0/0
First incidence (days)	401	288
Life table test		P=0.003
Logistic regression test		P=0.188
Fisher exact test		P=0.500
Zymbal's Gland: Carcinoma		
Overall rate	0/50 (0%)	2/50 (4%)
Adjusted rate	0.0%	37.3%
Terminal rate	0/1 (0%)	0/0
First incidence (days)	–	429
Life table test		P=0.044
Logistic regression test		P=0.117
Fisher exact test		P=0.247
All Organs: Hemangiosarcoma		
Overall rate	34/50 (68%)	14/50 (28%)
Adjusted rate	100.0%	100.0%
Terminal rate	1/1 (100%)	0/0
First incidence (days)	328	306
Life table test		P=0.190
Logistic regression test		P=0.053N
Fisher exact test		P<0.001N
All Organs: Hemangioma or Hemangiosarcoma		
Overall rate	34/50 (68%)	14/50 (28%)
Adjusted rate	100.0%	100.0%
Terminal rate	1/1 (100%)	0/0
First incidence (days)	328	306
Life table test		P=0.190
Logistic regression test		P=0.053N
Fisher exact test		P<0.001N

TABLE C3c
Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 312 ppm (52-Week) Exposure Group versus 625 ppm (26-Week) Exposure Group (continued)

	312 ppm (52 weeks)	625 ppm (26 weeks)
All Organs: Lymphocytic Malignant Lymphoma		
Overall rate	4/50 (8%)	30/50 (60%)
Adjusted rate	100.0%	81.5%
Terminal rate	1/1 (100%)	0/0
First incidence (days)	289	159
Life table test		P<0.001
Logistic regression test		P<0.001
Fisher exact test		P<0.001
All Organs: Malignant Lymphoma (Mixed or NOS)		
Overall rate	4/50 (8%)	3/50 (6%)
Adjusted rate	58.0%	43.3%
Terminal rate	0/1 (0%)	0/0
First incidence (days)	217	251
Life table test		P=0.244
Logistic regression test		P=0.613
Fisher exact test		P=0.500N
All Organs: Malignant Lymphoma (Lymphocytic, Mixed, or NOS)		
Overall rate	8/50 (16%)	33/50 (66%)
Adjusted rate	100.0%	89.5%
Terminal rate	1/1 (100%)	0/0
First incidence (days)	217	159
Life table test		P<0.001
Logistic regression test		P=0.002
Fisher exact test		P<0.001
All Organs: Histiocytic Sarcoma		
Overall rate	7/50 (14%)	2/50 (4%)
Adjusted rate	43.0%	15.6%
Terminal rate	0/1 (0%)	0/0
First incidence (days)	314	364
Life table test		P=0.610N
Logistic regression test		P=0.160N
Fisher exact test		P=0.080N
All Organs: Malignant Lymphoma and Histiocytic Sarcoma		
Overall rate	15/50 (30%)	35/50 (70%)
Adjusted rate	100.0%	91.2%
Terminal rate	1/1 (100%)	0/0
First incidence (days)	217	159
Life table test		P<0.001
Logistic regression test		P=0.033
Fisher exact test		P<0.001

TABLE C3c
Statistical Analysis of Primary Neoplasms in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene: 312 ppm (52-Week) Exposure Group versus 625 ppm (26-Week) Exposure Group (continued)

	312 ppm (52 weeks)	625 ppm (26 weeks)
All Organs: Benign Neoplasms		
Overall rate	41/50 (82%)	22/50 (44%)
Adjusted rate	100.0%	100.0%
Terminal rate	1/1 (100%)	0/0
First incidence (days)	326	306
Life table test		P=0.012
Logistic regression test		P=0.643N
Fisher exact test		P<0.001N
All Organs: Malignant Neoplasms		
Overall rate	50/50 (100%)	49/50 (98%)
Adjusted rate	100.0%	100.0%
Terminal rate	1/1 (100%)	0/0
First incidence (days)	217	159
Life table test		P<0.001
Logistic regression test		P=0.626N
Fisher exact test		P=0.500N
All Organs: Benign or Malignant Neoplasms		
Overall rate	50/50 (100%)	49/50 (98%)
Adjusted rate	100.0%	100.0%
Terminal rate	1/1 (100%)	0/0
First incidence (days)	217	159
Life table test		P<0.001
Logistic regression test		P=0.626N
Fisher exact test		P=0.500N

[a] Number of neoplasm-bearing animals/number of animals examined.Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, epididymis, gallbladder, heart, kidney, larynx, liver, lung, nose, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE C4
Two-Year Historical Incidence of Renal Tubule Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Northwest Laboratories			
Allyl glycidyl ether	0/49	0/49	0/49
p-Chloroacetophenone	0/50	0/50	0/50
Epinephrine hydrochloride	0/50	0/50	0/50
Ethyl chloride	0/50	0/50	0/50
p-Chlorobenzalmalononitrile (CS2)	0/49	0/49	0/49
Overall Historical Incidence			
Total	1/571 (0.2%)	0/571 (0.0%)	1/571 (0.2%)
Standard deviation	0.3%		0.3%
Range	0%-1%		0%-1%

[a] Data as of 3 April 1991

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene[a]

	200 ppm (40 weeks)	312 ppm (52 weeks)	625 ppm (13 weeks)	625 ppm (26 weeks)
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths			1	
Moribund	29	25	25	22
Natural deaths	12	24	19	28
Survivors				
Terminal sacrifice	9	1	5	
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(40)	(27)	(32)	(32)
Hyperplasia	1 (3%)		1 (3%)	
Intestine large, colon	(44)	(44)	(44)	(45)
Necrosis				1 (2%)
Intestine small, duodenum	(42)	(38)	(35)	(32)
Hemorrhage				1 (3%)
Intestine small, ileum	(44)	(40)	(37)	(40)
Angiectasis		1 (3%)		
Peyer's patch, hyperplasia		1 (3%)		
Intestine small, jejunum	(43)	(37)	(40)	(41)
Hemorrhage				1 (2%)
Peyer's patch, hyperplasia	1 (2%)			
Peyer's patch, necrosis				1 (2%)
Liver	(49)	(50)	(49)	(50)
Angiectasis	1 (2%)	1 (2%)	1 (2%)	
Basophilic focus	3 (6%)	2 (4%)	1 (2%)	
Clear cell focus	1 (2%)			
Degeneration, fatty		1 (2%)		2 (4%)
Eosinophilic focus	1 (2%)	4 (8%)	1 (2%)	3 (6%)
Hematopoietic cell proliferation	1 (2%)	4 (8%)	3 (6%)	9 (18%)
Infarct	2 (4%)	1 (2%)	3 (6%)	
Inflammation, chronic				1 (2%)
Inflammation, granulomatous, focal	2 (4%)		1 (2%)	
Mixed cell focus	1 (2%)			
Necrosis	8 (16%)	13 (26%)	10 (20%)	14 (28%)
Thrombosis		2 (4%)		
Biliary tract, cyst			2 (4%)	
Biliary tract, hyperplasia		2 (4%)		
Biliary tract, hypertrophy				1 (2%)
Centrilobular, degeneration, fatty	1 (2%)	4 (8%)	1 (2%)	1 (2%)
Centrilobular, necrosis		7 (14%)	1 (2%)	1 (2%)
Mesentery	(13)	(13)	(11)	(4)
Fat, angiectasis	6 (46%)	3 (23%)	2 (18%)	
Fat, hemorrhage		1 (8%)	1 (9%)	1 (25%)
Fat, inflammation, chronic	3 (23%)	1 (8%)		
Fat, necrosis	1 (8%)		2 (18%)	1 (25%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene (continued)

	200 ppm (40 weeks)	312 ppm (52 weeks)	625 ppm (13 weeks)	625 ppm (26 weeks)
Alimentary System (continued)				
Pancreas	(46)	(49)	(46)	(49)
Acinus, atrophy	1 (2%)	1 (2%)		1 (2%)
Acinus, focal cellular change	3 (7%)	2 (4%)		
Acinus, hyperplasia	1 (2%)	3 (6%)		
Acinus, vacuolization cytoplasmic		1 (2%)		
Pharynx	(1)			(2)
Palate, inflammation, chronic	1 (100%)			
Salivary glands	(48)	(48)	(50)	(50)
Infiltration cellular, mixed cell				1 (2%)
Inflammation			2 (4%)	
Stomach, forestomach	(48)	(48)	(50)	(50)
Angiectasis	1 (2%)			
Ulcer	3 (6%)	4 (8%)	2 (4%)	2 (4%)
Epithelium, hyperplasia	10 (21%)	20 (42%)	8 (16%)	15 (30%)
Stomach, glandular	(44)	(47)	(44)	(47)
Pigmentation, hemosiderin	2 (5%)	7 (15%)	3 (7%)	4 (9%)
Ulcer	2 (5%)	3 (6%)	1 (2%)	4 (9%)
Tooth	(6)		(4)	
Inflammation	6 (100%)		3 (75%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	2 (4%)	1 (2%)	1 (2%)	4 (8%)
Hemorrhage				1 (2%)
Inflammation, suppurative				2 (4%)
Mineralization		6 (12%)	9 (18%)	14 (28%)
Necrosis		1 (2%)		1 (2%)
Atrium, thrombosis		1 (2%)		1 (2%)
Endothelium, hyperplasia	6 (12%)	3 (6%)	7 (14%)	7 (14%)
Pericardium, inflammation, chronic	1 (2%)		1 (2%)	
Ventricle, thrombosis				1 (2%)
Endocrine System				
Adrenal gland, cortex	(45)	(49)	(50)	(50)
Focal cellular change	4 (9%)	1 (2%)		
Hematocyst		1 (2%)		
Hematopoietic cell proliferation				1 (2%)
Hyperplasia	5 (11%)	4 (8%)		1 (2%)
Hypertrophy	10 (22%)	12 (24%)	9 (18%)	2 (4%)
Adrenal gland, medulla	(45)	(48)	(49)	(48)
Hematopoietic cell proliferation				1 (2%)
Islets, pancreatic	(46)	(49)	(45)	(48)
Cytoplasmic alteration		1 (2%)		
Hyperplasia	3 (7%)	1 (2%)		1 (2%)
Parathyroid gland	(40)	(44)	(33)	(37)
Cyst	1 (3%)			

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene (continued)

	200 ppm (40 weeks)	312 ppm (52 weeks)	625 ppm (13 weeks)	625 ppm (26 weeks)
Endocrine System (continued)				
Pituitary gland	(44)	(43)	(43)	(43)
Pars distalis, cyst	1 (2%)	1 (2%)	2 (5%)	
Pars distalis, hemorrhage			1 (2%)	
Pars distalis, hyperplasia	1 (2%)		1 (2%)	
Thyroid gland	(48)	(49)	(50)	(49)
Cyst	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Hemorrhage	1 (2%)			
Inflammation	1 (2%)			
Follicular cell, hyperplasia	2 (4%)	1 (2%)	2 (4%)	
General Body System				
None				
Genital System				
Epididymis	(49)	(50)	(49)	(50)
Angiectasis				1 (2%)
Hypospermia	4 (8%)			
Infiltration cellular, mixed cell				1 (2%)
Inflammation, chronic		3 (6%)	1 (2%)	
Muscularis, hyperplasia	1 (2%)			
Penis	(4)			
Inflammation, suppurative	1 (25%)			
Preputial gland	(8)	(4)	(10)	(6)
Angiectasis		1 (25%)		
Degeneration, cystic	1 (13%)		1 (10%)	
Hyperplasia			2 (20%)	
Inflammation, suppurative	3 (38%)		6 (60%)	3 (50%)
Duct, dilatation	1 (13%)			
Prostate	(44)	(48)	(48)	(47)
Inflammation				1 (2%)
Inflammation, suppurative	3 (7%)		2 (4%)	
Seminal vesicle	(44)	(47)	(42)	(47)
Inflammation, suppurative	2 (5%)		1 (2%)	
Testes	(50)	(50)	(50)	(50)
Angiectasis		4 (8%)	1 (2%)	
Atrophy	5 (10%)	3 (6%)	3 (6%)	5 (10%)
Degeneration	2 (4%)			2 (4%)
Mineralization	2 (4%)			
Interstitial cell, hyperplasia			1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(49)	(48)	(49)
Angiectasis		1 (2%)		
Atrophy		5 (10%)	3 (6%)	2 (4%)
Fibrosis		1 (2%)		
Hyperplasia	9 (18%)	9 (18%)	11 (23%)	8 (16%)
Necrosis				1 (2%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene (continued)

	200 ppm (40 weeks)	312 ppm (52 weeks)	625 ppm (13 weeks)	625 ppm (26 weeks)
Hematopoietic System (continued)				
Lymph node	(50)	(50)	(49)	(50)
Axillary, hematopoietic cell proliferation				1 (2%)
Iliac, hematopoietic cell proliferation				1 (2%)
Iliac, hyperplasia			1 (2%)	
Inguinal, hematopoietic cell proliferation				1 (2%)
Pancreatic, hyperplasia				1 (2%)
Lymph node, bronchial	(43)	(37)	(40)	(41)
Congestion	1 (2%)			
Hematopoietic cell proliferation		2 (5%)		2 (5%)
Hyperplasia	5 (12%)	1 (3%)	1 (3%)	
Lymph node, mandibular	(42)	(31)	(39)	(43)
Hematopoietic cell proliferation	1 (2%)			2 (5%)
Hyperplasia	9 (21%)	3 (10%)	7 (18%)	
Necrosis				1 (2%)
Lymph node, mediastinal	(39)	(41)	(39)	(44)
Congestion				1 (2%)
Hematopoietic cell proliferation	1 (3%)	2 (5%)		3 (7%)
Hyperplasia	1 (3%)	2 (5%)	1 (3%)	
Inflammation	1 (3%)			
Lymph node, mesenteric	(44)	(44)	(43)	(48)
Angiectasis	7 (16%)	1 (2%)	2 (5%)	1 (2%)
Congestion	2 (5%)	1 (2%)	2 (5%)	
Hematopoietic cell proliferation	5 (11%)	2 (5%)	4 (9%)	1 (2%)
Hyperplasia	3 (7%)	1 (2%)		
Inflammation				1 (2%)
Spleen	(47)	(48)	(49)	(50)
Angiectasis			1 (2%)	
Depletion lymphoid		1 (2%)		
Hematopoietic cell proliferation	12 (26%)	21 (44%)	18 (37%)	18 (36%)
Hemorrhage				1 (2%)
Hyperplasia, lymphoid			2 (4%)	
Necrosis				1 (2%)
Thrombosis	1 (2%)			
Thymus	(41)	(37)	(37)	(40)
Infiltration cellular, mixed cell				1 (3%)
Inflammation, suppurative		1 (3%)		
Necrosis	14 (34%)	30 (81%)	10 (27%)	10 (25%)
Mediastinum, necrosis				1 (3%)
Integumentary System				
Skin	(50)	(49)	(50)	(50)
Cyst epithelial inclusion		1 (2%)		1 (2%)
Inflammation, chronic	2 (4%)	1 (2%)		1 (2%)
Hair follicle, atrophy		1 (2%)		1 (2%)
Prepuce, inflammation, suppurative	5 (10%)		2 (4%)	
Sebaceous gland, hyperplasia			1 (2%)	
Subcutaneous tissue, angiectasis	1 (2%)	1 (2%)		
Subcutaneous tissue, edema	1 (2%)	1 (2%)	1 (2%)	
Subcutaneous tissue, hemorrhage		3 (6%)	2 (4%)	1 (2%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene (continued)

	200 ppm (40 weeks)	312 ppm (52 weeks)	625 ppm (13 weeks)	625 ppm (26 weeks)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Developmental malformation	2 (4%)			
Osteopetrosis	1 (2%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hemorrhage	4 (8%)	6 (12%)	2 (4%)	3 (6%)
Inflammation, chronic	1 (2%)			
Mineralization	15 (30%)	9 (18%)	12 (24%)	6 (12%)
Necrosis		1 (2%)		2 (4%)
Pigmentation, hemosiderin		1 (2%)		
Respiratory System				
Larynx	(46)	(49)	(49)	(47)
Inflammation, suppurative	1 (2%)	1 (2%)		
Metaplasia, squamous				1 (2%)
Lung	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)			
Hemorrhage	3 (6%)	7 (14%)	5 (10%)	10 (20%)
Hyperplasia, lymphoid	1 (2%)			
Inflammation, chronic, focal			1 (2%)	
Inflammation, focal, chronic		1 (2%)		2 (4%)
Inflammation, suppurative	2 (4%)			2 (4%)
Thrombosis				1 (2%)
Alveolar epithelium, hyperplasia	18 (36%)	14 (28%)	10 (20%)	11 (22%)
Alveolus, infiltration cellular, histiocyte	18 (36%)	12 (24%)	9 (18%)	3 (6%)
Alveolus, pigmentation, hemosiderin		1 (2%)	1 (2%)	
Bronchiole, epithelium, hyperplasia		1 (2%)		
Pleura, inflammation, chronic	1 (2%)			1 (2%)
Nose	(49)	(49)	(50)	(50)
Inflammation, suppurative	14 (29%)	7 (14%)	7 (14%)	1 (2%)
Nasolacrimal duct, inflammation, suppurative	6 (12%)	8 (16%)	8 (16%)	1 (2%)
Nerve, hyperplasia			1 (2%)	
Olfactory epithelium, atrophy		2 (4%)	2 (4%)	1 (2%)
Respiratory epithelium, metaplasia, squamous		1 (2%)		
Trachea	(47)	(47)	(48)	(48)
Inflammation, suppurative	20 (43%)	12 (26%)	11 (23%)	7 (15%)
Special Senses System				
Eye	(1)	(4)	(4)	(3)
Degeneration			1 (25%)	
Cornea, hyperplasia		1 (25%)		
Cornea, inflammation, chronic		2 (50%)	2 (50%)	

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the Stop-Exposure Inhalation Study of 1,3-Butadiene (continued)

	200 ppm (40 weeks)	312 ppm (52 weeks)	625 ppm (13 weeks)	625 ppm (26 weeks)
Special Senses System (continued)				
Harderian gland	(48)	(48)	(42)	(36)
Hyperplasia	4 (8%)	6 (13%)	3 (7%)	7 (19%)
Inflammation, chronic		1 (2%)		
Urinary System				
Kidney	(48)	(49)	(50)	(50)
Cyst		1 (2%)	1 (2%)	
Hematopoietic cell proliferation				1 (2%)
Hemorrhage			1 (2%)	2 (4%)
Infarct				1 (2%)
Infiltration cellular, histiocyte	1 (2%)			
Inflammation, suppurative	1 (2%)		4 (8%)	1 (2%)
Metaplasia, osseous			1 (2%)	
Nephropathy	12 (25%)	4 (8%)	10 (20%)	4 (8%)
Pigmentation, hemosiderin	1 (2%)			
Capsule, angiectasis		1 (2%)		
Capsule, inflammation, chronic		1 (2%)		
Renal tubule, hyperplasia	4 (8%)	1 (2%)	1 (2%)	2 (4%)
Renal tubule, mineralization			1 (2%)	
Urinary bladder	(43)	(47)	(46)	(48)
Dilatation	8 (19%)		3 (7%)	
Inflammation	1 (2%)		1 (2%)	
Transitional epithelium, hyperplasia	2 (5%)	1 (2%)		

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

APPENDIX D
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA DESICCATOR PROTOCOL

A modification of the technique reported by Zeiger (1990) was used to expose the bacteria to gaseous 1,3-butadiene. Details of the *Salmonella* gas exposure protocol are presented in Zeiger *et al.* (1992). 1,3-Butadiene was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). The minimal glucose agar plates with the *Salmonella typhimurium* tester strains (TA97, TA98, TA100, and TA1535) either alone or with S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) were placed, without lids, in glass desiccator jars. All plates exposed to a particular concentration of butadiene, both with and without S9, were treated simultaneously in the same desiccator. The desiccators were then sealed and partially evacuated to allow the addition of the gas/air mixture. 1,3-Butadiene was equilibrated with air and introduced through valves into the sealed desiccators. The desiccators were incubated at 37° C for 48 hours. Each trial consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of 1,3-butadiene. The high dose was limited by toxicity. A positive response in the *S. typhimurium* assay is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants which is not dose-related, not reproducible, or is of insufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment.

MOUSE LYMPHOMA PROTOCOL

The experimental protocol is presented in detail by McGregor *et al.* (1991). 1,3-Butadiene was supplied as a coded aliquot by Radian Corporation. The high dose of 1,3-butadiene was determined by toxicity. Mouse lymphoma L5178Y cells were maintained at 37° C as suspension cultures in Fischer's medium supplemented with 2 mM *l*-glutamine, 110 μg/mL sodium pyruvate, 0.05% pluronic F68, antibiotics, and heat-inactivated horse serum; normal cycling time was about 10 hours. To reduce the number of spontaneously occurring trifluorothymidine (TFT) resistant cells, subcultures were exposed once to medium containing THMG (thymidine, hypoxanthine, methotrexate, glycine) for 1 day, to THG for 1 day, and to normal medium for 3 to 5 days. For cloning, horse serum content was increased and Noble agar was added. Freshly prepared S9 metabolic activation factors were obtained from the livers of either Aroclor 1254-induced or noninduced Fischer 344/N male rats.

All treatment levels within an experiment, including concurrent positive and solvent controls, were replicated. Treated cultures contained 6×10^6 cells in a 10 mL volume of medium. This volume included the S9 fraction in those experiments performed with metabolic activation. Cultures were housed in sterile plastic tubes closed with a tightly fitted Suba-seal cap, through which the 1,3-butadiene/air mixture was introduced. Tubes were partially evacuated so that internal pressure returned to ambient upon introduction of the 1,3-butadiene/air mixture. Incubation continued for 4 hours; during this time, the tubes were rotated on a horizontal axis roller drum. After the 4-hour incubation, the cultures were transferred to 50 mL sterile screw-capped tubes where cells were centrifuged, washed, and resuspended in 20 mL of fresh medium and incubated for an additional 48 hours to express the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine for selection of TFT-resistant cells ($TK^{+/-}$), and 600 cells were plated in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37° C in 5% CO_2 for 11 to 14 days. All data were evaluated statistically for both trend and peak response (for details, see McGregor *et al.*, 1988). Both responses had to be significant ($P<0.05$) for a chemical to be considered capable of inducing TFT resistance, a single significant response led to a "questionable" conclusion, and the absence of both a trend and a peak response resulted in a "negative" call. Minimum criteria for accepting an experiment as valid and a

detailed description of the statistical analysis and data evaluation are presented in Myhr *et al.* (1985). This assay was initially performed without S9; because a clearly positive response was not obtained, the experiment was repeated with induced S9.

DROSOPHILA PROTOCOL

The assays for induction of gene mutations were performed as described in Zimmering *et al.* (1985). 1,3-Butadiene was supplied as a coded aliquot from Radian Corporation. Toxicity tests were performed to set concentrations of 1,3-butadiene at a level that would induce approximately 30% mortality after 72 hours of exposure while keeping induced sterility at an acceptable level. For the sex-linked recessive lethal (SLRL) mutation test, Canton-S males (10 to 20 flies/vial) were exposed to 1,3-butadiene vapors for 72 hours. Exposed males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three matings of 3, 2, and 2 days; sample sperm from successive matings were treated at successively earlier post-meiotic stages. F_1 heterozygous females were allowed to mate with their siblings then placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters. (A cluster occurs when a number of mutants from a given male result from a single spontaneous premeiotic mutation event, and is identified when the number of mutants from that male exceeds the number predicted by a Poisson distribution.) If a cluster was identified, all data from the male in question were discarded. Presumptive lethal mutations were identified as vials containing no wild-type males after 17 days; these were retested.

Recessive lethal data were analyzed by the normal approximation to the binomial test (Margolin *et al.*, 1983). A test result was considered to be positive if the P value was less than 0.01 and the mutation frequency in the tested group was greater than 10%, or if the P value was less than 0.05 and the frequency in the treatment group was greater than 15%. A test was considered to be inconclusive if (a) the P value was between 0.05 and 0.01 but the frequency in the treatment group was between 10% and 15%, or (b) the P value was between 0.10 and 0.05 but the frequency in the treatment group was greater than 10%. A result was considered to be negative if the P value was greater than 0.10 or if the frequency in the treatment group was less than 10%.

IN VIVO MOUSE BONE MARROW CYTOGENETICS ASSAYS

Details of the protocols for the 2-week exposure studies for induction of chromosomal aberrations (Abs), sister chromatid exchanges (SCE), and micronuclei are presented in Tice *et al.* (1987). Briefly, male $B6C3F_1$ mice (12 animals/dose group) were exposed to ambient air or to 1,3-butadiene (6.25, 62.5, or 625 ppm) for 6 hours per day, excluding weekends, for a total of 10 exposures (total elapsed time = 15 days). One hour before the final exposure, a 50 mg bromodeoxyuridine tablet was implanted subcutaneously in each lightly anesthetized mouse (McFee *et al.*, 1983), and 2 hours before sacrifice, the mice received an intraperitoneal (IP) injection of 2 mg/kg colchicine (in saline). Peripheral blood smears for micronucleus analysis were prepared at the time of colchicine injection and processed as described below. Mice were killed 19.5 to 23.5 hours after implantation of BrdU to ensure sufficient numbers of first- and second-division cells for both chromosomal aberration and sister chromatid exchange analyses. Mice were killed by cervical dislocation; both femurs were removed and the marrow was flushed out with 5 mL phosphate-buffered saline (pH 7.4). The cells were treated with a hypotonic salt solution, fixed, and dropped onto chilled slides. Following a 24-hour drying period, the slides were stained by a modified (Tice *et al.*, 1987) fluorescence-plus-Giemsa method (Goto *et al.*, 1982) and scored. Twenty-five second-division metaphase cells were scored per animal for SCEs and 50 first-division metaphase cells were scored per animal for Abs. Responses were evaluated as SCEs per cell or, for Abs, as the percentage of aberrant metaphase cells, excluding gaps. The number of aberrations per cell (excluding gaps) was also analyzed to provide information on the extent of individual cell damage. The data were analyzed by a one-tailed trend test (Margolin *et al.*, 1986).

MOUSE PERIPHERAL BLOOD MICRONUCLEUS ASSAY

A detailed discussion of this assay, as it was conducted for the 13-week and 15-month exposure periods, is presented in Choy *et al.* (1986). The protocol for the 2-week study is presented in detail in Tice *et al.* (1987). Peripheral blood samples were obtained from male and female B6C3F$_1$ mice at the termination of the 2- and 13-week and 15-month studies. Smears were immediately prepared and fixed in absolute methanol. For the 2-week exposure study, the slides were stained with acridine-orange according to the method of Kato (1974), and for the 13-week and 15-month studies, the slides were stained with a chromatin-specific fluorescent dye mixture of Hoechst 33258/pyronin Y (MacGregor *et al.*, 1983) and coded. Slides were scanned to determine, for each animal per dose group, the frequency of micronuclei in 1,000 polychromatic erythrocytes (PCE) and 1,000 or 10,000 normochromatic erythrocytes (NCE). (NCE counts are for the 2-week exposures and the longer exposures, respectively.) In addition, the percent PCE among the total erythrocyte population was determined. For the 2-week exposure, a one-tailed trend test (Margolin *et al.*, 1986) was used to analyze the PCE and NCE data, and for the percent PCE data, a two-tailed trend test was used to determine if a treatment-related effect had occurred. Pairwise comparisons between individual dose groups and the concurrent control were conducted using Student's *t*-test with a Bonferroni correction for multiple comparisons. For the 13-week and 15-month studies, the frequency of micronuclei per NCE was analyzed by analysis of variance using the SAS GLM procedure after performing a log-transformation of the data and testing for normality by the Shapiro-Wilk test (SAS PROC UNIVARIATE) and for heterogeneity of variance by Cochran's test. Individual contrasts for the NCE data involved negative controls versus each dose group and linear trends without positive controls. These contrasts were evaluated using Student's t-test. The Cochran-Armitage trend test was used to analyze the PCE data. The percent PCE among total erythrocytes was analyzed using a test of variance on ranks (classed by sex), and a t-test on ranks was used to compare percent PCE in individual dose groups with their concurrent negative controls.

RESULTS

1,3-Butadiene was mutagenic in *S. typhimurium* strain TA1535 when tested as a gas in a sealed desiccator chamber, with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Table D1). The positive response observed with TA1535 in the absence of exogenous metabolic activation was unexpected and may, in fact, be an artifact of the exposure protocol. All plates to be exposed to a particular concentration of 1,3-butadiene, with or without S9, were housed together in a single desiccator and treated simultaneously. Previous investigations demonstrated that such an arrangement produced positive responses in cultures that did not contain S9 activation enzymes, whereas removing the S9-containing plates from the desiccator and treating only those cultures that did not contain S9 resulted in no increase in mutations (de Meester *et al.*, 1980). The induction of mutations in the cultures that did not contain S9 was believed to be caused by the formation of a volatile mutagenic intermediate in the S9-containing plates that migrated to the plates without S9. No mutagenic activity was detected for 1,3-butadiene in strain TA100, TA97, or TA98 under the same conditions.

No mutagenic activity was observed in the mouse lymphoma L5178Y cell assay, with or without Aroclor 1254-induced male Fischer rat liver S9 (Table D2; McGregor *et al.*, 1991). The maximum dose was 30% in air (v/v). One possible factor in the lack of mutagenic activity is the low solubility of 1,3-butadiene in the cell culture medium, which may have prevented adequate exposure. 1,3-Butadiene did not induce a significant increase in SLRL mutations in germ cells of male *D. melanogaster* exposed by inhalation to 360,000 ppm in air (Table D3).

Positive results were obtained with 1,3-butadiene in cytogenetic tests with mammalian cells *in vivo*. Significant increases in the frequency of Abs (Table D4) and SCEs (Table D5) were observed in bone marrow cells of male mice exposed for 2 weeks to 1,3-butadiene (6.25 to 625 ppm in air). For both tests, the trend analyses were significant; both the mid- and high-dose animals showed increases in SCEs, while only the high-dose mice had elevated levels of chromosomal Abs. In addition, cell cycle time was significantly lengthened as doses of 1,3-butadiene were increased, as indicated by the average generation

time measurements (Table D5). Peripheral blood smears prepared from these same animals (exposed to 1,3-butadiene by inhalation for 2 weeks) revealed significant increases in micronucleated PCEs and NCEs (Table D6). Elevations in the frequency of micronucleated PCEs (a measure of acute exposure) were observed in the mid- and high-dose mice, while only the high-dose mice showed a statistically significant increase in micronucleated NCEs; for both types of cells, the trend analyses were significant. The rate of erythropoiesis was increased in exposed mice, particularly at the 625 ppm dose level, as indicated by the increase in percent PCEs in the total erythrocyte population in the peripheral blood (Table D6). This, along with the increase in average generation time (Table D5), indicates cellular (bone marrow) toxicity induced by 1,3-butadiene. The frequencies of micronucleated PCEs and NCEs were also scored in peripheral blood samples of male and female mice exposed for 13 weeks (Table D7) or 15 months (Table D8) to 6.25 to 625 ppm 1,3-butadiene; both exposure regimens produced positive results in each sex. Also, the percent of PCEs in female mice exposed for 15 months to 1,3-butadiene was elevated at the two highest concentrations tested, which produced a positive trend (Table D8).

TABLE D1
Mutagenicity of 1,3-Butadiene in *Salmonella typhimurium*[a]

Strain	Dose (moles/liter)	Revertants/plate[b] -S9	+30% hamster S9	+30% rat S9
TA100	0.000	82 ± 2.4	109 ± 12.2	101 ± 11.9
	0.014	85 ± 8.5	109 ± 5.0	120 ± 12.6
	0.020	79 ± 5.0	115 ± 6.2	72 ± 3.8
	0.026	79 ± 4.3	78 ± 4.7	82 ± 3.1
	0.030	71 ± 6.9	84 ± 14.2	107 ± 9.0
	0.033	66 ± 10.8	114 ± 9.5	106 ± 5.2
Trial summary		Negative	Negative	Negative
Positive control[c]		391 ± 13.5	477 ± 1.5	844 ± 25.7
TA97	0.000	163 ± 15.8	188 ± 4.8	163 ± 6.2
	0.002	115 ± 4.7	175 ± 5.4	216 ± 7.8
	0.007	152 ± 5.2	194 ± 4.8	208 ± 2.6
	0.014	172 ± 3.4	162 ± 4.1	216 ± 9.9
	0.020	128 ± 5.8	154 ± 3.7	188 ± 12.3
	0.030	99 ± 5.7	165 ± 4.9	197 ± 9.5
Trial summary		Negative	Negative	Equivocal
Positive control		460 ± 19.2	875 ± 19.2	489 ± 12.2

Strain	Dose (moles/liter)	Revertants/plate -S9 Trial 1	-S9 Trial 2	+30% hamster S9	+30% rat S9 Trial 1	+30% rat S9 Trial 2
TA98	0.000	12 ± 2.0	11 ± 1.5	11 ± 1.5	22 ± 2.3	23 ± 3.9
	0.004		15 ± 3.7			23 ± 2.0
	0.007		13 ± 3.7			14 ± 2.7
	0.009		9 ± 1.5			17 ± 2.0
	0.014	6 ± 1.5	11 ± 1.0	10 ± 1.2	15 ± 0.9	19 ± 2.0
	0.020	7 ± 1.0	9 ± 0.9	12 ± 0.3	13 ± 1.0	13 ± 2.4
	0.026	6 ± 1.5		9 ± 1.7	9 ± 1.8	
	0.030	3 ± 1.5		10 ± 1.5	8 ± 1.8	
	0.033	4 ± 0.3		8 ± 1.8	13 ± 1.0	
Trial summary		Negative	Negative	Negative	Negative	Negative
Positive control		207 ± 26.7	170 ± 9.9	419 ± 8.4	240 ± 9.9	183 ± 15.1

TABLE D1
Mutagenicity of 1,3-Butadiene in *Salmonella typhimurium* (continued)

Strain	Dose (moles/liter)	Revertants/plate -S9 Trial 1	-S9 Trial 2	+30% hamster S9 Trial 1	+30% hamster S9 Trial 2	+30% rat S9 Trial 1	+30% rat S9 Trial 2
TA1535	0.000	11 ± 2.1	11 ± 2.0	15 ± 3.7	22 ± 0.7	12 ± 1.8	26 ± 3.2
	0.002	49 ± 3.1	95 ± 4.3	82 ± 8.1	142 ± 10.5	70 ± 9.3	94 ± 3.3
	0.007	84 ± 8.7	125 ± 8.1	116 ± 4.0	152 ± 13.4	122 ± 8.8	149 ± 15.9
	0.014	108 ± 1.2	171 ± 13.2	165 ± 5.6	224 ± 4.4	134 ± 6.0	189 ± 13.9
	0.020	113 ± 2.6	148 ± 9.9	180 ± 4.7	221 ± 9.7	144 ± 2.7	171 ± 8.7
	0.030	117 ± 6.4	115 ± 1.5	176 ± 5.2	226 ± 11.0	158 ± 4.3	152 ± 1.5
Trial summary		Positive	Positive	Positive	Positive	Positive	Positive
Positive control		189 ± 11.0	358 ± 14.5	95 ± 6.9	161 ± 8.4	130 ± 6.1	123 ± 25.5

[a] Study performed at Microbiological Associates. A detailed description of the protocol is presented in Zeiger *et al.* (1992). Cells and 1,3-butadiene or solvent (air) were incubated in the absence of exogenous metabolic activation (-S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague-Dawley rat liver. High dose was limited by toxicity; 0 mol/L dose is the control (air).

[b] Revertants are presented as mean ± standard error from three plates.

[c] 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was tested on TA98, sodium azide was tested on TA100 and TA1535, and 9-aminoacridine was tested on TA97.

TABLE D2
Induction of Trifluorothymidine Resistance in Mouse L5178Y Lymphoma Cells by 1,3-Butadiene[a]

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction[b]	Average Mutant Fraction[c]
-S9						
Trial 1						
Air		84	96	43	17	
		99	99	72	24	
		87	91	46	18	
		107	115	51	16	19
Methylmethanesulfonate	15	41	20	159	128	
		37	20	158	141	135[d]
1,3-Butadiene	2.5	107	111	68	21	
		86	112	61	24	22
	5	74	92	60	27	
		89	91	50	19	23
	10	95	92	53	19	
		82	104	59	24	21
	20	101	91	85	28	
		98	95	63	22	25
	30	91	90	61	22	
		94	89	47	17	20
Trial 2						
Air		99	96	61	21	
		101	103	56	18	
		89	108	43	16	
		104	92	93	30	21
Methylmethanesulfonate	15	33	24	191	194	
		41	31	225	184	189[d]
1,3-Butadiene	2.5	112	101	37	11	
		112	100	57	17	14
	5	86	90	72	28	
		97	97	54	18	23
	10	98	94	91	31	
		94	92	72	25	28
	20	112	88	75	22	
		93	76	42	15	19
	30	92	74	53	19	
		98	79	72	25	22

TABLE D2
Induction of Trifluorothymidine Resistance in Mouse L5178Y Lymphoma Cells by 1,3-Butadiene (continued)

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
+S9[c]						
Trial 1						
Air		83	91	51	20	
		70	79	62	30	
		88	97	78	30	
		107	133	52	16	24
Methylcolanthrene	2.5	39	30	281	240	
		40	24	255	213	227[d]
1,3-Butadiene	2.5	75	87	55	25	
		76	49	78	34	29
	5	97	58	79	27	
		91	50	82	30	29
	10	82	91	54	22	
		76	62	97	43	32
	20	66	62	49	25	
		81	72	72	30	27
	30	90	65	93	35	
		80	69	80	33	34
Trial 2						
Air		88	104	60	23	
		93	97	65	23	
		87	101	35	13	
		81	98	39	16	19
Methylcolanthrene	2.5	39	30	281	240	
		40	24	255	213	227[d]
1,3-Butadiene	2.5	71	80	40	19	
		98	86	43	15	17
	5	92	85	62	22	
		64	84	61	32	27
	10	78	87	98	42	
		82	99	40	16	29
	20	81	80	66	27	
		73	75	65	30	28
	30	68	75	75	37	
		76	76	57	26	31

TABLE D2
Induction of Trifluorothymidine Resistance in Mouse L5178Y Lymphoma Cells by 1,3-Butadiene (continued)

[a] Study performed at Inveresk Research International. The detailed protocol and these data are presented in McGregor *et al.* (1991). All doses were tested in duplicate; the average of the tests is presented in the table. Cells (6×10^5/mL) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.
[b] Mutant fraction (frequency) is a ratio of the mutant count to the cloning efficiency, divided by 3 (to arrive at MF/10^6 cells treated); MF=mutant fraction.
[c] Mean standard error from three replicate plates of approximately 10^6 cells each.
[d] Significant positive response ($P<0.05$)
[e] Tests conducted with metabolic activation were performed as described in [a] except that S9, prepared from the livers of Aroclor 1254-induced Fischer 344/N rats, was added at the same time as 1,3-butadiene and/or solvent.

TABLE D3
Induction of Sex-Linked Recessive Lethal Mutations in *Drosophila melanogaster* by 1,3-Butadiene[a]

Route of Exposure	Dose (ppm)	Incidence of Deaths (percent)	Incidence of Sterility (percent)	No. of Lethals/No. of X Chromosomes Tested			Total[b]
				Mating 1	Mating 2	Mating 3	
Inhalation	360,000	15	17	4/2,495	0/1,992	2/1,516	6/6,003 (0.10%)
	0			2/2,347	0/1,964	2/1,934	4/6,245 (0.06%)

[a] Study performed at University of Wisconsin, Madison. A detailed protocol of the sex-linked recessive lethal assay is presented in Zimmering *et al.* (1985). Exposed males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three broods of 3, 2, and 2 days. Sample sperm from successive matings were treated as spermatozoa (mating 1), spermatids (mating 2), and spermatocytes (mating 3). F_1 heterozygous females were crossed to their siblings and placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters; no clusters were found. Presumptive lethal mutations were identified as vials containing no wild-type males; after 17 days, these were retested. Results were not significant at the 5% level (Margolin *et al.*, 1983).

[b] Combined total number of lethal mutations/number of X chromosomes tested for three mating trials

TABLE D4
Induction of Chromosomal Aberrations in Mouse Bone Marrow Cells by 1,3-Butadiene[a]

Compound	Dose (ppm)	Aberrations/ Cell	Percent Cells with Abs
Air[b]		0.023 ± 0.0085	2.3 ± 0.85
1,3-Butadiene	6.25	0.016 ± 0.0036	1.6 ± 0.36
	62.5	0.033 ± 0.0125	3.3 ± 1.25
	625.0	0.178 ± 0.0450	14.0 ± 3.18
Trend test[c]		P<0.001	P<0.001

[a] Study performed at Brookhaven National Laboratories. The detailed protocol and these data are presented in Tice *et al.* (1987). 1,3-Butadiene was administered by inhalation, for 6 hours a day, 5 days a week for 2 weeks (total elapsed time of 15 days) to male B6C3F_1 mice. Fifty first-division metaphases were scored from each of 12 animals per dose group. Gaps were scored, but not used in the analysis of the data presented in this table. Data are presented as the mean ± standard error.

[b] Solvent control

[c] One-tailed trend test (Margolin *et al.*, 1986); significant at P<0.05.

TABLE D5
Induction of Sister Chromatid Exchanges in Mouse Bone Marrow Cells by 1,3-Butadiene[a]

Compound	Dose ppm	Mean SCEs/Cell	Average Generation Time[b]
Air[c]		5.51 ± 0.292	11.52 ± 0.382
1,3-Butadiene	6.25	6.49 ± 0.206	12.45 ± 0.362
	62.5	10.88 ± 0.398	13.31 ± 0.406
	625	35.09 ± 1.757	15.38 ± 0.482
		P<0.001[d]	P<0.001[d]

[a] Study performed at Brookhaven National Laboratories. The detailed protocol and these data are presented in Tice *et al.* (1987). 1,3-Butadiene was administered by inhalation, 6 hours a day, 5 days a week for 2 weeks (total elapsed time = 15 days) to male B6C3F$_1$ mice. Twenty-five second-division metaphases were scored from each of 12 animals per dose group. Data are presented as mean ± the standard error.
[b] Average cell generation time (in hours) based on 100 metaphase cells analyzed per animal.
[c] Solvent control
[d] One-tailed trend analysis (Margolin *et al.*, 1986); significant at P<0.05.

TABLE D6
Induction of Micronuclei in Peripheral Blood Erythrocytes of Male Mice Exposed for 2 Weeks to 1,3-Butadiene[a]

Compound	Dose (ppm)	Micronucleated Cells/1,000 Cells[b] PCE	NCE	PCE[b] (%)	Number of Mice
Control		3.75 ± 0.592	2.67 ± 0.414	2.78 ± 0.015	12
1,3-Butadiene	6.25	5.50 ± 0.417	3.33 ± 0.497	2.43 ± 0.023	12
	62.5	8.64 ± 0.789*	4.00 ± 0.618	3.08 ± 0.018	12
	625	30.00 ± 1.267*	7.17 ± 0.869	4.33 ± 0.038*	12
		P<0.001[c]	P<0.001[c]	P<0.001[d]	

* P<0.001. significant at alpha=0.017 (alpha=0.05 Bonferroni-corrected for three pairwise comparisons); pairwise comparison of dose group to control made by one-tailed Pearson chi-square for normochromatic and polychromatic erythrocytes and by two-tailed t-test for %PCE.
[a] Study performed at Brookhaven National Laboratories. The detailed protocol and these data are presented in Tice *et al*, (1987). Male B6C3F$_1$ mice were exposed to 1,3-butadiene or air (solvent control) for 6 hours a day, 5 days a week for 2 weeks (total duration of 15 days). At least 1,000 PCE and 1,000 NCE were scored per animal.
[b] Data presented as mean ± standard error.
[c] One-tailed trend test (Margolin *et al.*, 1986); significant at P<0.05.
[d] Two-tailed trend test, using individual animal data

TABLE D7
Induction of Micronuclei in Peripheral Blood Erythrocytes of Mice Exposed for 13 Weeks to 1,3-Butadiene[a]

Compound	Dose (ppm)	Micronucleated Cells/1,000 Cells[b] PCE	NCE	Number of Mice
Male				
Control		1.22 ± 0.29	1.83 ± 0.17	10
1,3-Butadiene	6.25		2.47 ± 0.19**	10
	62.5	5.72 ± 0.82**	4.80 ± 0.34**	10
	625	18.66 ± 1.01**	15.92 ± 0.84**	10
Female				
Control		1.88 ± 0.27	1.39 ± 0.15	10
1,3-Butadiene	6.25		1.83 ± 0.12*	10
	62.5	5.51 ± 0.62**	3.88 ± 0.18**	10
	625	14.10 ± 0.55**	11.72 ± 0.36**	10

* $P<0.05$ by Student's t-test for normochromatic erythrocyte analysis or Kastenbaum and Bowman binomial comparison for polychromatic erythrocyte analysis
** $P<0.01$ by Student's t-test
[a] Smears were prepared from peripheral blood samples obtained by cardiac puncture of dosed and control animals at the termination of the 13-week studies. Slides were stained with Hoechst 33258/pyronin Y (MacGregor *et al.*, 1983). At least 1,000 PCE and 10,000 NCE from each animal were scored for micronuclei.
[b] Values are presented as mean ± standard error.

TABLE D8
Induction of Micronuclei in Peripheral Blood Erythrocytes of Mice Exposed for 15 Months to 1,3-Butadiene[a]

Compound	Dose (ppm)	Micronucleated Cells/1,000 Cells[b] PCE	NCE	PCE[b] (%)	Number of Mice
Male					
Control		1.26 ± 0.25	1.60 ± 0.13	1.70 ± 0.09	10
1,3-Butadiene	6.25	2.21 ± 0.28	2.03 ± 0.13	1.70 ± 0.12	10
	20	2.98 ± 0.64**	2.04 ± 0.10*	1.99 ± 0.12	10
	62.5	3.81 ± 0.57**	2.25 ± 0.20**	1.72 ± 0.14	10
	200	3.93 ± 0.55**	3.45 ± 0.21**	1.85 ± 0.05	10
	625	9.18 ± 1.44**	7.36 ± 0.59**	2.47 ± 0.56*	7
		P<0.001[c]	P<0.001[c]	P=0.162[d]	
Female					
Control		1.20 ± 0.32	111 ± 0.13	1.84 ± 0.19	10
1,3-Butadiene	6.25	0.93 ± 0.31	1.17 ± 0.10	1.46 ± 0.16	10
	20	2.19 ± 0.37	1.24 ± 0.13	1.56 ± 0.13	10
	62.5	2.45 ± 0.35*	1.70 ± 0.18**	1.54 ± 0.12	10
	200	5.89 ± 0.95**	3.29 ± 0.33**	5.16 ± 2.19	10
	625	10.68 ± 1.04**	7.13 ± 0.85**	8.51 ± 3.95	2
		P<0.001[c]	P<0.001[c]	P=0.015[d]	

* P<0.05. Group means vs. the control by Kastenbaum-Bowman's binomial test for polychromatic erythrocytes or all Student *t*-tests for normochromatic erythrocytes or t-tests on ranks for percent PCE.
** P<0.01
[a] Smears of peripheral blood samples obtained by cardiac puncture of dosed and control animals at the termination of 15 months of exposure to butadiene. Slides were stained with Hoechst 33258/Pyronin Y (MacGregor *et al.*, 1983). At least 1,000 PCE and 10,000 NCE were scored per animal.
[b] Values are mean ± standard error.
[c] Cochran-Armitage linear regression of proportions for PCEs or linear contrasts from analysis of variance for NCEs.
[d] Analysis of variance on ranks

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

TABLE E1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 9-Month Interim Evaluation in the 2-Year Inhalation Study of 1,3-Butadiene[a]

	0 ppm	6.25 ppm	20 ppm	62.5 ppm	200 ppm	625 ppm
Male						
n	10	10	10	10	10	10
Necropsy body wt	40.4 ± 1.0	40.2 ± 1.3	41.8 ± 1.6	36.5 ± 2.0	40.2 ± 1.1	37.5 ± 1.6
Brain						
Absolute	0.480 ± 0.006	0.487 ± 0.005	0.484 ± 0.003	0.474 ± 0.006	0.477 ± 0.003	0.455 ± 0.004**
Relative	11.91 ± 0.22	12.22 ± 0.34	11.74 ± 0.44	13.40 ± 0.82	11.92 ± 0.28	12.30 ± 0.43
Heart						
Absolute	0.175 ± 0.007	0.178 ± 0.005	0.173 ± 0.004	0.170 ± 0.006	0.158 ± 0.005	0.173 ± 0.006
Relative	4.32 ± 0.12	4.46 ± 0.14	4.18 ± 0.12	4.77 ± 0.29	3.93 ± 0.06	4.65 ± 0.17
R. Kidney						
Absolute	0.363 ± 0.011	0.358 ± 0.016	0.361 ± 0.009	0.350 ± 0.011	0.359 ± 0.009	0.349 ± 0.011
Relative	8.99 ± 0.24	8.90 ± 0.19	8.71 ± 0.23	9.83 ± 0.57	8.93 ± 0.10	9.44 ± 0.47
Liver						
Absolute	1.537 ± 0.085	1.465 ± 0.066	1.518 ± 0.080	1.377 ± 0.069	1.484 ± 0.070	1.529 ± 0.060
Relative	37.83 ± 1.34	36.40 ± 0.88	36.30 ± 1.03	38.13 ± 1.46	36.77 ± 0.97	40.95 ± 1.02
Lungs						
Absolute	0.226 ± 0.007	0.226 ± 0.007	0.226 ± 0.008	0.211 ± 0.007	0.219 ± 0.006	0.230 ± 0.008
Relative	5.59 ± 0.13	5.66 ± 0.20	5.47 ± 0.25	5.92 ± 0.33	5.47 ± 0.18	6.20 ± 0.25
Spleen						
Absolute	0.066 ± 0.005	0.064 ± 0.003	0.059 ± 0.002	0.064 ± 0.005	0.060 ± 0.002	0.085 ± 0.019
Relative	1.63 ± 0.11	1.60 ± 0.08	1.42 ± 0.04	1.84 ± 0.23	1.49 ± 0.04	2.22 ± 0.42
R. Testis						
Absolute	0.117 ± 0.002	0.117 ± 0.003	0.114 ± 0.003	0.103 ± 0.004**	0.102 ± 0.002**	0.059 ± 0.003**
Relative	2.89 ± 0.06	2.92 ± 0.09	2.76 ± 0.09	2.87 ± 0.12	2.54 ± 0.05**	1.57 ± 0.03**
Thymus						
Absolute	0.039 ± 0.007	0.036 ± 0.006	0.032 ± 0.002	0.033 ± 0.008	0.033 ± 0.005	0.024 ± 0.005[b]
Relative	0.97 ± 0.18	0.90 ± 0.14	0.77 ± 0.05	0.87 ± 0.18	0.82 ± 0.13	0.63 ± 0.14[b]

TABLE E1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 9-Month Interim Evaluation in the 2-Year Inhalation Study of 1,3-Butadiene (continued)

	0 ppm	6.25 ppm	20 ppm	62.5 ppm	200 ppm	625 ppm
Female						
n	10	10	10	10	10	8
Necropsy body wt	33.6 ± 2.3	34.7 ± 1.4	32.3 ± 1.7	36.8 ± 1.8	38.5 ± 2.1	35.7 ± 1.2
Brain						
Absolute	0.498 ± 0.006	0.491 ± 0.005	0.497 ± 0.005	0.491 ± 0.005	0.484 ± 0.005	0.469 ± 0.008**
Relative	15.42 ± 1.03	14.38 ± 0.65	15.73 ± 0.75	13.62 ± 0.68	12.90 ± 0.69*	13.20 ± 0.41*
Heart						
Absolute	0.131 ± 0.003	0.133 ± 0.003	0.132 ± 0.003	0.134 ± 0.003	0.135 ± 0.002	0.149 ± 0.008**
Relative	4.03 ± 0.24	3.88 ± 0.14	4.15 ± 0.14	3.70 ± 0.17	3.60 ± 0.20	4.18 ± 0.21
R. Kidney						
Absolute	0.222 ± 0.008	0.229 ± 0.005	0.235 ± 0.007	0.238 ± 0.005	0.238 ± 0.006	0.258 ± 0.009**
Relative	6.77 ± 0.31	6.65 ± 0.19	7.38 ± 0.27	6.57 ± 0.29	6.33 ± 0.34	7.23 ± 0.21
Liver						
Absolute	1.280 ± 0.043	1.339 ± 0.036	1.345 ± 0.032	1.430 ± 0.032**	1.464 ± 0.037**	1.509 ± 0.055**
Relative	39.04 ± 1.66	39.00 ± 1.48	42.31 ± 1.58	39.34 ± 1.29	38.69 ± 1.55	42.26 ± 0.90
Lungs						
Absolute	0.236 ± 0.007	0.227 ± 0.006	0.242 ± 0.009	0.228 ± 0.007	0.226 ± 0.007	0.251 ± 0.015
Relative	7.26 ± 0.43	6.62 ± 0.28	7.60 ± 0.32	6.35 ± 0.41	6.00 ± 0.32	7.08 ± 0.44
Spleen						
Absolute	0.090 ± 0.010	0.077 ± 0.004	0.080 ± 0.003	0.082 ± 0.003	0.070 ± 0.002*	0.081 ± 0.005[c]
Relative	2.72 ± 0.28	2.24 ± 0.12	2.51 ± 0.11	2.27 ± 0.12*	1.85 ± 0.07**	2.30 ± 0.14**[c]
Thymus						
Absolute	0.030 ± 0.002	0.028 ± 0.002	0.029 ± 0.003	0.029 ± 0.001	0.028 ± 0.002	0.019 ± 0.002**[d]
Relative	0.91 ± 0.03	0.81 ± 0.06	0.91 ± 0.08	0.81 ± 0.05	0.74 ± 0.04*	0.54 ± 0.06**[d]

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9
[c] n=7
[d] n=8

TABLE E2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Inhalation Study of 1,3-Butadiene[a]

	0 ppm	6.25 ppm	20 ppm	62.5 ppm	200 ppm	625 ppm
Male						
n	10	10	10	10	10	7
Necropsy body wt	44.3 ± 1.2	40.7 ± 1.3	41.9 ± 1.2	42.3 ± 1.0	42.1 ± 1.4	39.5 ± 2.1
Brain						
Absolute	0.478 ± 0.005	0.464 ± 0.006	0.468 ± 0.006	0.477 ± 0.004	0.453 ± 0.006**	0.434 ± 0.006**
Relative	10.84 ± 0.23	11.48 ± 0.34	11.22 ± 0.25	11.31 ± 0.22	10.87 ± 0.36	11.18 ± 0.62
Heart						
Absolute	0.187 ± 0.008	0.176 ± 0.005	0.190 ± 0.004	0.192 ± 0.006	0.186 ± 0.006	0.179 ± 0.009
Relative	4.21 ± 0.12	4.34 ± 0.13	4.55 ± 0.10	4.53 ± 0.06	4.45 ± 0.15	4.56 ± 0.26
R. Kidney						
Absolute	0.376 ± 0.013	0.352 ± 0.006	0.370 ± 0.010	0.391 ± 0.016	0.370 ± 0.010	0.359 ± 0.016
Relative	8.50 ± 0.24	8.70 ± 0.22	8.86 ± 0.25	9.22 ± 0.24	8.85 ± 0.24	9.13 ± 0.30
Liver						
Absolute	1.519 ± 0.067	1.493 ± 0.101	1.596 ± 0.084	1.540 ± 0.045	1.628 ± 0.092	2.254 ± 0.346**
Relative	34.16 ± 0.82	37.55 ± 4.03	38.05 ± 1.65	36.38 ± 0.67	38.71 ± 1.74	58.78 ± 9.97**
Lungs						
Absolute	0.245 ± 0.010	0.223 ± 0.007	0.244 ± 0.007	0.257 ± 0.024	0.259 ± 0.020	0.309 ± 0.039*
Relative	5.54 ± 0.20	5.50 ± 0.15	5.84 ± 0.17	6.04 ± 0.49	6.13 ± 0.35	8.19 ± 1.42**
Spleen						
Absolute	0.064 ± 0.005	0.056 ± 0.003	0.054 ± 0.003	0.068 ± 0.004	0.071 ± 0.006	0.114 ± 0.031**
Relative	1.44 ± 0.08	1.39 ± 0.09	1.29 ± 0.06	1.63 ± 0.14	1.69 ± 0.12	2.95 ± 0.85**
R. Testis						
Absolute	0.116 ± 0.003	0.113 ± 0.003	0.104 ± 0.004	0.112 ± 0.003	0.100 ± 0.003**	0.071 ± 0.004**
Relative	2.62 ± 0.07	2.79 ± 0.08	2.48 ± 0.04	2.66 ± 0.07	2.39 ± 0.05*	1.80 ± 0.05**
Thymus						
Absolute	0.063 ± 0.006	0.050 ± 0.005	0.060 ± 0.007	0.059 ± 0.004	0.051 ± 0.005	0.054 ± 0.007
Relative	1.40 ± 0.10	1.21 ± 0.10	1.40 ± 0.13	1.39 ± 0.10	1.20 ± 0.12	1.37 ± 0.15

TABLE E2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Inhalation Study of 1,3-Butadiene (continued)

	0 ppm	6.25 ppm	20 ppm	62.5 ppm	200 ppm	625 ppm
Female						
n	10	10	10	10	10	2
Necropsy body wt	41.2 ± 2.9	39.2 ± 2.2	39.6 ± 2.3	47.1 ± 1.8	43.8 ± 1.7	40.5 ± 0.4
Brain						
Absolute	0.482 ± 0.006	0.491 ± 0.005	0.497 ± 0.004	0.496 ± 0.004	0.480 ± 0.005	0.440 ± 0.020**
Relative	12.21 ± 0.82	12.92 ± 0.78	13.01 ± 0.91	10.71 ± 0.52	11.10 ± 0.43	10.87 ± 0.40
Heart						
Absolute	0.141 ± 0.003	0.137 ± 0.004	0.154 ± 0.010	0.157 ± 0.003	0.177 ± 0.009**	0.175 ± 0.005*
Relative	3.55 ± 0.22	3.56 ± 0.14	4.03 ± 0.37	3.37 ± 0.11	4.05 ± 0.17	4.33 ± 0.16
R. Kidney						
Absolute	0.247 ± 0.007	0.252 ± 0.009	0.257 ± 0.004	0.274 ± 0.008*	0.274 ± 0.012*	0.270 ± 0.000
Relative	6.21 ± 0.37	6.56 ± 0.32	6.71 ± 0.44	5.88 ± 0.21	6.34 ± 0.36	6.68 ± 0.06
Liver						
Absolute	1.438 ± 0.067	1.342 ± 0.050	1.399 ± 0.023	1.528 ± 0.040	1.943 ± 0.239**	1.590 ± 0.030
Relative	35.67 ± 1.49	34.72 ± 1.13	36.38 ± 2.10	32.74 ± 1.08	43.79 ± 4.20	39.30 ± 0.40
Lungs						
Absolute	0.229 ± 0.006	0.239 ± 0.007	0.238 ± 0.004	0.238 ± 0.005	0.292 ± 0.036*	0.300 ± 0.050
Relative	5.76 ± 0.33	6.23 ± 0.33	6.18 ± 0.34	5.11 ± 0.19	6.73 ± 0.86	7.43 ± 1.30
Spleen						
Absolute	0.087 ± 0.005	0.083 ± 0.004	0.095 ± 0.005	0.091 ± 0.007	0.135 ± 0.020**	0.205 ± 0.015**
Relative	2.16 ± 0.12	2.17 ± 0.15	2.46 ± 0.17	1.99 ± 0.20	3.14 ± 0.53	5.07 ± 0.41**
Thymus						
Absolute	0.042 ± 0.004	0.036 ± 0.003	0.040 ± 0.003	0.056 ± 0.005	0.046 ± 0.006	0.035 ± 0.003
Relative	1.05 ± 0.10	0.91 ± 0.07	1.03 ± 0.07	1.17 ± 0.09	1.04 ± 0.13	0.85 ± 0.05

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

APPENDIX F
HEMATOLOGY AND CLINICAL CHEMISTRY RESULTS

TABLE F1
Hematology and Clinical Chemistry Data for Mice at the 9-Month Interim Evaluation in the 2-Year Inhalation Study of 1,3-Butadiene[a]

	0 ppm	6.25 ppm	20 ppm	62.5 ppm	200 ppm	625 ppm
Male						
n	10	10	10	10	10	10
Hematology						
Packed red cell volume (mL/dL)	48.1 ± 0.5	47.8 ± 0.5	48.2 ± 0.7	45.9 ± 0.7*	45.4 ± 0.9**	39.9 ± 1.7**
Hemoglobin (g/dL)	16.5 ± 0.1	16.4 ± 0.2	16.7 ± 0.2	15.9 ± 0.2*	15.6 ± 0.3**	13.5 ± 0.6**
Erythrocytes (10^6/μL)	10.38 ± 0.09	10.29 ± 0.10	10.40 ± 0.13	9.86 ± 0.12**	9.60 ± 0.14**	7.55 ± 0.38**
Howell-Jolly bodies (% erythrocytes)	0.29 ± 0.10	0.20 ± 0.04	0.27 ± 0.05	0.29 ± 0.07	0.34 ± 0.08	0.85 ± 0.13**
Mean cell volume (fL)	46.3 ± 0.3	46.4 ± 0.3	46.3 ± 0.3	46.7 ± 0.4	47.2 ± 0.3	53.2 ± 0.9**
Mean cell hemoglobin (pg)	15.9 ± 0.1	16.0 ± 0.1	16.1 ± 0.1	16.1 ± 0.1	16.2 ± 0.1*	17.9 ± 0.3**
Mean cell hemoglobin concentration (g/dL)	34.4 ± 0.1	34.4 ± 0.1	34.7 ± 0.4	34.6 ± 0.2	34.3 ± 0.1	33.7 ± 0.2*
Platelets (10^3/μL)	979.7 ± 30.1	1,003.7 ± 24.2	1,028.9 ± 25.6	1,040.5 ± 61.4	1,030.4 ± 52.1	1,197.5 ± 94.6**
Reticulocytes (10^6/μL)	0.11 ± 0.02	0.06 ± 0.01	0.10 ± 0.01	0.12 ± 0.02	0.08 ± 0.02	0.11 ± 0.02
Leukocytes (10^3/μL)	2.71 ± 0.38	1.69 ± 0.17*	2.35 ± 0.30	2.15 ± 0.39	1.53 ± 0.12**	1.56 ± 0.12**
Segmented neutrophils (10^3/μL)	1.20 ± 0.39	0.61 ± 0.13	0.88 ± 0.13	0.88 ± 0.19	0.54 ± 0.05*	0.57 ± 0.08
Lymphocytes (10^3/μL)	1.45 ± 0.12	1.04 ± 0.08**	1.42 ± 0.17	1.21 ± 0.20	0.96 ± 0.10*	0.96 ± 0.09*
Monocytes (10^3/μL)	0.06 ± 0.02	0.04 ± 0.01	0.05 ± 0.01	0.07 ± 0.03	0.03 ± 0.01	0.04 ± 0.01
Eosinophils (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Nucleated erythrocytes/100 leukocytes	0.00 ± 0.00	0.20 ± 0.20	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Clinical Chemistry						
Creatine kinase (U/L)	664.7 ± 154.0[b]	922.8 ± 222.0	935.5 ± 146.0	1003.2 ± 227.0	783.6 ± 131.0	737.2 ± 146.3
Creatine kinase-1 (%)	15.23 ± 2.13	13.22 ± 2.59[b]	15.50 ± 1.81	14.97 ± 2.14	13.58 ± 2.24	13.28 ± 1.32
Creatine kinase-2 (%)	16.07 ± 3.11	9.20 ± 1.37[b]	13.54 ± 1.98	11.61 ± 1.85	9.43 ± 1.03	11.02 ± 1.77
Creatine kinase-3 (%)	68.70 ± 4.44	77.58 ± 2.13[b]	70.95 ± 2.54	73.42 ± 3.68	76.99 ± 2.83	75.69 ± 2.60
Lactate dehydrogenase (IU/L)	445 ± 49	495 ± 30	577 ± 76	485 ± 38	466 ± 53	406 ± 53
LDH-1 (%)	13 ± 1	13 ± 1	12 ± 1	14 ± 1	13 ± 1	14 ± 1

TABLE F1
Hematology and Clinical Chemistry Data for Mice at the 9-Month Interim Evaluation in the 2-Year Inhalation Study of 1,3-Butadiene (continued)

	0 ppm	6.25 ppm	20 ppm	62.5 ppm	200 ppm	625 ppm
Male (continued)						
n	10	10	10	10	10	10
Clinical Chemistry (continued)						
LDH-2 (%)	9 ± 1	9 ± 0	9 ± 1	8 ± 0	9 ± 0	8 ± 0
LDH-3 (%)	11 ± 0	11 ± 0	11 ± 1	11 ± 0	11 ± 0	10 ± 0*
LDH-4 (%)	9 ± 0	9 ± 0	9 ± 0	9 ± 1	9 ± 0	10 ± 1
LDH-5 (%)	57 ± 1	59 ± 1	59 ± 2	58 ± 2	58 ± 1	58 ± 1
Female						
n	10	10	10	10	10	8
Hematology						
Packed red cell volume (mL/dL)	47.7 ± 1.5	49.6 ± 0.3	49.7 ± 0.5	49.1 ± 0.4	47.1 ± 0.3**	40.5 ± 2.0**
Hemoglobin (g/dL)	15.8 ± 0.5	16.5 ± 0.1	16.4 ± 0.2	16.3 ± 0.1	15.5 ± 0.1**	13.3 ± 0.7**
Erythrocytes (10^6/μL)	9.93 ± 0.33	10.25 ± 0.05	10.27 ± 0.08	10.12 ± 0.07	9.39 ± 0.07**	7.31 ± 0.50**
Howell-Jolly bodies (% erythrocytes)	0.08 ± 0.03	0.09 ± 0.04	0.12 ± 0.03	0.17 ± 0.04	0.34 ± 0.06**	0.64 ± 0.07**
Mean cell volume (fL)	48.0 ± 0.3	48.4 ± 0.2	48.3 ± 0.2	48.6 ± 0.3	50.2 ± 0.1**	55.9 ± 1.5**
Mean cell hemoglobin (pg)	15.9 ± 0.1	16.1 ± 0.1	16.0 ± 0.1	16.1 ± 0.1	16.5 ± 0.1**	18.4 ± 0.4**
Mean cell hemoglobin concentration (g/dL)	33.2 ± 0.1	33.2 ± 0.1	33.0 ± 0.1	33.2 ± 0.1	32.9 ± 0.1	32.9 ± 0.2
Platelets (10^3/μL)	912.0 ± 30.8	867.7 ± 12.1	879.9 ± 25.6	827.3 ± 14.9	892.6 ± 14.5	944.0 ± 70.0
Reticulocytes (10^6/μL)	0.09 ± 0.01	0.11 ± 0.01	0.09 ± 0.01	0.09 ± 0.01	0.07 ± 0.01	0.09 ± 0.02
Leukocytes (10^3/μL)	2.31 ± 0.34	2.11 ± 0.23	2.71 ± 0.30	2.09 ± 0.18	1.51 ± 0.16*	1.56 ± 0.18*
Segmented neutrophils (10^3/μL)	0.73 ± 0.13	0.66 ± 0.09	0.87 ± 0.09	0.66 ± 0.08	0.50 ± 0.08	0.53 ± 0.16
Lymphocytes (10^3/μL)	1.53 ± 0.24	1.39 ± 0.17	1.75 ± 0.22	1.39 ± 0.13	0.98 ± 0.11*	1.00 ± 0.15
Monocytes (10^3/μL)	0.05 ± 0.01	0.05 ± 0.01	0.09 ± 0.03	0.04 ± 0.01	0.03 ± 0.01	0.04 ± 0.01
Eosinophils (10^3/μL)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.003 ± 0.002*	0.001 ± 0.001
Nucleated erythrocytes/100 leukocytes	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00

TABLE F1
Hematology and Clinical Chemistry Data for Mice at the 9-Month Interim Evaluation in the 2-Year Inhalation Study of 1,3-Butadiene (continued)

	0 ppm	6.25 ppm	20 ppm	62.5 ppm	200 ppm	625 ppm
Female (continued)						
n	10	10	10	10	10	8
Clinical Chemistry						
Creatine kinase (U/L)	868.0 ± 195.0	660.0 ± 129.0	747.7 ± 142.0	583.2 ± 80.1	682.6 ± 101.0	448.9 ± 77.1
Creatine kinase-1 (%)	16.73 ± 2.63	18.81 ± 2.32	14.27 ± 1.96[b]	14.45 ± 2.28	14.14 ± 1.36	15.30 ± 1.92
Creatine kinase-2 (%)	12.55 ± 2.51	12.88 ± 2.17	7.32 ± 0.94[b]	12.89 ± 2.34	12.02 ± 2.22	8.88 ± 1.37
Creatine kinase-3 (%)	70.72 ± 4.42	68.31 ± 3.90	78.41 ± 2.53[b]	72.65 ± 4.01	73.83 ± 3.34	75.82 ± 2.86
Lactate dehydrogenase (IU/L)	275 ± 24	261 ± 18	294 ± 33	282 ± 23	314 ± 32	323 ± 38
LDH-1 (%)	17 ± 1	17 ± 2	16 ± 1	15 ± 1	13 ± 1*	13 ± 2
LDH-2 (%)	9 ± 1	9 ± 1	10 ± 1	8 ± 0	8 ± 0	7 ± 1*
LDH-3 (%)	9 ± 0	10 ± 1	10 ± 1	9 ± 0	9 ± 0	9 ± 0
LDH-4 (%)	9 ± 1	10 ± 1	10 ± 1	8 ± 0	9 ± 0	8 ± 1
LDH-5 (%)	56 ± 2	54 ± 2	55 ± 2	60 ± 1	61 ± 2	63 ± 2*

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error. LDH=lactate dehydrogenase
[b] n=9

TABLE F2
Hematology and Clinical Chemistry Data for Mice at the 15-Month Interim Evaluation in the 2-Year Inhalation Study of 1,3-Butadiene[a]

	0 ppm	6.25 ppm	20 ppm	62.5 ppm	200 ppm	625
Male						
n	10	10	10	10	10	7
Hematology						
Packed red cell volume (mL/dL)	45.4 ± 0.6	44.9 ± 0.8	46.1 ± 0.6	45.1 ± 0.4	44.0 ± 1.4	35.7 ± 2.0**
Hemoglobin (g/dL)	16.0 ± 0.3	15.5 ± 0.1	15.7 ± 0.2	15.5 ± 0.2	15.7 ± 0.6*	12.2 ± 0.6**
Erythrocytes ($10^6/\mu L$)	10.02 ± 0.12	9.92 ± 0.22	10.07 ± 0.15	9.73 ± 0.08	9.80 ± 0.47*	7.38 ± 0.40**
Howell-Jolly bodies (% erythrocytes)	0.24 ± 0.05	0.21 ± 0.04	0.29 ± 0.08	0.20 ± 0.05	0.31 ± 0.05	0.51 ± 0.11
Mean cell volume (fL)	45.3 ± 0.3	45.3 ± 0.9	45.8 ± 0.5	46.4 ± 0.2*	45.1 ± 0.6	48.4 ± 1.5*
Mean cell hemoglobin (pg)	16.0 ± 0.2	15.7 ± 0.3	15.6 ± 0.1	15.9 ± 0.1	16.1 ± 0.2	16.6 ± 0.4
Mean cell hemoglobin concentration (g/dL)	35.3 ± 0.5	34.7 ± 0.5	34.1 ± 0.3	34.3 ± 0.3	35.6 ± 0.4	34.4 ± 0.6
Platelets ($10^3/\mu L$)	1,050.3 ± 36.3	1,038.7 ± 17.7	999.2 ± 31.8	998.9 ± 21.6	1,066.5 ± 27.1	1,316.6 ± 121*
Reticulocytes ($10^6/\mu L$)	0.19 ± 0.01	0.21 ± 0.02[b]	0.24 ± 0.03	0.20 ± 0.01	0.23 ± 0.02	0.24 ± 0.05
Leukocytes ($10^3/\mu L$)	3.53 ± 0.48	3.39 ± 0.47	3.28 ± 0.33	3.09 ± 0.28	2.43 ± 0.26[b]	3.53 ± 0.82[c]
Segmented neutrophils ($10^3/\mu L$)	1.70 ± 0.37	1.43 ± 0.24	1.39 ± 0.16	1.55 ± 0.19	0.98 ± 0.13[b]	2.62 ± 0.82[c]
Lymphocytes ($10^3/\mu L$)	1.69 ± 0.24	1.86 ± 0.27	1.75 ± 0.20	1.40 ± 0.10	1.44 ± 0.16	1.17 ± 0.37
Monocytes ($10^3/\mu L$)	0.13 ± 0.03	0.09 ± 0.04	0.14 ± 0.03	0.13 ± 0.04	0.10 ± 0.05	0.06 ± 0.03[c]
Eosinophils ($10^3/\mu L$)	0.01 ± 0.01	0.02 ± 0.01	0.00 ± 0.00	0.01 ± 0.00	0.00 ± 0.00	0.01 ± 0.01
Nucleated erythrocytes/100 leukocytes	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Total bone marrow cellularity (10^6/femur)	35.90 ± 1.16	36.29 ± 1.22	35.46 ± 2.10	34.99 ± 1.35	32.27 ± 3.04	28.59 ± 3.84
Clinical Chemistry						
Creatine kinase (U/L)	295.2 ± 53.3	466.3 ± 84.4	734.3 ± 229.0	401.8 ± 85.9	487.3 ± 104.0	331.9 ± 98.4
Creatine kinase-1 (%)	14.75 ± 2.63	10.74 ± 2.08	13.19 ± 1.96	11.29 ± 1.87	12.20 ± 2.04	15.02 ± 3.96
Creatine kinase-2 (%)	7.82 ± 1.02	5.78 ± 0.68	8.08 ± 1.47	7.00 ± 1.02	5.97 ± 0.69	7.20 ± 2.09
Creatine kinase-3 (%)	77.43 ± 3.48	83.47 ± 2.67	78.73 ± 3.13	81.71 ± 2.49	81.83 ± 2.68	77.77 ± 5.95
Lactate dehydrogenase (IU/L)	351 ± 27	423 ± 68	392 ± 39	338 ± 25	782 ± 383	688 ± 176
LDH-1 (%)	21 ± 2	19 ± 2	21 ± 2	23 ± 2	18 ± 2	13 ± 2**
LDH-2 (%)	11 ± 1	11 ± 1	11 ± 0	12 ± 1	9 ± 1	7 ± 1*

TABLE F2
Hematology and Clinical Chemistry Data for Mice at the 15-Month Interim Evaluation in the 2-Year Inhalation Study of 1,3-Butadiene (continued)

	0 ppm	6.5 ppm	20 ppm	62.5 ppm	200 ppm	625 ppm
Male (continued)						
n	10	10	10	10	10	7
Clinical Chemistry (continued)						
LDH-3 (%)	10 ± 1	11 ± 1	11 ± 1	10 ± 0	10 ± 1	11 ± 1
LDH-4 (%)	7 ± 1	7 ± 0	8 ± 1	7 ± 0	8 ± 1	8 ± 1
LDH-5 (%)	51 ± 2	52 ± 2	50 ± 1	47 ± 3	56 ± 1*	62 ± 3**
Female						
n	10	10	10	10	10	2
Hematology						
Packed red cell volume (mL/dL)	45.7 ± 0.2	46.1 ± 0.4	45.8 ± 0.4	44.7 ± 0.5	42.3 ± 2.3	31.7 ± 3.0*
Hemoglobin (g/dL)	15.3 ± 0.1	15.5 ± 0.1	15.5 ± 0.1	15.1 ± 0.2	14.1 ± 0.8	10.7 ± 1.3*
Erythrocytes ($10^6/\mu L$)	10.02 ± 0.09	10.07 ± 0.08	9.90 ± 0.10	9.58 ± 0.12**	9.05 ± 0.62**	6.19 ± 0.91**
Howell-Jolly bodies (% erythrocytes)	0.04 ± 0.02	0.06 ± 0.03	0.12 ± 0.04	0.14 ± 0.04*	0.11 ± 0.03	0.65 ± 0.05**
Mean cell volume (fL)	45.9 ± 0.3	45.6 ± 0.3	46.2 ± 0.3	46.7 ± 0.2	47.3 ± 0.8*	51.5 ± 2.5*
Mean cell hemoglobin (pg)	15.3 ± 0.1	16.1 ± 0.1	16.0 ± 0.1	16.1 ± 0.1	16.5 ± 0.1**	17.3 ± 0.5**
Mean cell hemoglobin concentration (g/dL)	33.5 ± 0.2	33.7 ± 0.1	33.8 ± 0.2	33.8 ± 0.2	33.4 ± 0.2	33.6 ± 0.8
Platelets ($10^3/\mu L$)	873.1 ± 14.0	933.6 ± 19.1	830.0 ± 19.1	798.5 ± 19.1*	802.7 ± 85.9	395.0 ± 40.0*
Reticulocytes ($10^6/\mu L$)	0.21 ± 0.03	0.21 ± 0.03	0.19 ± 0.02	0.14 ± 0.01	0.39 ± 0.12	0.82 ± 0.19
Leukocytes ($10^3/\mu L$)	2.37 ± 0.22	1.95 ± 0.17	2.34 ± 0.19	1.99 ± 0.21	3.06 ± 0.47	5.05 ± 0.25
Segmented neutrophils ($10^3/\mu L$)	0.79 ± 0.09	0.68 ± 0.04	0.89 ± 0.10	0.81 ± 0.08	1.26 ± 0.21	3.59 ± 0.18*
Lymphocytes ($10^3/\mu L$)	1.49 ± 0.15	1.18 ± 0.14	1.35 ± 0.13	1.10 ± 0.17	1.61 ± 0.34	1.14 ± 0.08
Monocytes ($10^3/\mu L$)	0.08 ± 0.02	0.08 ± 0.02	0.09 ± 0.03	0.06 ± 0.01	0.17 ± 0.02*	0.33 ± 0.01*
Eosinophils ($10^3/\mu L$)	0.02 ± 0.01	0.02 ± 0.01	0.01 ± 0.01	0.01 ± 0.00	0.03 ± 0.02	0.00 ± 0.00
Nucleated erythrocytes/100 leukocytes	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Total bone marrow cellularity (10^6/femur)	31.19 ± 1.80	31.93 ± 1.02	30.76 ± 1.04	29.83 ± 0.92	32.43 ± 2.15[b]	42.30 ± 0.70

TABLE F2
Hematology and Clinical Chemistry Data for Mice at the 15-Month Interim Evaluation in the 2-Year Inhalation Study of 1,3-Butadiene (continued)

	0 ppm	6.5 ppm	20 ppm	62.5 ppm	200 ppm	625 ppm
Female (continued)						
n	10	10	10	10	10	2
Clinical Chemistry						
Creatine kinase (U/L)	409.1 ± 76.2	475.5 ± 62.0	422.8 ± 152	577.4 ± 221	316.2 ± 74.9	340.5 ± 172
Creatine kinase-1 (%)	20.09 ± 1.83	18.02 ± 2.01	25.52 ± 3.41	19.66 ± 2.13	24.24 ± 2.97	17.78 ± 5.81
Creatine kinase-2 (%)	8.63 ± 0.91	9.82 ± 1.09	10.20 ± 1.24	11.58 ± 1.56	10.41 ± 1.06	11.32 ± 3.31
Creatine kinase-3 (%)	71.27 ± 2.42	72.16 ± 2.88	64.27 ± 4.25	69.66 ± 3.27	65.34 ± 3.64	70.90 ± 9.12
Lactate dehydrogenase (IU/L)	253 ± 27	354 ± 24*	274 ± 34	320 ± 58	859 ± 313**	1,315 ± 281**
LDH-1 (%)	21 ± 2	15 ± 1**	21 ± 2	23 ± 3	14 ± 1**	12 ± 5
LDH-2 (%)	9 ± 1	7 ± 1*	8 ± 0	8 ± 1	7 ± 1*	4 ± 1**
LDH-3 (%)	8 ± 0	7 ± 0	8 ± 0	8 ± 0	9 ± 1	8 ± 0
LDH-4 (%)	9 ± 0	10 ± 1	10 ± 1	8 ± 0	9 ± 0	9 ± 1
LDH-5 (%)	54 ± 2	62 ± 2	55 ± 2	53 ± 4	62 ± 2	67 ± 4

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error. LDH=lactate dehydrogenase
[b] n=9
[c] n=6

APPENDIX G
CHEMICAL CHARACTERIZATION, ANALYSIS, AND GENERATION OF CHAMBER CONCENTRATIONS

CHEMICAL CHARACTERIZATION, ANALYSIS, AND GENERATION OF CHAMBER CONCENTRATIONS

PROCUREMENT AND CHARACTERIZATION OF 1,3-BUTADIENE

1,3-Butadiene was obtained as a liquified gas from Phillips Chemical Company, Philtex Plant (Borger, TX) and shipped directly to Battelle Pacific Northwest in seven lots (J-014, J-025, J-038, J-050, J-149, J-217, and J-375) for use in the 2-year and stop-exposure studies. Identity and purity analyses of a representative lot (F850) were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). The reports on analyses performed in support of the 1,3-butadiene studies are on file at the National Institute of Environmental Health Sciences.

The study chemical, a clear, colorless gas, was identified as 1,3-butadiene by infrared and nuclear magnetic resonance spectroscopy. All spectra were consistent with those expected for the structure and with the literature spectra (*Sadtler Standard Spectra*) of 1,3-butadiene, as shown in Figures G1 and G2. The purity of lot F-850, which was not used in the studies, was determined by approximation of the amount of the inhibitor, *t*-butylcatechol, and by gas chromatography. Approximation of the amount of the inhibitor, *t*-butylcatechol, was performed by mixing a sample of 1,3-butadiene with 1.0 N sodium hydroxide and comparing the sample to a *t*-butylcatechol standard. Gas chromatography was performed with a flame ionization detector (FID) and a nitrogen carrier gas, using two systems:

A) Porapak QS on 80/100 mesh, with a carrier gas flow rate of 40 mL/minute, and an oven temperature of 100° C, and
B) 80/100 mesh Carbopack C/0.1% SP-1000, with a carrier gas flow rate of 45 mL/minute, and an oven temperature of 40° C.

Quantitation of the dimer, 4-vinyl-1-cyclohexane, in the sample liquid and headspace was performed with gas chromatography using system A, but with a carrier gas flow rate of 30 mL/minute and an oven temperature of 150° C. Approximation of the concentration of the inhibitor, *t*-butylcatechol, in the liquid phase indicated approximately 4 ppm. Gas chromatography indicated a major peak and no impurities with areas of 0.1% or greater relative to the major peak. The level of 4-vinyl-1-cyclohexane was determined to be 35 ± 1 ppm for the liquid and less than 1 ppm for the headspace. The overall purity of lot F-850 was determined to be greater than 99%.

Lots J-014, J-025, J-038, J-050, J-149, J-217, and J-375 were analyzed by Battelle Pacific Northwest for identity by infrared spectroscopy and for purity and dimer concentration by gas chromatography using system A.

GENERATION AND MONITORING OF CHAMBER CONCENTRATIONS

Generation System: 1,3-Butadiene gas was supplied in the proper amount to each chamber by the generation system shown in Figure G3. The gas was obtained from the headspace of the 1,3-butadiene cylinder with a pressure regulator.

The gas was piped through stainless steel tubing to a main shutoff valve, distribution manifold, and flow control system. The main shutoff valve was computer controlled, with manual operation capability. The distribution manifold served to direct the flow of gas to the six flow-limiting valves. These valves provided coarse control of gas flow. Fine control of gas flow was provided by the six metering valves in conjunction with flow meters that were calibrated to deliver 1,3-butadiene at rates appropriate to the desired chamber concentrations.

Gas was injected into the chamber inlet air stream at a point sufficiently removed from the chamber to allow for proper mixing with incoming air, assuring uniformity of the chemical-laden atmosphere within the chamber. The mice were exposed and maintained in 2.3 m^3 chambers (Hazleton 2000, Lab Products, Inc.)

Concentration Monitoring: The concentration of 1,3-butadiene in the exposure chambers and room air was measured using a Hewlett-Packard Model 5840 gas chromatograph equipped with a FID operated at 300° C. The separation of 1,3-butadiene from other components was achieved using a stationary phase consisting of a 1% coating of SP-1000 on a solid support of 60/80 mesh Carbopack B in a 12 × 1/8 inch nickel column. The mobile phase was nitrogen at a flow rate of 20 mL/minute; the column was operated isothermally at 120° C. Under these conditions, 1,3-butadiene exhibited a retention time of approximately 0.3 minutes. The retention time of an unretained peak was approximately 0.15 minutes. An oven-mounted, 12-port, stream-select valve provided the interface between the sample locations and the on-line gas chromatograph. This valve directed a continuous stream of chamber gas through a 1.0 mL nickel sample loop located on an oven-mounted sampling valve. Automatic switching of the stream-select valve allowed sequential analysis of samples from all exposure chambers, room air, and the on-line standard. The time required for a complete set of analyses from all 12 ports was approximately 30 minutes.

The on-line standard of 200 ppm 1,3-butadiene in nitrogen was used to detect instrument drift; it was not used to establish instrument calibration. When excessive drift was detected, the monitor was recalibrated. Standards for calibration were prepared volumetrically in gastight bags and injected directly into the on-line gas chromatograph.

The monthly mean exposure concentrations are presented in Figures G4 through G8. A summary of chamber concentrations is shown in Table G1.

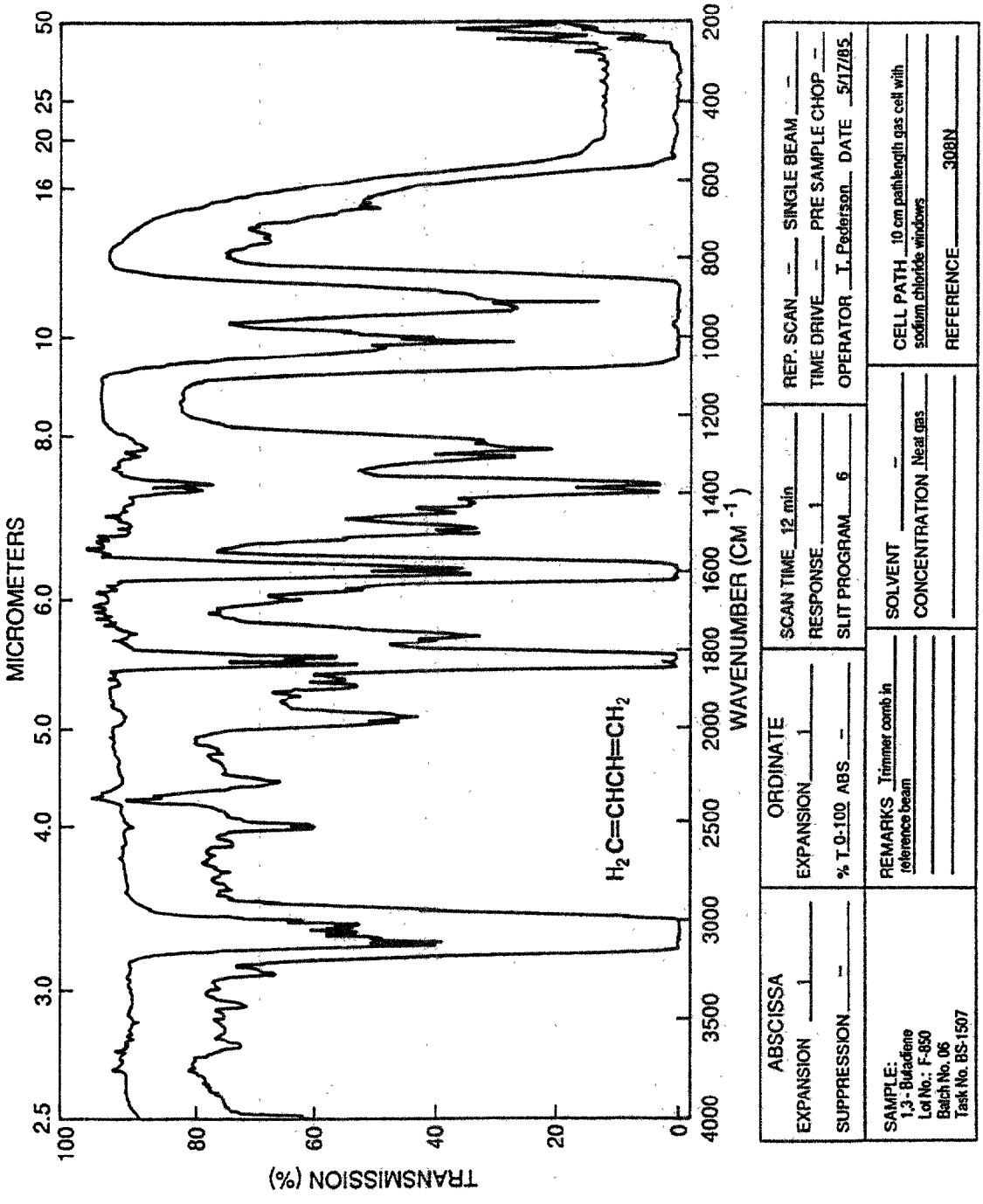
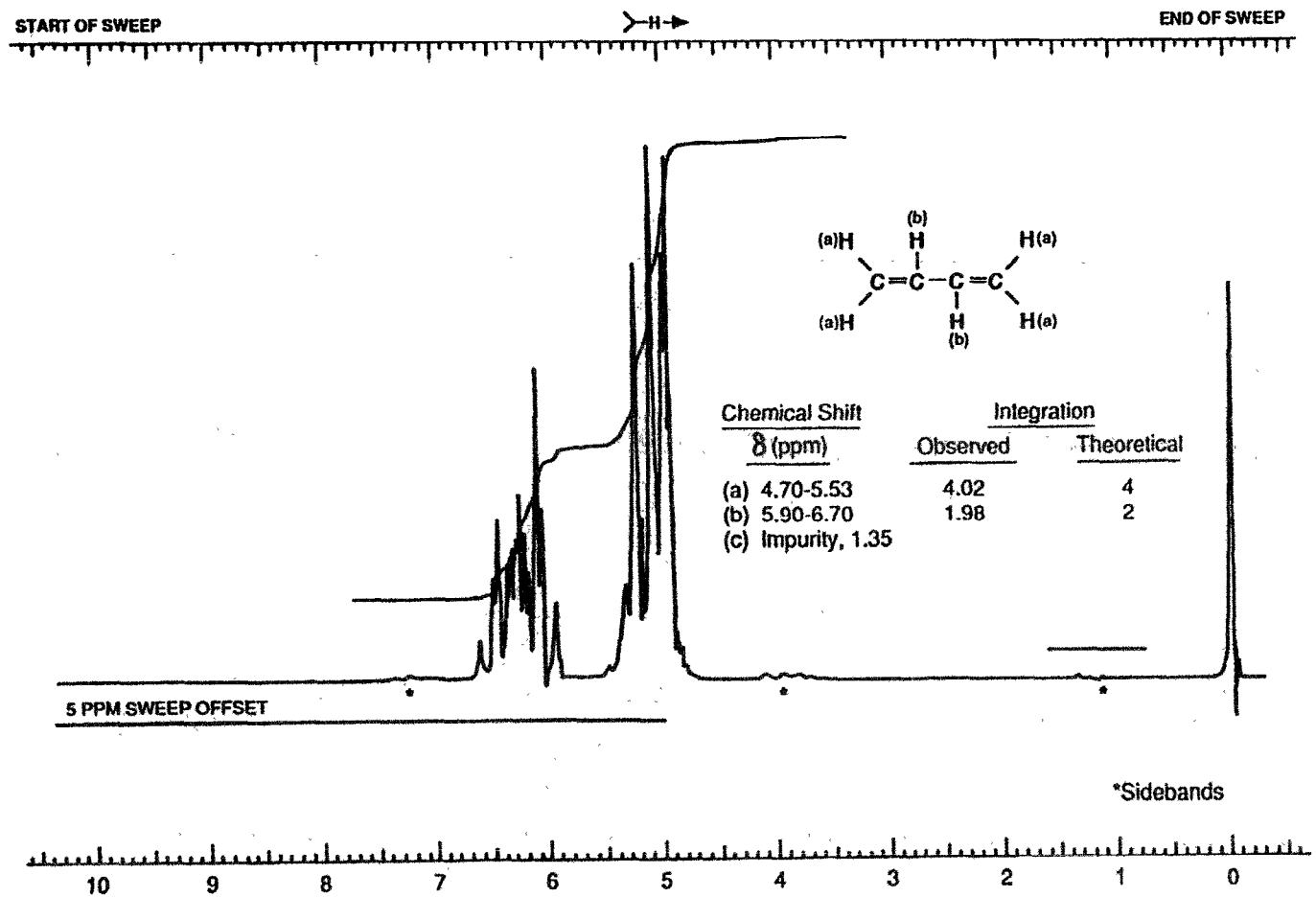


FIGURE G1
Infrared Absorption Spectrum of 1,3-Butadiene



Spectrum Ampl. 13 x 10
Filter 0.1 sec.
RF Power 0.05 mG

Sweep Time 5 min
Sweep Width 10 ppm or Hz
End of Sweep 0 ppm or Hz

Sample: 1,3 - Butadiene
Lot No. F-850
Batch No. 06
Task No. BS-1507
Solvent: $CDCl_3$

Remarks:
*Sidebands

Operator: T. Pederson
Date: 5/23/85
Spectrum No.: 308N

FIGURE G2
Nuclear Magnetic Resonance Spectrum of 1,3-Butadiene

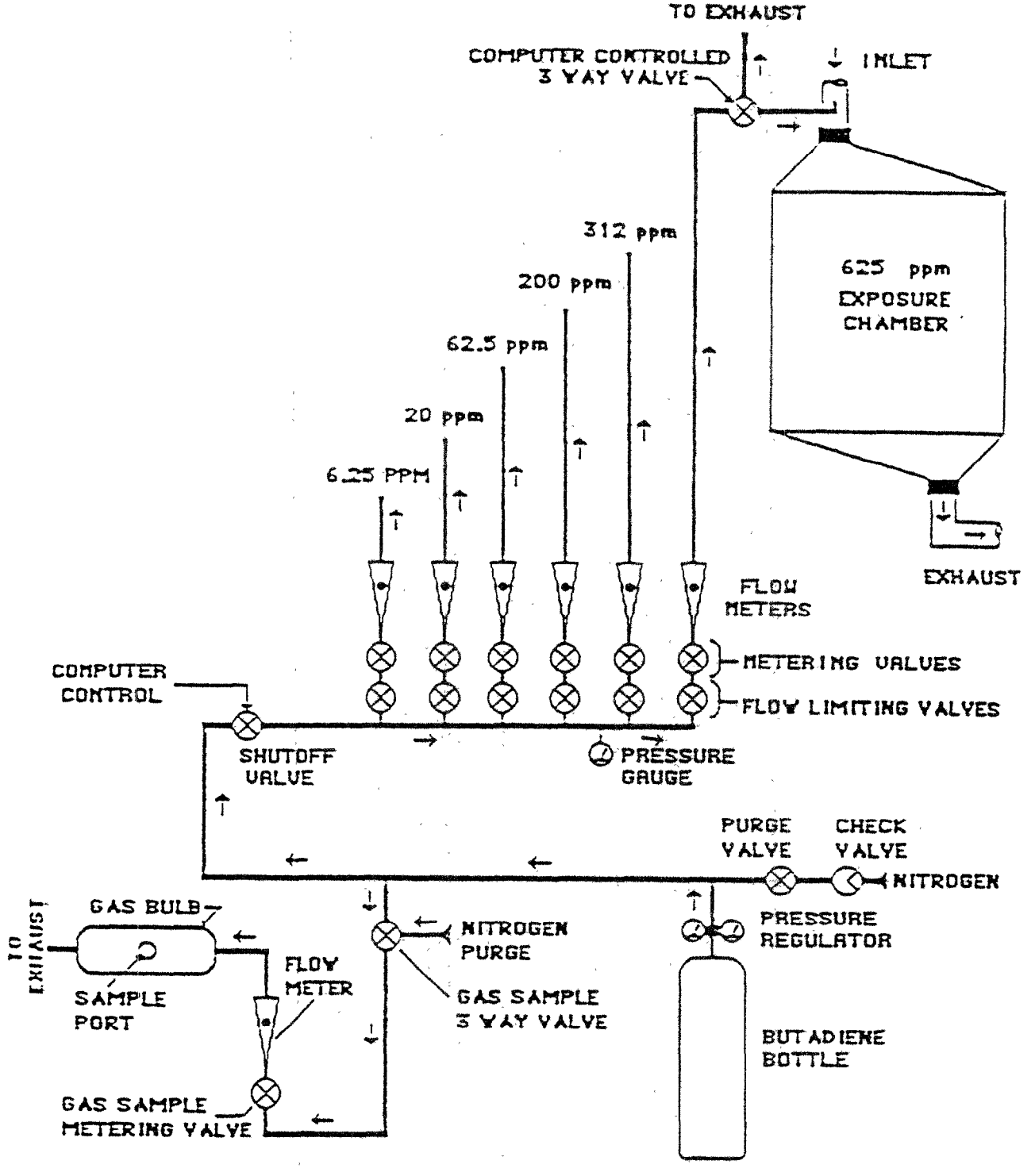


FIGURE G3
Generation System for 1,3-Butadiene

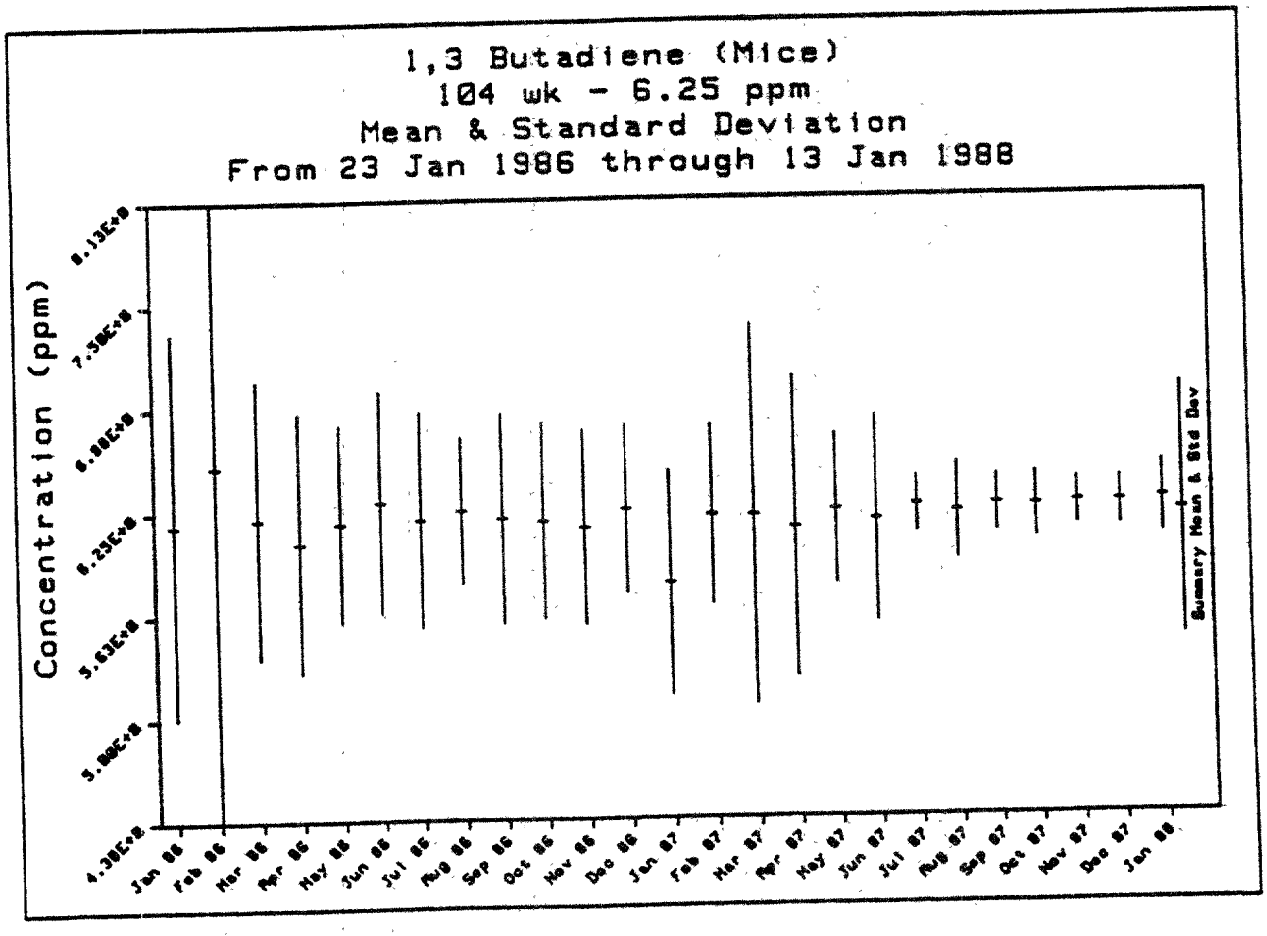


FIGURE G4
Monthly Mean Concentration and Standard Deviation in the 6.25 ppm 1,3-Butadiene Mouse Exposure Chamber for the 2-Year Studies

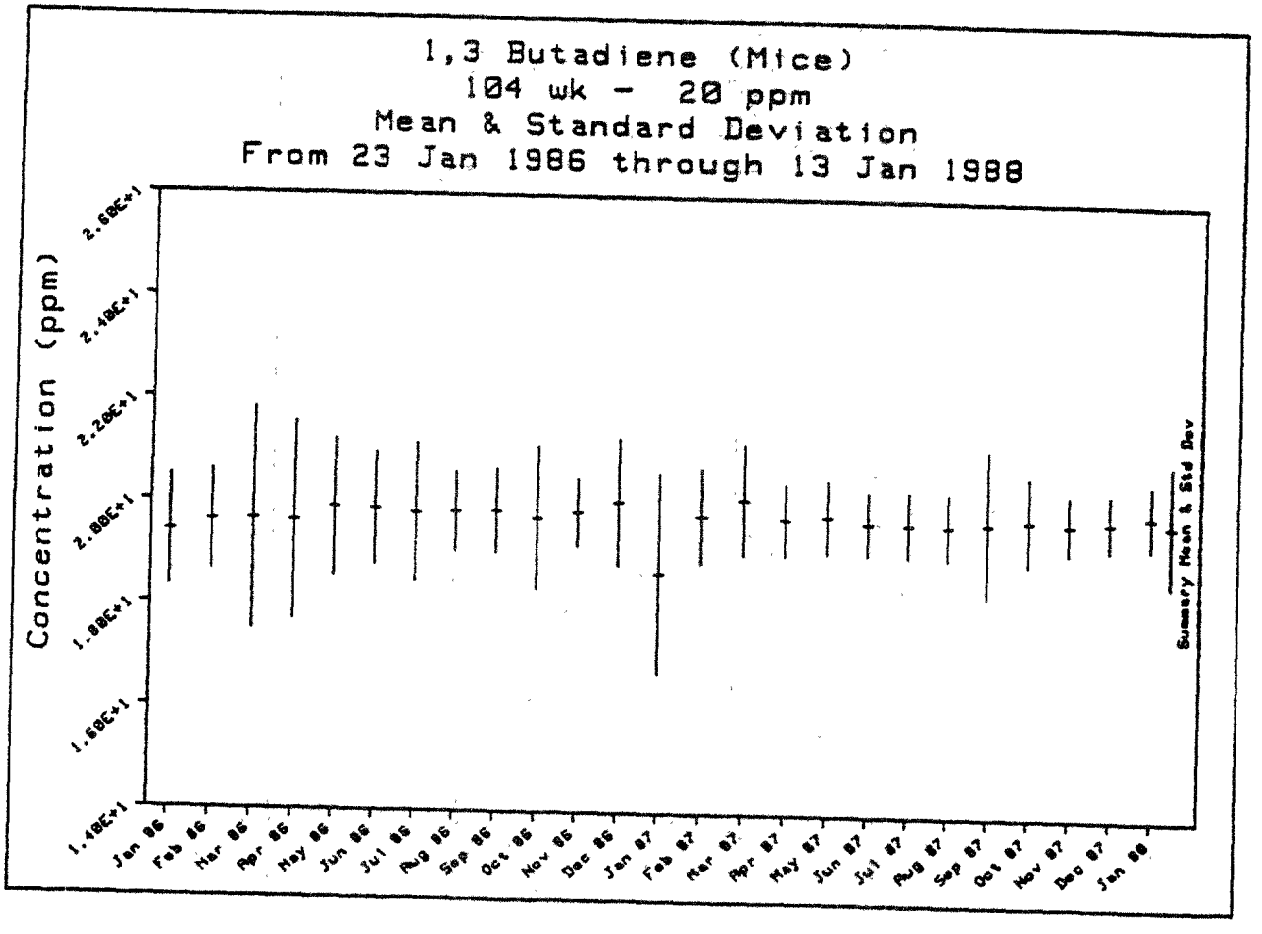


FIGURE G5
Monthly Mean Concentration and Standard Deviation in the 20 ppm 1,3-Butadiene Mouse Exposure Chamber for the 2-Year Studies

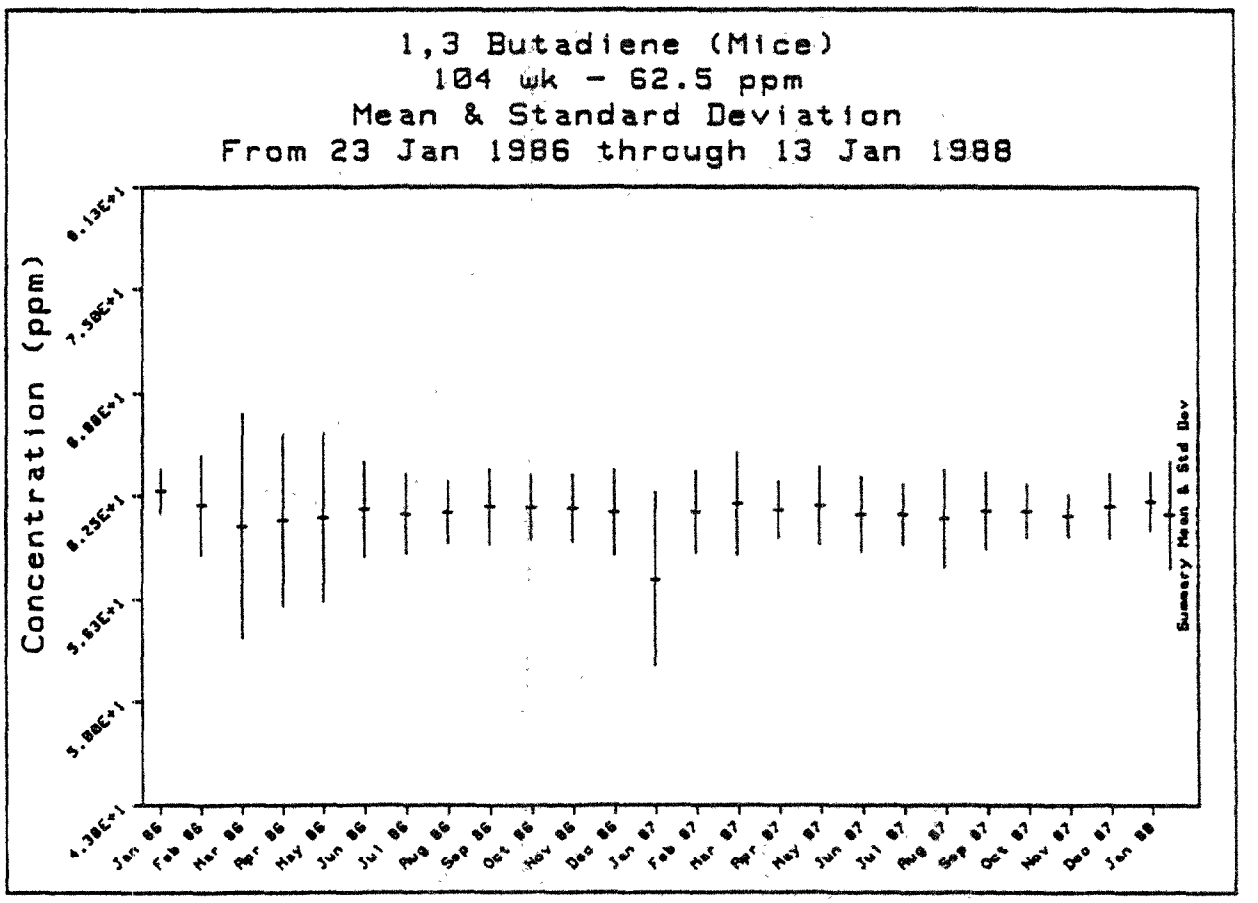


FIGURE G6
Monthly Mean Concentration and Standard Deviation in the 62.5 ppm 1,3-Butadiene Mouse Exposure Chamber for the 2-Year Studies

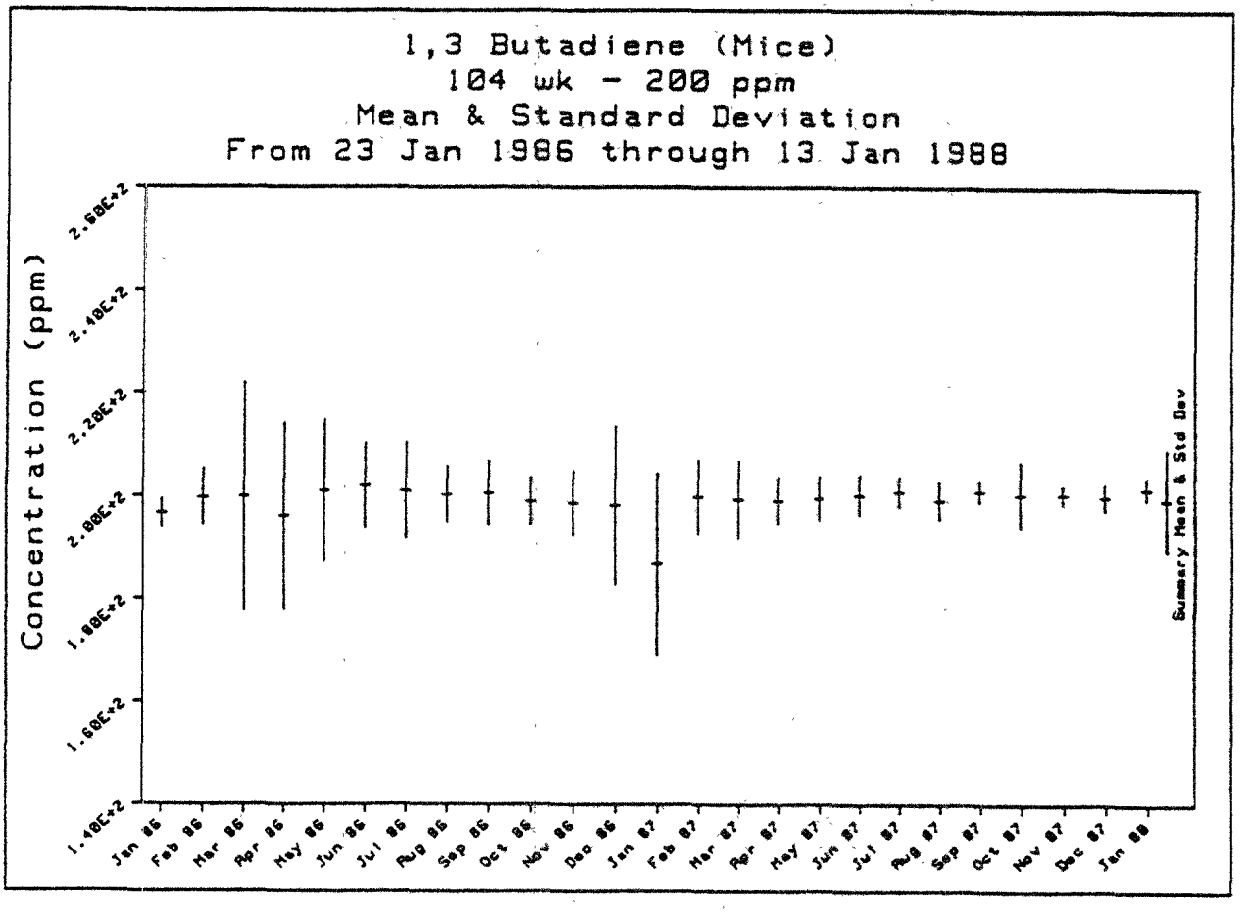


FIGURE G7
Monthly Mean Concentration and Standard Deviation in the 200 ppm 1,3-Butadiene Mouse Exposure Chamber for the 2-Year Studies

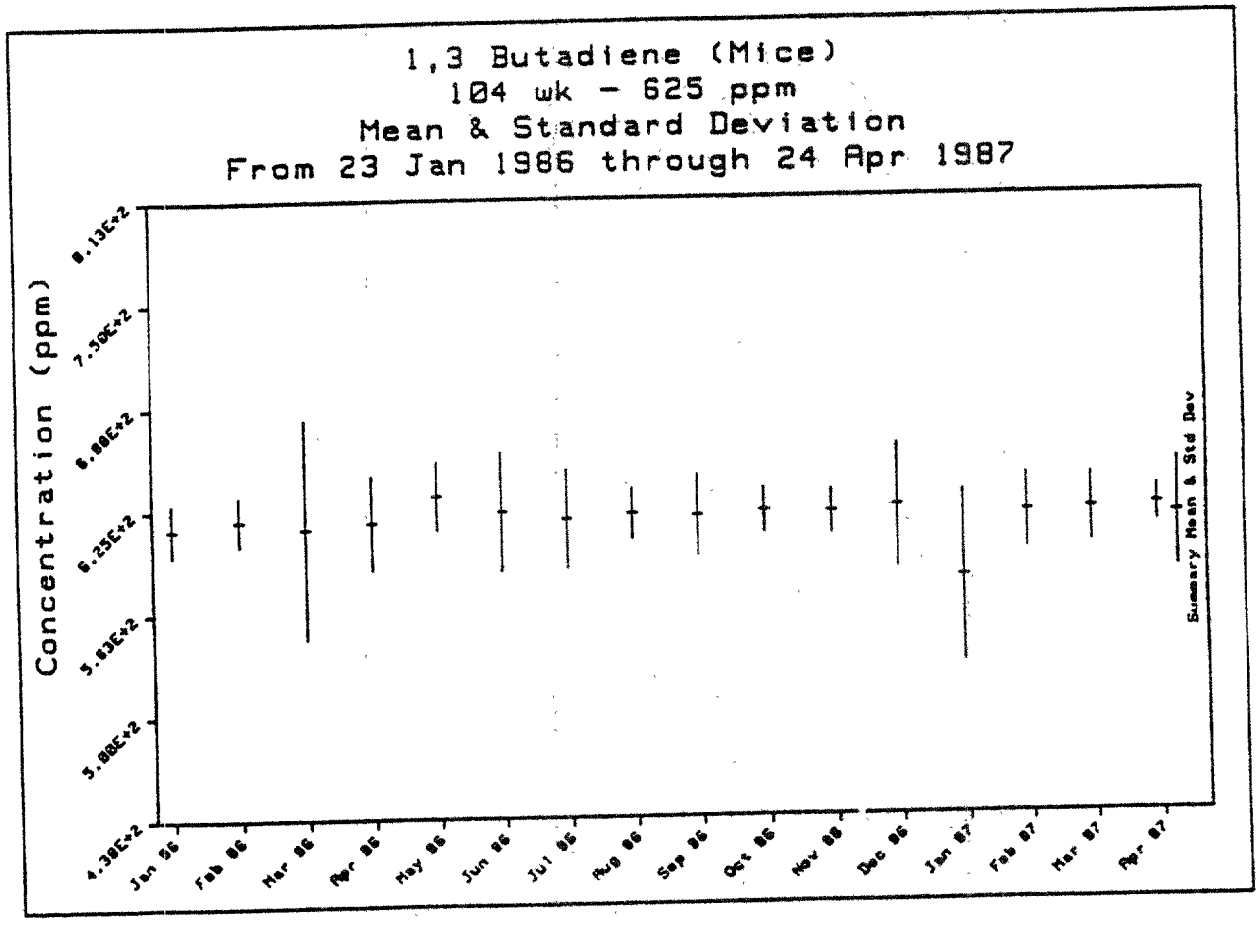


FIGURE G8
Monthly Mean Concentration and Standard Deviation in the 625 ppm 1,3-Butadiene Mouse Exposure Chamber for the 2-Year Studies

TABLE G1
Summary of Chamber Concentrations in the 2-Year Inhalation Studies of 1,3-Butadiene

Target Concentration (ppm)	Total Number of Readings	Mean Concentration[a] (ppm)
6.25	5,534	6.21 ± 0.76
20	5,847	19.8 ± 1.17
62.5	5,869	61.4 ± 3.24
200	5,788	199 ± 9.86
625	3,626	619 ± 32.7

[a] Mean ± standard deviation

APPENDIX H
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH-07 RAT AND MOUSE RATION

TABLE H1
Ingredients of NIH-07 Rat and Mouse Ration[a]

Ingredients[b]	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Dried brewer's yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

[a] NCI, 1976; NIH, 1978
[b] Ingredients ground to pass through a U.S. Standard Screen No. 16 before being mixed

TABLE H2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D-activated animal sterol
K_3	2.8 g	Menadione
d-α-Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B_{12}	4,000 μg	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	*d*-Biotin
Minerals		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

[a] Per ton (2,000 lb) of finished product

TABLE H3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.33 ± 0.49	21.7 – 23.6	17
Crude fat (% by weight)	5.49 ± 0.27	4.9 – 6.0	17
Crude fiber (% by weight)	3.37 ± 0.29	2.7 – 4.0	17
Ash (% by weight)	6.57 ± 0.32	6.1 – 7.1	17
Amino Acids (% of total diet)			
Arginine	1.308 ± 0.606	1.210 – 1.390	8
Cystine	0.306 ± 0.084	0.181 – 0.400	8
Glycine	1.150 ± 0.047	1.060 – 1.210	8
Histidine	0.576 ± 0.024	0.531 – 0.607	8
Isoleucine	0.917 ± 0.029	0.881 – 0.944	8
Leucine	1.946 ± 0.055	1.850 – 2.040	8
Lysine	1.270 ± 0.058	1.200 – 1.370	8
Methionine	0.448 ± 0.128	0.306 – 0.699	8
Phenylalanine	0.987 ± 0.140	0.665 – 1.110	8
Threonine	0.877 ± 0.042	0.824 – 0.940	8
Tryptophan	0.236 ± 0.176	0.107 – 0.671	8
Tyrosine	0.676 ± 0.105	0.564 – 0.794	8
Valine	1.103 ± 0.040	1.050 – 1.170	8
Essential Fatty Acids (% of total diet)			
Linoleic	2.393 ± 0.258	1.830 – 2.570	7
Linolenic	0.280 ± 0.040	0.210 – 0.320	7
Vitamins			
Vitamin A (IU/kg)	7,302 ± 2,451	4,700 – 13,000	17
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 – 6,300	4
α–Tocopherol (ppm)	37.95 ± 9.41	22.50 – 48.90	8
Thiamine (ppm)	20.59 ± 2.48	15.0 – 26.0	17
Riboflavin (ppm)	7.92 ± 0.87	6.10 – 9.00	8
Niacin (ppm)	103.4 ± 26.6	65.0 – 150.0	8
Pantothenic acid (ppm)	29.54 ± 3.60	23.0 – 34.0	8
Pyridoxine (ppm)	9.55 ± 3.48	5.60 – 14.0	8
Folic acid (ppm)	2.25 ± 0.73	1.80 – 3.70	8
Biotin (ppm)	0.254 ± 0.042	0.19 – 0.32	8
Vitamin B_{12} (ppb)	38.45 ± 22.01	10.6 – 65.0	8
Choline (ppm)	3,089 ± 329	2,400 – 3,430	8
Minerals			
Calcium (%)	1.17 ± 0.11	1.00 – 1.40	17
Phosphorus (%)	0.93 ± 0.04	0.86 – 1.00	17
Potassium (%)	0.883 ± 0.078	0.772 – 0.971	6
Chloride (%)	0.526 ± 0.092	0.380 – 0.635	8
Sodium (%)	0.313 ± 0.390	0.258 – 0.371	8
Magnesium (%)	0.168 ± 0.010	0.151 – 0.181	8
Sulfur (%)	0.280 ± 0.064	0.208 – 0.420	8
Iron (ppm)	361 ± 100	255.0 – 523.0	8
Manganese (ppm)	92.0 ± 6.01	81.70 – 99.40	8
Zinc (ppm)	54.72 ± 5.67	46.10 – 64.50	8
Copper (ppm)	11.06 ± 2.50	8.090 – 15.39	8
Iodine (ppm)	3.37 ± 0.92	1.52 – 4.13	6
Chromium (ppm)	1.79 ± 0.36	1.04 – 2.09	8
Cobalt (ppm)	0.68 ± 0.14	0.490 – 0.780	4

TABLE H4
Contaminant Levels in NIH-07 Rat and Mouse Ration

Contaminants	Mean ± Standard Deviation[a]	Range	Number of Samples
Arsenic (ppm)	0.54 ± 0.11	0.14 – 0.98	17
Cadmium (ppm)[b]	0.11 ± 0.02	0.10 – 0.20	17
Lead (ppm)	0.35 ± 0.26	0.05 – 0.96	17
Mercury (ppm)	<0.05		17
Selenium (ppm)	0.37 ± 0.05	0.26 – 0.48	17
Aflatoxins (ppb)	<5.0		17
Nitrate nitrogen (ppm)[c]	21.53 ± 9.06	12.0 – 41.0	17
Nitrite nitrogen (ppm)[c]	0.51 ± 0.81	<0.10 – 2.60	17
BHA (ppm)[d]	2.53 ± 1.01	<2.00 – 5.00	17
BHT (ppm)[d,e]	1.18 ± 0.73	<1.00 – 4.00	17
Aerobic plate count (CFU/g)[f]	47,681 ± 74,541	4,500 – 300,000	16
Aerobic plate count (CFU/g)[g]	100,171 ± 228,137	4,500 – 940,000	17
Coliform (MPN/g)[h]	3.13 ± 0.34	<3.00 – 4.00	16
Coliform (MPN/g)[i]	11.77 ± 35.63	<3.00 – 150	17
E. coli (MPN/g)	<3.00		17
Total nitrosamines (ppb)[j]	9.80 ± 4.31	3.90 – 20.00	17
N-Nitrosodimethylamine (ppb)[j]	8.38 ± 4.15	2.90 – 19.00	17
N-Nitrosopyrrolidine (ppb)[j]	1.42 ± 0.92	1.00 – 4.50	17
Pesticides (ppm)			
α-BHC[k]	<0.01		17
β-BHC	<0.02		17
γ-BHC	<0.01		17
δ-BHC	<0.01		17
Heptachlor	<0.01		17
Aldrin	<0.01		17
Heptachlor epoxide	<0.01		17
DDE	<0.01		17
DDD	<0.01		17
DDT	<0.01		17
HCB	<0.01		17
Mirex	<0.01		17
Methoxychlor	<0.05		17
Dieldrin	<0.01		17
Endrin	<0.01		17
Telodrin	<0.01		17
Chlordane	<0.05		17
Toxaphene	<0.1		17
Estimated PCBs	<0.2		17
Ronnel	<0.01		17
Ethion	<0.02		17
Trithion	<0.05		17
Diazinon	<0.1		17
Methyl parathion	<0.02		17
Ethyl parathion	<0.02		17
Malathion[l]	0.14 ± 0.12	<0.05 – 0.35	17
Endosulfan I	<0.01		17
Endosulfan II	<0.01		17
Endosulfan sulfate	<0.03		17

TABLE H4
Contaminant Levels in NIH-07 Rat and Mouse Ration (continued)

[a] For values less than the limit of detection, the detection limit is given as the mean.
[b] One lot milled 3 June 1987 contained 0.20 ppm; all others measured 0.10 ppm or less.
[c] Sources of contamination: alfalfa, grains, and fish meal
[d] Sources of contamination: soy oil and fish meal
[e] One lot milled 6 December 1985 contained 4.00 ppm; all others measured 1.00 ppm or less.
[f] CFU=colony forming unit. Mean, standard deviation, and range exclude one high value of 940,000 CFU/g obtained in the lot milled on 5 November 1987.
[g] Mean, standard deviation, and range include the high value from the lot milled on 5 November 1987.
[h] MPN=most probable number. Mean, standard deviation, and range exclude one high value of 150 CFU/g obtained in the lot milled on 5 November 1987.
[i] Mean, standard deviation, and range include the value obtained in the lot milled on 5 November 1987.
[j] All values were corrected for percent recovery.
[k] BHC is hexacholorcyclohexane or benzenehexachloride.
[l] Eight lots contained more than 0.05 ppm.

APPENDIX I
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals and the study animals are subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Prior to the beginning of the 2-year studies, samples for viral screening were collected from five mice of each sex and tested by Battelle Pacific Northwest Laboratories (Richland, WA). Fifteen B6C3F$_1$ mice of each sex were selected at the time of randomization and allocation of the animals to the various study groups to serve as sentinel animals. Five animals of each designated sentinel group were killed at 6, 12, and 18 months on study. Samples for viral screening at 24 months were collected from five mice of each sex from the 62.5 ppm exposure group. Blood collected from each animal was allowed to clot and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates, Incorporated (Bethesda, MD) for determination of the virus antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Complement fixation	
LCM (lymphocytic choriomeningitis virus)	6 months
ELISA	
Ectromelia virus	6, 12, 18, and 24 months
GDVII (mouse encephalomyelitis virus)	Preinitiation, 6, 12, 18, and 24 months
LCM	18 and 24 months
Mouse adenoma virus	6, 12, 18, and 24 months
MHV (mouse hepatitis virus)	Preinitiation, 6, 12, 18, and 24 months
MVM (minute virus of mice)	18 and 24 months
Mycoplasma arthritidis	6 and 24 months
Mycoplasma pulmonis	6 and 24 months
PVM (pneumonia virus of mice)	Preinitiation, 6, 12, 18, and 24 months
Reovirus 3	6, 12, 18, and 24 months
Sendai	Preinitiation, 6, 12, 18, 24 months
Hemagglutination Inhibition	
K (papovavirus)	6, 12, 18, and 24 months
Polyoma virus	6, 12, 18, and 24 months
MVM	6 and 12 months
Immunofluorescence assay	
EDIM (Epizootic diarrhea of infant mice)	6, 12, 18, and 24 months
LCM	12 months
MVM	12 months

RESULTS

The serology results for sentinel animals are presented in Table I1.

TABLE I1
Murine Virus Antibody Determinations for Mice in the 2-Year Inhalation Studies of 1,3-Butadiene[a]

Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
Preinitiation	0/10	None positive
6 months	1/10	*M. arthritidis*
12 months	1/10	MVM
18 months	0/9	None positive
24 months	1/10	*M. arthritidis*

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TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal)
206	1,2-Dibromo-3-chloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butyl Benzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-Ethylhexyl)phthalate
219	2,6-Dichloro-p-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
228	Vinylidene Chloride
229	Guar Gum
230	Agar
231	Stannous Chloride
232	Pentachloroethane
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	*D*-Mannitol
237	1,1,1,2-Tetrachloroethane
238	Ziram
239	Bis(2-chloro-1-Methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
243	Trichlorethylene (Rats and Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
246	Chrysotile Asbestos (Hamsters)
247	L-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos (Hamsters)
250	Benzyl Acetate
251	2,4- & 2,6-Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
254	Dichloromethane (Methylene Chloride)
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
266	Monuron
267	1,2-Propylene Oxide
269	Telone II® (1,3-Dichloropropene)
271	HC Blue No. 1
272	Propylene

TR No.	CHEMICAL
273	Trichloroethylene (Four Rat Strains)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
277	Tremolite
278	2,6-Xylidine
279	Amosite Asbestos
280	Crocidolite Asbestos
281	HC Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethyl) phosphonium Sulfate & Tetrakis(hydroxymethyl) phosponium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane (Methylene Chloride)
307	Ephedrine Sulfate
308	Chlorinated Pariffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
313	Mirex
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
320	Rotenone
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate
329	1,2-Epoxybutane
330	4-Hexylresorcinol
331	Malonaldehyde, Sodium Salt
332	2-Mercaptobenzothiazole
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol
335	C.I. Acid Orange 3

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