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EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

VINYL CHLORIDE PATHOLOGY REPORT

Submitted to
Manufacturing Chemists Association
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EPL 01992

VINYL CHLORIDE PATHOLOGY REPORT

I. Introduction

At the request of the Manufacturing Chemists Association, Experimental Pathology Laboratories, Inc. provided a pathologist (Dr. William Busey) to assist in a partial pathology audit of a chronic inhalation study on vinyl chloride conducted at Industrial Bio-Test Laboratories in Decatur, Illinois. This audit was conducted during the week of February 20, 1978 at the IBT Laboratory in Decatur, Illinois. Dr. Busey participated as a member of the audit team and initially his responsibilities were to audit the histopathological findings. Because of the size of the study (2500 animals), and the number of tissues (31 organs per animal) called for to be examined in the protocol, the members of the audit task force were divided into three teams. Dr. Busey was assigned to audit team No. 1 along with Dr. G.K. Hatfield from Diamond Shamrock Corporation, and Drs. Sullivan and Vlaovic from IBT. The details of the tasks performed by audit team No. 1 are presented in the following section of this report.

Prior to the initiation of the audit, EPL was provided with a protocol of the study. The following table depicts the experimental design and group designations:

Experimental Design for Vinyl Chloride Study

Group	Number of Animals						Specified Exposure Levels+
	Mice		Rats		Hamsters		
	M	F	M	F	M	F	
Control	100	100	100	100	100	100	-
T1*	100	100	100	100	100	100	50 ppm vinyl chloride
T2*	100	100	100	100	100	100	200 ppm vinyl chloride
T3*	100	100	100	100	100	100	2500 ppm vinyl chloride
T4**	-	-	100#		-	-	2500 ppm vinyl chloride

+Exposure levels have not been verified by audit team

*No food, water, or bedding in cages during exposure

**Food, water, and bedding to remain in cages during exposure

#All rats of same sex, either sex permitted

The protocol as amended called for exposure of the above groups six hours per day, five days per week. Mice were to be exposed for nine months, rats and hamsters for twelve months. These groups were originally scheduled to be held for equal additional periods of time (nine or twelve months) but subsequently it was agreed they would be kept for their lifetime or sacrificed if seriously ill. All animals were to be necropsied either at the time of death or sacrifice and a specified set of tissues was to be preserved in 10% neutral buffered formalin. These tissues were to be examined from all animals in the control, T2 and T3 groups. If exposure related lesions were detected in the organs of the T2 or T3 groups, these same organs from the T1 group were to be examined.

II. Audit Tasks

Several tasks were assigned to audit team No. 1. These tasks were directed toward: (a) an assessment of the histopathology data developed by the IBT pathologists, (b) an enumeration of the neoplasms diagnosed by IBT, and (c) a verification of the number of tissues examined by IBT microscopically. In addition, EPL was asked to summarize the tissue counts performed by IBT from examination of all of the wet tissue bags, paraffin blocks and microscope slides. This latter task was subsequently performed at EPL.

A. Examination of IBT Histopathology Data from Computer Printouts

The recorded diagnoses of the IBT pathologists had been input into a computer which in turn generated a series of printouts listing the findings and separating the neoplastic from the non-neoplastic diagnoses. Working with the IBT printout of the neoplastic diagnoses, summary neoplasm tables were generated by EPL for each of the three species. The number of organs indicated as examined by IBT pathologists was tabulated by the audit team, thus providing a denominator for comparative purposes. These neoplasm summaries are found in Tables I, II, and III.

In addition to summarizing all of the neoplasms, the audit team extracted all of the diagnoses of angiosarcoma and prepared a separate incidence table for this diagnosis. A summary of the diagnosis of angiosarcoma in any organ, expressed as a percentage of the number of animals examined, is found in Table IV.

B. Microscopic Examination of Selected Neoplastic and Non-neoplastic Lesions Diagnosed by IBT Pathologists

Following examination of the computer printout containing the diagnoses rendered by the IBT pathologists for the various organs examined, selected tissues were examined microscopically. In general, this second microscopic examination correlated well with the original diagnoses and no discrepancies were noted. The only discrepancies noted were set of slides from apparently two different animals containing the same animal numbers. Since all of the slides were not examined, no assessment of the magnitude of this problem could be made.

C. Verification of Number of Tissues Examined Microscopically

During the audit selected neoplastic and non-neoplastic lesions were reexamined microscopically, and tissue counts were made from the microscope slides for selected animals. These counts were then checked against the rough pathology reports to assess whether all of the tissues available for microscopic examination were in fact examined. For these selected animals, no discrepancies were noted and the number of tissues available for microscopic examination correlated well with those that were reported.

D. Summarization of Counts of Wet Tissue, Paraffin Blocks and Microscope Slides Conducted by IBT Personnel

At the request of the vinyl chloride audit task force, IBT examined all of the wet tissues, paraffin blocks and slides from the animals used in the study. This examination consisted of the identi-

fication and counting of the various tissues that were available for possible microscopic evaluation. These counts were submitted on several individual forms and in order to properly evaluate these data, EPL summarized these counts by group, sex, and species. These summaries are presented in Tables V, VI, and VII.

III. Summary and Recommendation

Inspection of the recorded IBT histopathologic findings clearly indicate that the inhalation exposure of rats, hamsters, and mice to vinyl chloride at 50, 200 and 2500 ppm results in a carcinogenic effect in the liver. This carcinogenic effect was manifest by the development of angiosarcomas, many of which metastasized to regional lymph nodes and the lung. Even though the histopathology is incomplete, the number of angiosarcomas observed clearly indicates the carcinogenicity of vinyl chloride to these three species of laboratory animals. Other neoplasms were observed and reported but because of the paucity of numbers of specific organs examined, conclusive statements about their relationship to vinyl chloride exposure cannot be made. Tumors of Zymbal's gland were seen in all of the exposure groups in the rats and probably are related to the exposure to vinyl chloride. However, only a small number of these organs were examined in each of the control and exposed groups. Malignant tumors of the mammary gland were seen to a greater degree in the exposed female rats; but, here again, the number of mammary glands examined was small and inconsistent. Therefore, conclusive statements

cannot be made. Four tumors of the central nervous system were seen. One of these occurred in a Group II male and three occurred in Group III males. These are important findings in light of recent epidemiological data in man, but their relationship to the exposure to vinyl chloride in this study is undetermined because of the small number of brains examined.

Primary lung tumors occurred with greater frequency in both sexes of vinyl chloride exposed mice at all concentrations. These primary lung tumors were both benign and malignant and were diagnosed as alveolo-genic adenomas and carcinomas. Inspection of the IBT pathology reports indicates that approximately 50% of the lungs from the mice were examined microscopically. This number of lungs is sufficient to conclude that the inhalation exposure of vinyl chloride to male and female mice had a carcinogenic effect in the lungs.

Primary lung tumors were only seen in the male and female hamsters exposed to 2500 ppm of vinyl chloride. Two bronchiolar carcinomas were seen in the males and one in the females, and one bronchiolar adenoma was seen in the males. Primary lung tumors of the hamster are relatively rare; therefore, the presence of these five neoplasms may be meaningful and related to vinyl chloride exposure.

Since microscopic examination of a few selected neoplastic and non-neoplastic lesions diagnosed by the IBT pathologists did not reveal any meaningful discrepancies, it would appear that the histopathology conducted on the tissues from these animals was done accurately. Similar

spotchecks of the number of tissues reported to have been examined did not reveal any significant discrepancies.

Inspection of the tissue counts conducted by the IBT personnel of the wet tissue, paraffin blocks and microscope slides indicate that significantly fewer tissues were available for microscopic examination than were called for by the protocol. The reason for this discrepancy became apparent when the necropsy sheets and animal observation books were examined. The tissue from a large number of the animals in this study was not obtained. This discrepancy is unfortunate in light of the fact that the inhalation exposure of these three species of laboratory animals to vinyl chloride might have provided further definition of the pathology produced, the relationship to dose and the variation between species.

In conclusion, the results of this investigation revealed some rather severe deficiencies in the conduct of this study, primarily with regard to the numbers of tissues that were saved. The pathologic evaluation of the limited material that was available appears to have been conducted accurately. The available data indicate that vinyl chloride at 50, 200 and 2500 ppm has a carcinogenic effect on the liver of rats, mice and hamsters and a carcinogenic effect on the Zymbal's gland of the rat. Similarly, there appears to be a carcinogenic effect in the lungs of the mice. These conclusions are based upon the assumption that the concentrations expressed in this report were actually achieved

and maintained throughout the course of the study. Any significant excursions in the low level (50 ppm) may negate the conclusion of the carcinogenic effect of vinyl chloride at this level. Because of the serious deficiency in the number of tissues saved from animals in both the control and exposed groups, it is recommended to MCA that no further pathology work be done on this study.



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Pathologist

1/9/77

WMB/sfh

TABLE I
RAT - TUMOR SUMMARY DATA

	Control Male	Control Female	T1 Male	T1 Female	T2 Male	T2 Female
ADRENAL (No. Examined)	(11)	(26)	(8)	(9)	(19)	(7)
Cortical Carcinoma		1		1		
Cortical Adenoma		1				
Medullary Carcinoma						
BRAIN (No. Examined)	(10)	(21)	(8)	(7)	(18)	(4)
Neuroepithelioma					1	
CECUM (No. Examined)	(10)	(21)	(8)	(7)	(17)	(4)
Lymphosarcoma					1	
DUODENUM (No. Examined)	(7)	(9)	(1)	(6)	(16)	(4)
Lymphosarcoma					1	
HEART (No. Examined)	(69)	(60)	(74)	(52)	(64)	(59)
Angiosarcoma						
KIDNEYS (No. Examined)	(70)	(72)	(75)	(60)	(68)	(70)
Lymphosarcoma			1		1	
Nephroblastoma			1			
Reticulum Cell Sarcoma	2		1	1		
Tubular Adenoma			3	1		
Lipoma						1
Metastatic Angiosarcoma				1		
LIVER (No. Examined)	(70)	(73)	(77)	(62)	(69)	(72)
Angiosarcoma			11	17	35	47
Hepatocellular Carcinoma					1	
Lymphosarcoma			1		2	

TABLE I
RAT - TUMOR SUMMARY DATA

	T3 Male	T3 Female	T4 Female	T4 Male None		
ADRENAL (No. Examined)	(5)	(5)	(6)			
Cortical Carcinoma						
Cortical Adenoma						
Medullary Carcinoma			1			
BRAIN (No. Examined)	(6)	(0)	(5)			
Neuroepithelioma	3					
CECUM (No. Examined)	(3)	(0)	(5)			
Lymphosarcoma						
DUODENUM (No. Examined)	(3)	(1)	(5)			
Lymphosarcoma						
HEART (No. Examined)	(71)	(62)	(64)			
Angiosarcoma			1			
KIDNEYS (No. Examined)	(75)	(69)	(69)			
Lymphosarcoma		1				
Nephroblastoma						
Reticulum Cell Sarcoma						
Tubular Adenoma						
Lipoma						
Metastatic Angiosarcoma						
LIVER (No. Examined)	(78)	(69)	(70)			
Angiosarcoma	51	63	49			
Heptocellular Carcinoma						
Lymphosarcoma						

TABLE I
RAT - TUMOR SUMMARY DATA

	Control Male	Control Female	T1 Male	T1 Female	T2 Male	T2 Female
LIVER (continued)						
Reticulum Cell Sarcoma	3	4	2	1		
Metastatic Adreno-cortical Carcinoma				1		
LUNG (No. Examined)	(73)	(73)	(77)	(58)	(71)	(68)
Alveologenic Adenoma			1			
Bronchogenic Adenocarcinoma					1	
Bronchogenic Adenoma	1		1		1	
Bronchiolar-Alveolar Adenoma			1		1	
Angiosarcoma						2
Lymphosarcoma					2	
Reticulum Cell Sarcoma	2	4	2	1		
Metastatic Angiosarcoma			9	7	24	28
Metastatic Hepatocellular Carcinoma					1	
Metastatic Fibrosarcoma	1					
Metastatic Mammary Gland Adenocarcinoma		1		2		
Metastatic Zymbal's Gland Carcinoma						1
Metastatic Adreno-cortical Carcinoma		1				
Metastatic Adenocarcinoma N.O.S.						
MESENTERY (No. Examined)	(2)	(3)	(12)	(11)	(31)	(43)
Metastatic Hepatocellular Carcinoma					1	

TABLE I
RAT - TUMOR SUMMARY DATA

	T3 Male	T3 Female	T4 Female	T4 Male None		
LIVER (continued)						
Reticulum Cell Sarcoma	1					
Metastatic Adreno-cortical Carcinoma						
LUNG (No. Examined)	(78)	(70)	(69)			
Alveologenic Adenoma	2					
Bronchogenic Adenocarcinoma						
Bronchogenic Adenoma						
Bronchiolar-Alveolar Adenoma						
Angiosarcoma	1	2				
Lymphosarcoma						
Reticulum Cell Sarcoma	1					
Metastatic Angiosarcoma	32	37	36			
Metastatic Hepatocellular Carcinoma						
Metastatic Fibrosarcoma						
Metastatic Mammary Gland Adenocarcinoma		2				
Metastatic Zymbal's Gland Carcinoma						
Metastatic Adreno-cortical Carcinoma						
Metastatic Adenocarcinoma N.O.S.			1			
MESENTERY (No. Examined)	(37)	(37)	(43)			
Metastatic Hepatocellular Carcinoma						

TABLE I
RAT - TUMOR SUMMARY DATA

	Control Male	Control Female	T1 Male	T1 Female	T2 Male	T2 Female
MESENTERY (continued)						
Angiosarcoma	2			12	29	42
Reticulum Cell Sarcoma		2	1			
PANCREAS (No. Examined)	(35)	(39)	(38)	(23)	(23)	(8)
Islet Cell Adenoma	7	1	1			
PARATHYROID (No. Examined)	(6)	(5)	(2)	(9)	(8)	(1)
Adenoma	1					
PITUITARY (No. Examined)	(9)	(18)	(9)	(5)	(12)	(5)
Chromophobe	8	14	4	3	5	
PLEURA (No. Examined)	(0)	(0)	(0)	(1)	(4)	(7)
Angiosarcoma					4	5
Reticulum Cell Sarcoma						
Metastatic Angiosarcoma				1		1
PROSTATE (No. Examined)	(9)		(10)		(19)	
Adenocarcinoma					1	
SKIN (No. Examined)	(19)	(12)	(12)	(4)	(17)	(4)
Fibroma	7	1	5	1		
Fibrosarcoma	2	2	1	3		1
Lipoma	1					
Liposarcoma						
Sarcoma, N.O.S.	1	1				
Reticulum Cell Sarcoma				1		
Squamous Cell Carcinoma	2					

TABLE I
RAT - TUMOR SUMMARY DATA

	T3 Male	T3 Female	T4 Female	T4 Male None		
MESENTERY (continued)						
Angiosarcoma	38	41	42			
Reticulum Cell Sarcoma						
PANCREAS (No. Examined)	(4)	(2)	(4)			
Islet Cell Adenoma						
PARATHYROID (No. Examined)	(3)	(2)	(0)			
Adenoma						
PITUITARY (No. Examined)	(4)	(0)	(4)			
Chromophobe			2			
PLEURA (No. Examined)	(4)	(5)	(4)			
Angiosarcoma	3	4	4			
Reticulum Cell Sarcoma	1					
Metastatic Angiosarcoma		1				
PROSTATE (No. Examined)	(3)					
Adenocarcinoma	3					
SKIN (No. Examined)	(3)	(1)	(3)			
Fibroma						
Fibrosarcoma	1					
Lipoma						
Liposarcoma	1					
Sarcoma, N.O.S.						
Reticulum Cell Sarcoma						
Squamous Cell Carcinoma	1	1				

TABLE I
RAT - TUMOR SUMMARY DATA

	Control Male	Control Female	T1 Male	T1 Female	T2 Male	T2 Female
MAMMARY GLAND (No. Examined)	(1)	(62)	(4)	(52)	(3)	(19)
Fibroadenoma	1	75	4	45	4	10
Adenoma		23		8		7
Adenocarcinoma		5		24		8
ZYMBAL'S GLAND (No. Examined)	(9)	(16)	(7)	(7)	(17)	(6)
Carcinoma			2	1		2
SPLEEN (No. Examined)	(65)	(69)	(66)	(54)	(62)	(65)
Angiosarcoma			1			
Lymphosarcoma			1		1	
Reticulum Cell Sarcoma	2	2	2	1		
SKELETAL MUSCLE (No. Exam.)	(9)	(15)	(6)	(7)	(14)	(3)
Metastatic Angioma						
STOMACH (No. Examined)	(9)	(20)	(8)	(7)	(18)	(4)
Lymphosarcoma					1	
TESTIS (No. Examined)	(54)		(64)		(41)	
Interstitial Cell Tumor			2			
Angioma					1	
THYMUS (No. Examined)	(1)	(0)	(0)	(0)	(2)	(4)
Lymphosarcoma					2	
THYROID (No. Examined)	(11)	(22)	(12)	(11)	(16)	(4)
Lymphosarcoma					1	
C-Cell Adenoma	1					

TABLE I
RAT - TUMOR SUMMARY DATA

	T3 Male	T3 Female	T4 Female	T4 Male None		
MAMMARY GLAND (No. Examined)						
Fibroadenoma		3	5			
Adenoma		1	2			
Adenocarcinoma	1	8	14			
ZYMBAL'S GLAND (No. Examined)	(8)	(5)				
Carcinoma	9	4	4			
SPLEEN (No. Examined)	(71)	(67)	(0)			
Angiosarcoma						
Lymphosarcoma						
Reticulum Cell Sarcoma	1					
SKELETAL MUSCLE (No. Exam.)	(1)	(0)	(0)			
Metastatic Angioma						
STOMACH (No. Examined)	(3)	(0)	(0)			
Lymphosarcoma						
TESTIS (No. Examined)	(5)					
Interstitial Cell Tumor						
Angioma						
THYMUS (No. Examined)	(0)	(1)	(0)			
Lymphosarcoma						
THYROID (No. Examined)	(3)	(2)	(0)			
Lymphosarcoma						
C-Cell Adenoma						

TABLE I
RAT - TUMOR SUMMARY DATA

	Control Male	Control Female	T1 Male	T1 Female	T2 Male	T2 Female
THYROID (continued)						
Follicular Adenoma		1				
Follicular Adenocarcinoma		1				
TRACHEA (No. Examined)	(14)	(27)	(17)	(15)	(23)	(9)
Lymphosarcoma					1	
UTERUS (No. Examined)		(36)		(35)		(11)
Reticulum Cell Sarcoma		1				
LYMPH NODE (No. Examined)	(12)	(21)	(8)	(7)	(17)	(5)
Fibrosarcoma				1		
Total Number Neoplasms	44	141	58	134	123	155
No. Animals with Angiosarcomas	S) 0	0	1	2	7	3
	PM) 0	0	12	13	33	62
	NR) 2	0	0	0	0	4
	T) 2	0	13	20	40	69
	%) 2.4	0	15.7	26.7	52.6	84.1
Total No. Primary Angiosarcomas	2	0	12	29	69	96
No. Primary Angiosarcomas per Rat	0.0125	0	0.145	0.387	0.908	1.170
S=Sacrificed						
PM=Died During Study						
T=Total						

NR=Newly Read

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TABLE I
RAT - TUMOR SUMMARY DATA

	T3 Male	T3 Female	T4 Female	T4 Male None		
THYROID (continued)						
Follicular Adenoma						
Follicular Adenocarcinoma						
TRACHEA (No. Examined)	(4)	(3)	(0)			
Lymphosarcoma						
UTERUS (No. Examined)		(2)	(0)			
Reticulum Cell Sarcoma						
LYMPH NODE (No. Examined)	(3)	(0)	(0)			
Fibrosarcoma						
Total Number Neoplasms	148	168	161			
No. Animals with Angiosarcomas	S) 10 PM) 41 NR) 2 T) 53 %) 63.9	8 50 8 64 79.0	5 53 3 61 81.3			
Total No. Primary Angiosarcomas	93	110	96			
No. Primary Angiosarcomas per Rat	1.069	1.358	1.28			
S=Sacrificed PM=Died During Study T=Total NR=Newly Read						

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TABLE II
MICE - TUMOR SUMMARY DATA

	Control Male	Control Female		T1 Male	T1 Female	
HEART (No. Examined)	(50)	(45)		(56)	(58)	
Lymphosarcoma	2			1		
Angiosarcoma						
KIDNEY (No. Examined)	(52)	(45)		(58)	(62)	
Angiosarcoma				3	7	
Lymphosarcoma	3	2		2	2	
Reticulum Cell Sarcoma	2			1		
Metastatic Angiosarcoma					1	
LIVER (No. Examined)	(52)	(45)		(59)	(62)	
Angiosarcoma				18	28	
Hepatocellular Carcinoma				1		
Lymphosarcoma	3	3		2	1	
Reticulum Cell Sarcoma	1	1		1		
Metastatic Mammary Carcinoma						
Hepatocellular Adenoma	1					
Metastatic Squamous Cell Carcinoma					1	
LUNG (No. Examined)	(51)	(45)		(58)	(62)	
Alveologenic Adenoma	8	2		68	34	
Alveologenic Carcinoma	1			4	6	
Lymphosarcoma	3	2		2	2	
Reticulum Cell Sarcoma	2			1		
Metastatic Mammary Carcinoma					7	
Metastatic Angiosarcoma					1	
Metastatic Squamous Cell Carcinoma					2	

TABLE II
MICE - TUMOR SUMMARY DATA

	T2 Male	T2 Female		T3 Male	T3 Female	
HEART (No. Examined)	(64)	(59)		(46)	(40)	
Lymphosarcoma						
Angiosarcoma		1				
KIDNEY (No. Examined)	(69)	(62)		(50)	(48)	
Angiosarcoma		1		2		
Lymphosarcoma	1	1			1	
Reticulum Cell Sarcoma	1					
Metastatic Angiosarcoma				2		
LIVER (No. Examined)	(70)	(64)		(51)	(50)	
Angiosarcoma	71	60		52	61	
Hepatocellular Carcinoma						
Lymphosarcoma	1	1			1	
Reticulum Cell Sarcoma	1					
Metastatic Mammary Carcinoma					1	
Hepatocellular Adenoma					1	
Metastatic Squamous Cell Carcinoma						
LUNG (No. Examined)	(70)	(64)		(51)	(50)	
Alveologenic Adenoma	66	53		92	61	
Alveologenic Carcinoma	1	3		10	8	
Lymphosarcoma	1				1	
Reticulum Cell Sarcoma	1					
Metastatic Mammary Carcinoma		4		2	6	
Metastatic Angiosarcoma		1		4	5	
Metastatic Squamous Cell Carcinoma						

TABLE II
MICE - TUMOR SUMMARY DATA

	Control Male	Control Female		T1 Male	T1 Female	
LYMPH NODE (No. Examined)	(3)	(2)		(2)	(2)	
Lymphosarcoma	1	2				
Angiosarcoma				1		
Reticulum Cell Sarcoma	1					
MESENTERY (No. Examined)	(2)	(2)		(10)	(27)	
Angiosarcoma				7	29	
Lymphosarcoma	1	1		2	1	
Reticulum Cell Sarcoma	1			1		
Fibrosarcoma					1	
OVARY (No. Examined)		(10)			(5)	
Angiosarcoma		1*			1	
PANCREAS (No. Examined)	(4)	(14)		(11)	(5)	
Angiosarcoma				1	1	
Lymphosarcoma	1					
SALIVARY GLAND (No. Examined)	(0)	(0)		(7)	(1)	
Angiosarcoma						
SKELETAL MUSCLE (No. Examined)	(0)	(0)		(6)	(2)	
Lymphosarcoma						
SKIN (No. Examined)	(0)	(3)		(3)	(4)	
Lymphosarcoma				1		
Fibrosarcoma		1			1	
Squamous Cell Carcinoma					1	

*Diagnosed angioma

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TABLE II
MICE - TUMOR SUMMARY DATA

	T2 Male	T2 Female		T3 Male	T3 Female	
LYMPH NODE (No. Examined)	(0)	(2)		(0)	(1)	
Lymphosarcoma					1	
Angiosarcoma						
Reticulum Cell Sarcoma						
MESENTERY (No. Examined)	(12)	(10)		(6)	(7)	
Angiosarcoma	11	10		10	8	
Lymphosarcoma	1					
Reticulum Cell Sarcoma						
Fibrosarcoma						
OVARY (No. Examined)		(4)			(1)	
Angiosarcoma		1				
PANCREAS (No. Examined)	(3)	(4)		(1)	(1)	
Angiosarcoma						
Lymphosarcoma						
SALIVARY GLAND (No. Examined)	(1)	(1)		(2)	(0)	
Angiosarcoma		1				
SKELETAL MUSCLE (No. Examined)	(1)	(2)		(0)	(0)	
Lymphosarcoma	1					
SKIN (No. Examined)	(1)	(2)		(1)	(1)	
Lymphosarcoma						
Fibrosarcoma						
Squamous Cell Carcinoma		2		1		

TABLE II
MICE - TUMOR SUMMARY DATA

	Control Male	Control Female		T1 Male	T1 Female	
MAMMARY GLAND (No. Examined)	(0)	(1)		(1)	(24)	
Adenosquamous Carcinoma		1		1	9	
Adenocarcinoma					19	
SPLEEN (No. Examined)	(46)	(41)		(57)	(62)	
Angiosarcoma					3	
Lymphosarcoma	2	3		2	2	
Reticulum Cell Sarcoma	1	1		1		
Metastatic Angiosarcoma						
Metastatic Mammary Carcinoma						
STOMACH (No. Examined)	(8)	(17)		(6)	(2)	
Adenocarcinoma				1		
Lymphosarcoma	1					
Reticulum Cell Sarcoma	1					
URINARY BLADDER (No. Examined)	(6)	(8)		(5)	(1)	
Lymphosarcoma	1					
UTERUS (No. Examined)		(14)			(5)	
Sarcoma, N.O.S.		1				
Total Neoplasms	31	19		120	145	
No. Animals with Angiosarcomas	S) 0	0		4	3	
	PM) 0	0		0	0	
	T) 0	1		20	40	
	%) 0	2.2		33.3	61.5	
Total No. Primary Angiosarcomas	0	1		30	69	
No. Primary Angiosarcomas/Mouse	0	.02		0.5	1.06	

S=Sacrificed, PM=Died During Study, T=Total

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EPL 02015

TABLE II
MICE - TUMOR SUMMARY DATA

	T2 Male	T2 Female		T3 Male	T3 Female	
MAMMARY GLAND (No. Examined)	(0)	(9)		(3)	(7)	
Adenosquamous Carcinoma		6		1	8	
Adenocarcinoma		5		2	8	
SPLEEN (No. Examined)	(68)	(63)		(47)	(50)	
Angiosarcoma	3	1			2	
Lymphosarcoma	1	1			1	
Reticulum Cell Sarcoma	1					
Metastatic Angiosarcoma	1					
Metastatic Mammary Carcinoma					1	
STOMACH (No. Examined)	(0)	(2)		(0)	(1)	
Adenocarcinoma						
Lymphosarcoma						
Reticulum Cell Sarcoma						
URINARY BLADDER (No. Examined)	(0)	(1)		(0)	(0)	
Lymphosarcoma						
UTERUS (No. Examined)		(2)			(0)	
Sarcoma, N.O.S.						
Total Neoplasms	152	136		160	127	
No. Animals with Angiosarcomas	S) 3	0		9	12	
	PM) 0	0		0	0	
	T) 74	65		51	63	
	%) 96.1	91.5		89.5	88.7	
Total No. Primary Angiosarcomas	85	75		64	71	
No. Primary Angiosarcomas/Mouse	1.10	1.05		1.12	1.0	

S=Sacrificed, PM=Died During Study, T=Total

TABLE III
HAMSTERS - TUMOR SUMMARY DATA

	Control Male	Control Female		T1 Male	T1 Female	
ADRENAL (No. Examined)	(9)	(4)		(12)	(4)	
Cortical Adenoma						
Cortical Carcinoma				1		
HEART (No. Examined)	(45)	(32)		(41)	(30)	
Lymphosarcoma						
KIDNEYS (No. Examined)	(53)	(36)		(43)	(33)	
Angiosarcoma						
Reticulum Cell Sarcoma				1		
Tubular Adenoma				1	1	
Metastatic Mammary Adeno- carcinoma						
LIVER (No. Examined)	(50)	(33)		(44)	(30)	
Angiosarcoma				5	2	
Lymphosarcoma						
Metastatic Granulosa Cell						
Metastatic Mammary Adeno- carcinoma						
LUNG (No. Examined)	(49)	(32)		(42)	(29)	
Alveolar Adenoma						
Angiosarcoma						
Bronchiolar Carcinoma						
Bronchiolar Adenoma						
Metastatic Angiosarcoma						
Metastatic Melanosarcoma				1		
Metastatic Adenocarcinoma						

TABLE III
HAMSTERS - TUMOR SUMMARY DATA

	T2 Male	T2 Female		T3 Male	T3 Female	
ADRENAL (No. Examined)	(18)	(11)		(5)	(2)	
Cortical Adenoma		1		1		
Cortical Carcinoma	1					
HEART (No. Examined)	(35)	(51)		(45)	(23)	
Lymphosarcoma				1		
KIDNEYS (No. Examined)	(40)	(57)		(50)	(24)	
Angiosarcoma	2					
Reticulum Cell Sarcoma						
Tubular Adenoma						
Metastatic Mammary Adeno- carcinoma		1				
LIVER (No. Examined)	(36)	(52)		(48)	(26)	
Angiosarcoma	1	11		38	18	
Lymphosarcoma				1		
Metastatic Granulosa Cell		1				
Metastatic Mammary Adeno- carcinoma		1				
LUNG (No. Examined)	(36)	(49)		(44)	(26)	
Alveolar Adenoma				1		
Angiosarcoma				2		
Bronchiolar Carcinoma				2	1	
Bronchiolar Adenoma				1		
Metastatic Angiosarcoma	1	2		7	4	
Metastatic Melanosarcoma	1					
Metastatic Adenocarcinoma		1				

TABLE III
HAMSTERS - TUMOR SUMMARY DATA

	Control Male	Control Female		T1 Male	T1 Female	
LUNG (Continued)						
Metastatic Mammary Adeno- carcinoma						
Metastatic Uterine Adeno- carcinoma						
MESENTERY (No. Examined)	(0)	(0)		(5)	(3)	
Angiosarcoma				1	1	
Melanosarcoma				1		
Adenocarcinoma, N.O.S.						
ESOPHAGUS (No. Examined)	(7)	(2)		(7)	(3)	
Papilloma						
OVARIES (No. Examined)		(16)			(13)	
Granulosa Cell, Malignant						
Thecal Cell		1			1	
PANCREAS (No. Examined)	(14)	(4)		(20)	(11)	
Islet Cell Adenoma				1		
PLEURA (No. Examined)	(0)	(0)		(0)	(0)	
Metastatic Angiosarcoma						
SKELETAL MUSCLE (No. Examined)	(3)	(3)		(7)	(2)	
Lymphosarcoma						
SKIN (No. Examined)	(5)	(2)		(7)	(4)	
Angiosarcoma						

TABLE III
HAMSTERS - TUMOR SUMMARY DATA

	T2 Male	T2 Female		T3 Male	T3 Female	
LUNG (Continued)						
Metastatic Mammary Adeno- carcinoma		2				
Metastatic Uterine Adeno- carcinoma		1				
MESENTERY (No. Examined)	(11)	(3)		(8)	(4)	
Angiosarcoma	2	3		7	4	
Melanosarcoma						
Adenocarcinoma, N.O.S.		1				
ESOPHAGUS (No. Examined)	(14)	(9)		(4)	(3)	
Papilloma		1				
OVARIES (No. Examined)		(16)			(2)	
Granulosa Cell, Malignant		1				
Thecal Cell		1				
PANCREAS (No. Examined)	(16)	(12)		(4)	(3)	
Islet Cell Adenoma	1				1	
PLEURA (No. Examined)	(0)	(0)		(1)	(0)	
Metastatic Angiosarcoma				1		
SKELETAL MUSCLE (No. Examined)	(16)	(5)		(5)	(3)	
Lymphosarcoma				1		
SKIN (No. Examined)	(16)	(12)		(7)	(3)	
Angiosarcoma	2					

TABLE III
HAMSTERS - TUMOR SUMMARY DATA

	Control Male	Control Female		T1 Male	T1 Female	
SKIN (Continued)						
Fibroma						
Fibrosarcoma						
Melanosarcoma					1	
Metastatic Uterine Adeno- carcinoma					1	
MAMMARY GLAND (No. Examined)	(0)	(2)		(0)	(4)	
Adenocarcinoma						
Adenoma						
SPLEEN (No. Examined)	(40)	(31)		(36)	(26)	
Angiosarcoma				3	2	
Metastatic Mammary Adeno- carcinoma						
Lymphosarcoma						
STOMACH (No. Examined)	(3)	(3)		(8)	(3)	
Papilloma	1			3		
THYMUS (No. Examined)	(0)	(0)		(0)	(0)	
Lymphosarcoma						
UTERUS (No. Examined)		(22)			(15)	
Adenocarcinoma						
Angiosarcoma		1*				
Papilloma						

* Diagnosed as angioma.

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TABLE III
HAMSTERS - TUMOR SUMMARY DATA

	T2 Male	T2 Female		T3 Male	T3 Female	
SKIN (Continued)						
Fibroma		1				
Fibrosarcoma		2				
Melanosarcoma						
Metastatic Uterine Adeno- carcinoma						
MAMMARY GLAND (No. Examined)	(0)	(12)		(0)	(3)	
Adenocarcinoma		3			1	
Adenoma		1				
SPLEEN (No. Examined)	(34)	(47)		(41)	(22)	
Angiosarcoma	5	11		8	9	
Metastatic Mammary Adeno- carcinoma		1				
Lymphosarcoma				1		
STOMACH (No. Examined)	(16)	(14)		(7)	(4)	
Papilloma	1	10		2	2	
THYMUS (No. Examined)	(2)	(3)		(2)	(0)	
Lymphosarcoma				1		
UTERUS (No. Examined)		(33)			(4)	
Adenocarcinoma		2				
Angiosarcoma		1			1	
Papilloma		1				

TABLE III
HAMSTERS - TUMOR SUMMARY DATA

	Control Male	Control Female		T1 Male	T1 Female	
Total Neoplasms	2	2		18	9	
No. Animals with Angiosarcomas	S) 0	1		2	1	
	PM) 0	0		5	3	
	T) 0	1		7	4	
	%) 0	2.7		15.21	12.9	
Total No. Primary Angiosarcomas	0	1		9	5	
No. Primary Angiosarcomas/ Hamster	0	0.027		1.28	1.25	
S=Sacrificed PM=Died During Study T=Total						

TABLE III
HAMSTERS - TUMOR SUMMARY DATA

	T2 Male	T2 Female		T3 Male	T3 Female	
Total Neoplasms	17	61		75	41	
No. Animals with Angiosarcomas S)	3	2		8	4	
PM)	5	15		31	16	
T)	8	17		39	20	
%)	21.6	26.98		75.0	64.5	
Total No. Primary Angiosarcomas	12	25		55	32	
No. Primary Angiosarcomas/ Hamster	1.50	1.47		1.40	1.60	
S=Sacrificed						
PM=Died During Study						
T=Total						

TABLE IV

PERCENTAGE OF ANIMALS WITH PRIMARY ANGIOSARCOMAS

	<u>Untreated Control</u>	<u>T1</u>	<u>T2</u>	<u>T3</u>	<u>T4*</u>
RATS					
Male	2.4	15.7	52.6	63.9	-
Female	0	26.7	84.1	79.0	81.3
MICE					
Male	0	33.3	96.1	89.5	-
Female	2.2	61.5	91.5	88.7	-
HAMSTERS					
Male	0	15.2	21.6	75.0	-
Female	2.7	12.9	27.0	64.5	-

*Allowed feed and bedding during exposure

TABLE V
TISSUE COUNTS - MALE RATS

	Untreated Control	T-1	T-2	T-3		
Number of Animals	81	82	75	86		
ADRENAL	18	15	22	22		
BONE	18	15	23	24		
BRAIN	19	15	23	23		
EPIDIDYMIS	79	79	73	81		
ESOPHAGUS	59	69	63	73		
EXT. & MID. EAR	10	6	19	0		
EYES	19	15	22	24		
HEART	81	80	74	86		
KIDNEYS	81	80	73	86		
LIVER	81	80	74	86		
LUNG & BRONCHI	81	81	74	86		
MUSCLE	19	17	23	22		
OVARIES		1				
PANCREAS	69	65	65	71		

TABLE V
TISSUE COUNTS - MALE RATS

	Untreated Control	T-1	T-2	T-3		
PITUITARY	14	13	16	21		
PROSTATE	11	15	23	8		
SALIVARY GLAND	17	15	23	22		
SEMINAL VESICLE	8	5	14	0		
SKIN	24	14	25	22		
SPINAL CORD	17	13	21	20		
SPLEEN	81	78	73	85		
STOMACH	19	15	25	20		
TESTIS	78	79	73	81		
THYMUS	4	3	1	8		
THYROID	26	27	30	36		
TISSUE MASS	21	24	37	62		
TRACHEA	49	48	49	52		
URINARY BLADDER	18	15	25	20		
UTERUS		1				

TABLE V
TISSUE COUNTS - MALE RATS

	Untreated Control	T-1	T-2	T-3		
AORTA	18	13	19	17		
OPTIC NERVE	16	13	15	20		
INTESTINES	21	15	24	23		
LYMPH NODE	32	32	38	54		
PERIPHERAL NERVE	18	13	21	16		
STERNUM	15	14	23	8		
TONGUE	18	15	22	22		
NOSE	9	12	23	16		
DIAPHRAGM	1	0	0	2		
FAT	1	0	0	0		
UNKNOWN	40	47	39	35		
ZYMBAL'S GLAND	0	0	0	0		
SKULL	0	13	22	0		

TABLE V
TISSUE COUNTS - FEMALE RATS

	Untreated Control	T-1	T-2	T-3	T-4	
Number of Animals	92	76	79	79	74	
ADRENAL	30	12	10	15	9	
BONE	28	13	10	16	10	
BRAIN	28	14	10	17	11	
EPIDIDYMIS						
ESOPHAGUS	60	54	71	75	67	
EXT. & MID. EAR	18	7	5	3	1	
EYES	28	13	11	18	11	
HEART	79	65	73	78	73	
KIDNEYS	78	65	74	77	72	
LIVER	77	65	75	79	72	
LUNG & BRONCHI	78	63	74	78	73	
MUSCLE	30	15	12	11	10	
OVARIES	72	62	71	69	67	
PANCREAS	69	56	67	61	50	

TABLE V
TISSUE COUNTS - FEMALE RATS

	Untreated Control	T-1	T-2	T-3	T-4	
PITUITARY	24	9	11	12	8	
PROSTATE						
SALIVARY GLAND	33	12	13	17	10	
SEMINAL VESICLE						
SKIN	58	29	19	13	12	
SPINAL CORD	26	13	8	14	9	
SPLEEN	78	64	74	79	70	
STOMACH	34	14	11	12	13	
TESTIS						
THYMUS	2	1	2	3	2	
THYROID	31	21	29	32	22	
TISSUE MASS	60	61	69	67	67	
TRACHEA	55	47	56	19	44	
URINARY BLADDER	28	14	11	13	14	
UTERUS	75	64	71	73	66	

TABLE V
TISSUE COUNTS - FEMALE RATS

	Untreated Control	T-1	T-2	T-3	T-4	
AORTA	27	9	9	15	5	
OPTIC NERVE	26	10	7	15	9	
INTESTINES	31	17	10	15	13	
LYMPH NODE	41	28	38	62	51	
PERIPHERAL NERVE	21	8	7	9	9	
STERNUM	26	10	9	5	5	
TONGUE	24	11	11	10	9	
NOSE	16	13	10	8	6	
DIAPHRAGM	0	0	0	0	0	
FAT	0	0	0	0	0	
UNKNOWN	65	59	48	38	53	
ZYMBAL'S GLAND	7	1	0	0	0	
SKULL	14	9	10	10	8	

TABLE VI
TISSUE COUNTS - MALE MICE

	Untreated Control	T-1	T-2	T-3		
Number of Animals	61	61	82	71		
ADRENAL	14	27	51	52		
BONE	6	13	7	16		
BRAIN	5	13	3	14		
EPIDIDYMIS	56	57	81	66		
ESOPHAGUS	2	3	13	22		
EXT. & MID. EAR	1	0	1	6		
EYES	6	7	2	13		
GALL BLADDER	8	6	5	16		
HEART	60	60	82	71		
KIDNEYS	61	60	82	70		
LIVER	60	61	82	71		
LUNG	60	61	82	71		
MUSCLE	6	13	7	13		
NASAL CAVITY	0	0	1	12		

TABLE VI
TISSUE COUNTS - MALE MICE

	Untreated Control	T-1	T-2	T-3		
OVARIES						
PANCREAS	26	17	36	69		
PITUITARY	0	0	3	12		
PROSTATE	8	8	0	0		
SALIVARY GLAND	3	9	5	14		
SEMINAL VESICLE	6	5	0	0		
SKIN	7	11	10	13		
SPINAL CORD	2	9	4	12		
SPLEEN	60	58	79	71		
STOMACH	51	60	82	67		
TESTIS	52	57	81	64		
THYMUS	0	0	0	0		
THYROID	0	3	1	1		
TISSUE MASS	4	4	19	12		
TRACHEA	12	8	9	22		

TABLE VI
TISSUE COUNTS - MALE MICE

	Untreated Control	T-1	T-2	T-3		
URINARY BLADDER	46	47	77	65		
UTERUS						
AORTA	2	1	1	1		
INTESTINES	53	59	82	70		
LYMPH NODE	11	6	33	33		
PERIPHERAL NERVE	0	5	1	5		
STERNUM	0	7	0	0		
TONGUE	2	1	3	11		
SKULL	3	6	4	9		
UNKNOWN	3	11	20	10		
OPTIC NERVE	6	7	0	0		
FEET	0	0	0	0		
LEGS	0	0	0	0		
LIMBS	0	0	1	0		
ZYMBAL'S GLAND	0	0	0	6		

TABLE VI
TISSUE COUNTS - FEMALE MICE

	Untreated Control	T-1	T-2	T-3		
Number of Animals	45	76	77	72		
ADRENAL	20	29	77	64		
BONE	6	9	9	16		
BRAIN	2	6	8	13		
EPIDIDYMIS						
ESOPHAGUS	7	2	48	39		
EXT. & MID. EAR	0	2	3	3		
EYES	1	5	8	14		
GALL BLADDER	16	6	38	19		
HEART	43	75	75	71		
KIDNEYS	44	75	77	72		
LIVER	44	76	77	72		
LUNG	44	75	76	72		
MUSCLE	9	11	5	14		
NASAL CAVITY	0	0	5	12		

TABLE VI
TISSUE COUNTS - FEMALE MICE

	Untreated Control	T-1	T-2	T-3		
OVARIES	28	53	68	64		
PANCREAS	20	10	71	69		
PITUITARY	1	1	5	10		
PROSTATE						
SALIVARY GLAND	0	2	8	15		
SEMINAL VESICLE						
SKIN	3	18	11	19		
SPINAL CORD	3	3	8	13		
SPLEEN	43	75	75	71		
STOMACH	44	74	76	70		
TESTIS						
THYMUS	0	0	2	2		
THYROID	4	1	6	5		
TISSUE MASS	3	52	21	27		
TRACHEA	12	3	37	33		

TABLE VI
TISSUE COUNTS - FEMALE MICE

	Untreated Control	T-1	T-2	T-3		
URINARY BLADDER	23	30	64	60		
UTERUS	38	48	75	69		
AORTA	1	0	4	5		
INTESTINES	43	73	74	72		
LYMPH NODE	11	2	53	50		
PERIPHERAL NERVE	0	2	1	8		
STERNUM	2	3	1	0		
TONGUE	1	0	8	8		
SKULL	1	10	5	8		
UNKNOWN	3	45	19	19		
OPTIC NERVE	1	5	7	0		
FEET	1	0	0	1		
LEGS	0	2	0	0		
LIMBS	0	0	0	0		
ZYMBAL'S GLAND	0	0	0	8		

TABLE VII
TISSUE COUNTS - MALE HAMSTERS

	Untreated Control	T-1	T-2	T-3		
Total Number of Animals	57	45	46	61		
ADRENAL	13	12	21	9		
BONE	5	7	17	9		
BRAIN	5	7	17	9		
EPIDIDYMIS	56	41	45	56		
ESOPHAGUS	10	9	17	11		
EXT. & MID. EAR	2	7	15	4		
EYES	4	7	17	9		
GALL BLADDER	24	26	25	21		
HEART	57	45	46	61		
KIDNEYS	57	45	46	61		
LIVER	57	45	46	61		
LUNG & BRONCHI	57	45	46	61		
MUSCLE	3	8	19	9		
NASAL CAVITY (NOSE)		2				

TABLE VII
TISSUE COUNTS - MALE HAMSTERS

	Untreated Control	T-1	T-2	T-3		
OVARIES						
PANCREAS	24	28	27	21		
PITUITARY	0	5	7	0		
PROSTATE	13	12	20	11		
RIB (JUNCTION)		1				
SALIVARY GLAND	3	8	17	8		
SEMINAL VESICLE	7	10	19	11		
SKIN	5	6	17	8		
SPINAL CORD	4	8	16	4		
SPLEEN	52	41	43	59		
STOMACH	10	14	31	41		
TESTIS	55	41	44	54		
THYMUS	1	2	2	1		
THYROID	6	9	11	4		
TISSUE MASS	3	2	7	4		

TABLE VII
TISSUE COUNTS - MALE HAMSTERS

	Untreated Control	T-1	T-2	T-3		
TRACHEA	18	17	23	30		
URINARY BLADDER	12	19	30	36		
UTERUS						
AORTA	22	20	10	4		
OPTIC NERVE	2	5	9			
INTESTINES	16	13	32	46		
LYMPH NODE	3	7	15	2		
PERIPHERAL NERVE	1	3	7	1		
STERNUM	4	3	15	7		
TONGUE	3	6	16	8		
SKULL	1	5	15	2		
UNKNOWN	13	14	10	16		
PAPILLARY PROJECTION		2	3	6		
FEET		1	2			
CYST						

TABLE VII
TISSUE COUNTS - FEMALE HAMSTERS

	Untreated Control	T-1	T-2	T-3		
Total Number of Animals	35	36	61	31		
ADRENAL	6	7	7	9		
BONE	3	5	8	7		
BRAIN	3	5	8	8		
EPIDIDYMIS						
ESOPHAGUS	7	6	10	8		
EXT. & MID. EAR	1	5	8	3		
EYES	4	5	7	7		
GALL BLADDER	8	14	23	12		
HEART	35	36	60	31		
KIDNEYS	35	36	60	31		
LIVER	35	36	60	31		
LUNG & BRONCHI	35	36	59	31		
MUSCLE	3	4	7	4		
NASAL CAVITY (NOSE)						

TABLE VII
TISSUE COUNTS - FEMALE HAMSTERS

	Untreated Control	T-1	T-2	T-3		
OVARIES	18	22	34	18		
PANCREAS	17	20	27	13		
PITUITARY	0	2	2	1		
PROSTATE						
RIB (JUNCTION)						
SALIVARY GLAND	3	5	12	5		
SEMINAL VESICLE						
SKIN	3	3	12	5		
SPINAL CORD	3	4	7	4		
SPLEEN	34	34	57	30		
STOMACH	15	14	30	26		
TESTIS						
THYMUS	4	0	2	1		
THYROID	3	3	7	2		
TISSUE MASS	3	3	4	3		

TABLE VII
TISSUE COUNTS - FEMALE HAMSTERS

	Untreated Control	T-1	T-2	T-3		
TRACHEA	12	14	18	19		
URINARY BLADDER	16	12	21	22		
UTERUS	32	34	50	28		
AORTA	2	6	20	6		
OPTIC NERVE	3	2	6			
INTESTINES	18	18	30	28		
LYMPH NODE	3	3	8	3		
PERIPHERAL NERVE	2	3	3	1		
STERNUM	2	4	7	4		
TONGUE	2	3	6	4		
SKULL	2	4	3	3		
UNKNOWN	3	2	20	6		
PAPILLARY PROJECTION	1		13	2		
FEET						
CYST		1				