Spontaneous Neoplastic Lesions in the Crl:CD-1®(ICR)BR Mouse

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CHARLES RIVER
LABORATORIES

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INTRODUCTION

The data presented in these tables was gathered from 51 toxicology studies of at least 78 weeks duration. All studies were performed in the United States or Europe by contract laboratories or industrial toxicology facilities.

PURPOSE

The purpose of this compilation is to offer the study director, reviewing toxicologist and/or study pathologist some reported incidences of neoplasms in Crl:CD-1 (ICR)BR mice, maintained as control animals, in studies of 78-104 weeks duration. Diagnoses in this compilation are intentionally grouped in a manner to provide the user with a range of reported incidences of similar types of lesions. This compilation is not intended in any way to propose a system of standardized nomenclature nor does it separately include each and every variant of the lesion.

COMMON STUDY PARAMETERS

The 51 studies included in this publication were initiated between January 1987 and December of 1996 in seven different laboratories. All studies used male and/or female Crl:CD-1® (ICR)BR mice from three different Charles River Laboratories production sites: Raleigh, North Carolina; Kingston, New York and Portage Michigan.

The mice in these studies were from control groups of dietary or gavage studies and were approximately 4-7 weeks of age at study initiation. Some groups were untreated while others received the study vehicle, all served as control groups.

The mice included in this publication were generally singly housed in hanging wire mesh cages, fed a diet of Purina 5002 Certified Rodent Chow and had free access to water. The animal rooms were generally maintained at average temperatures of 72 +/- 5° Fahrenheit with an average relative humidity of 30-70%. A 12hr/12hr light/dark cycle was employed in all studies. Since these studies were conducted in different facilities over a period of several years, there was some variation in environmental conditions. The overall environmental conditions were not considered by those performing the studies to have had any effect on the quality or integrity of the studies. Information on the health monitoring, other than that associated with pathological examination conducted in accordance with scheduled or moribund sacrifices, was not available.

DATA SETS PRESENTED

Survival data are presented by study as the actual number surviving to terminal sacrifice and as a percent survival at terminal sacrifice, Tables1 and 2. The survival data are also presented in graphic form, Graphs 1 and 2. Survival data were not available for all studies at the time of publication. Only those studies for which data were available are represented on the graphs.

The overall incidences of all neoplastic lesions observed in any organ are reported and summarized by sex, Tables 3 and 4. These data also include neoplastic lesions from mice that died or were found moribund and killed prior to terminal sacrifice. It does not include information from mice that were killed at any interim sacrifice. Due to the apparent diversity in terminology and the variability among studies in the incidence of

particular lesions, the individual study incidences of lesions in selected organs/systems are also presented, Tables 5 and 6. These organs/systems include liver, lung and whole body/multiple organ.

SUMMARY TABLE CALCULATIONS

The following is a description of how each of the parameters in the tables was calculated.

Number of Studies (# Studies)

This is the number of studies in which a particular tissue/organ was examined. In this publication, the number of studies is usually 46 for males and 48 for females. It is important for the reader to realize that some of the studies reported in this document were performed in only males or females and occasionally a specific tissue/organ was not examined in a particular study.

Total Number of Organs (Total # Organs)

This number represents the sum of the total number of tissues or organs examined in all of the control groups from all studies combined. Widespread tumors which showed involvement of multiple organs were listed on the basis of the total number of animals examined. Occasionally a tumor would be noticed in a tissue not designated for histological examination by the study protocol. In these instances, the tumor incidence was based on the total number of animals examined as any such tumor or lesion would have been noticed on gross examination of the animal. Autolysis did not routinely exclude tissues from diagnosis. Tissue numbers were adjusted only if the individual study table indicated that some tissues were missing or inadequate for examination. Some laboratories presented data separately for different regions within a organ (i.e., duodenum, jejunum, and ileum) while most presented data by the organ (i.e., small intestine). When data were presented separately by organ region, they were grouped under the organ and calculations were based on the number of organs examined.

Total Number of lesions (# Lesions)

This represents the total number of occurrences of this lesion in a specific organ in all studies examined.

Percent of Total

These values represent the particular incidence of a particular lesion/diagnosis in the total number (all studies combined) of a particular organ examined. These values were calculated by dividing the total number of lesions by the total number of organs/animals examined and multiplying by 100 to express the value as a percent. Values are expressed to the second decimal place. Some caution is indicated in using this number, since not all pathologists or institutions will include all diagnoses in their lexicon.

Number of Studies Using This Diagnosis

This is the number of studies in which a particular diagnosis was reported. This number may be useful in interpreting the overall incidence (percent of total) of a particular diagnosis, see above.

Minimum and Maximum Percent Found (Minimum and Maximum % Found)

The range reported is the lowest and highest percent incidence for each lesion from the studies where the diagnosis was made. Therefore, if a study did not include a particular diagnosis, it was excluded from these calculations. The minimum and maximum percent found values should be considered in conjunction with the Number of Studies Using the Diagnosis.

The individual study percentages, Minimum % Found and Maximum % Found, were calculated by dividing the number of times each diagnosis was made by the total number of organs examined in each study and then multiplying the resultant value by 100 to express it as a percent. Values are expressed to the second decimal place.

ADDITIONAL INFORMATION

If additional information is desired regarding the conduct of these studies or the incidence of a particular neoplasm please contact Mary Giknis through Charles River Laboratories, or via e-mail at MLAGIKNIS@att.net.

SYNONYMS

Synonymous terms or diagnoses were frequently encountered in different studies and were combined under a single, often broad diagnosis, which was considered to be the primary diagnosis. Although some effort was made to use currently acceptable terms, it is beyond the scope of this publication to propose a system of preferred diagnoses. The synonyms which were included in the various diagnoses are presented in the synonym list which follows. Where possible, terminology is consistent with the classification system proposed by the Society of Toxicologic Pathologists.

Skin:
Nerve Sheath Tumor = Schwannoma

Testis:
Sertoli Cell Tumor, Benign = Sertoliform Adenoma

Uterus:
Endometrium, Adenocarcinoma = Endometrial Carcimoma
Endometrial Stromal Sarcoma = Endometrial Sarcoma

Whole Body/Multiple Organ:
Lymphoma, Malignant = Lymphosarcoma
Mast Cell Tumor = Mastocytoma

ABBREVIATIONS

NR = Not Recorded or not available at the time of publication.

ACKNOWLEDGEMENTS

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REQUEST FOR DATA

The purpose of these publications is to assist you, our clients, in evaluating your data. Our aim is to provide you with the data that you need to do your job well. We welcome any suggestions that you may have to improve this document as well as suggested topics for future documents. However, please realize that the publication is only as good as the data. To this end we invite you to participate in and support this worthwhile project by sending us your control data. If you or someone at your laboratory is willing to participate, please contact Mary Giknis through Charles River Laboratories, 251 Ballardvale Street, Wilmington, MA 01887 or at MLAGIKNIS@att.net.

Table 1: Summary of Individual Study Information and Survival/Males

Study Identification	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Study Initiation Date	1987	1988	1988	1988	1988	1988	1989	1989	1989	1990	1990	1990	1990	1991	1991	1991
Total Number on Study	53	47	50	49	50	59	50	60	50	48	50	50	69	50	59	60
Number Surviving to Termination	NR	40	NR	NR	31	NR	NR	45	NR	NR	NR	47	NR	31	38	NR
% Survival		85.11			62.00			75.00				94.0		62.0	64.4	
Study Duration in Weeks	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78

Study Identification	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Study Initiation Date	1992	1992	1992	1992	1993	1993	1993	1993	1994	1995	1989	1992	1990	1991	1991	1993
Total Number on Study	50	50	50	50	50	50	60	50	50	70	50	49	60	70	65	60
Number Surviving to Termination	35	39	NR	NR	NR	NR	NR	NR	NR	NR	30	39	11	40	NR	22
% Survival	70.0	78.0									60.0	79.6	18.3	57.1		36.7
Study Duration in Weeks	78	78	78	78	78	78	78	78	78	78	97	100	104	104	104	104

Study Identification	33	34	35	36	37	38	39	40	41	42	43	44	45	46
Study Initiation Date	1993	1993	1993	1993	1994	1994	1994	1995	1995	1995	1995	1996	1996	1996
Total Number on Study	70	50	65	50	50	65	65	60	60	60	80	50	50	116
Number Surviving to Termination	17	18	24	NR	22	43	28	26	29	NR	NR	27	22	NR
% Survival	24.3	36.0	36.9		44.0	66.2	43.1	43.3	48.3			54.0	44.0	
Study Duration in Weeks	104	104	104	104	104	104	104	104	104	104	104	104	104	104

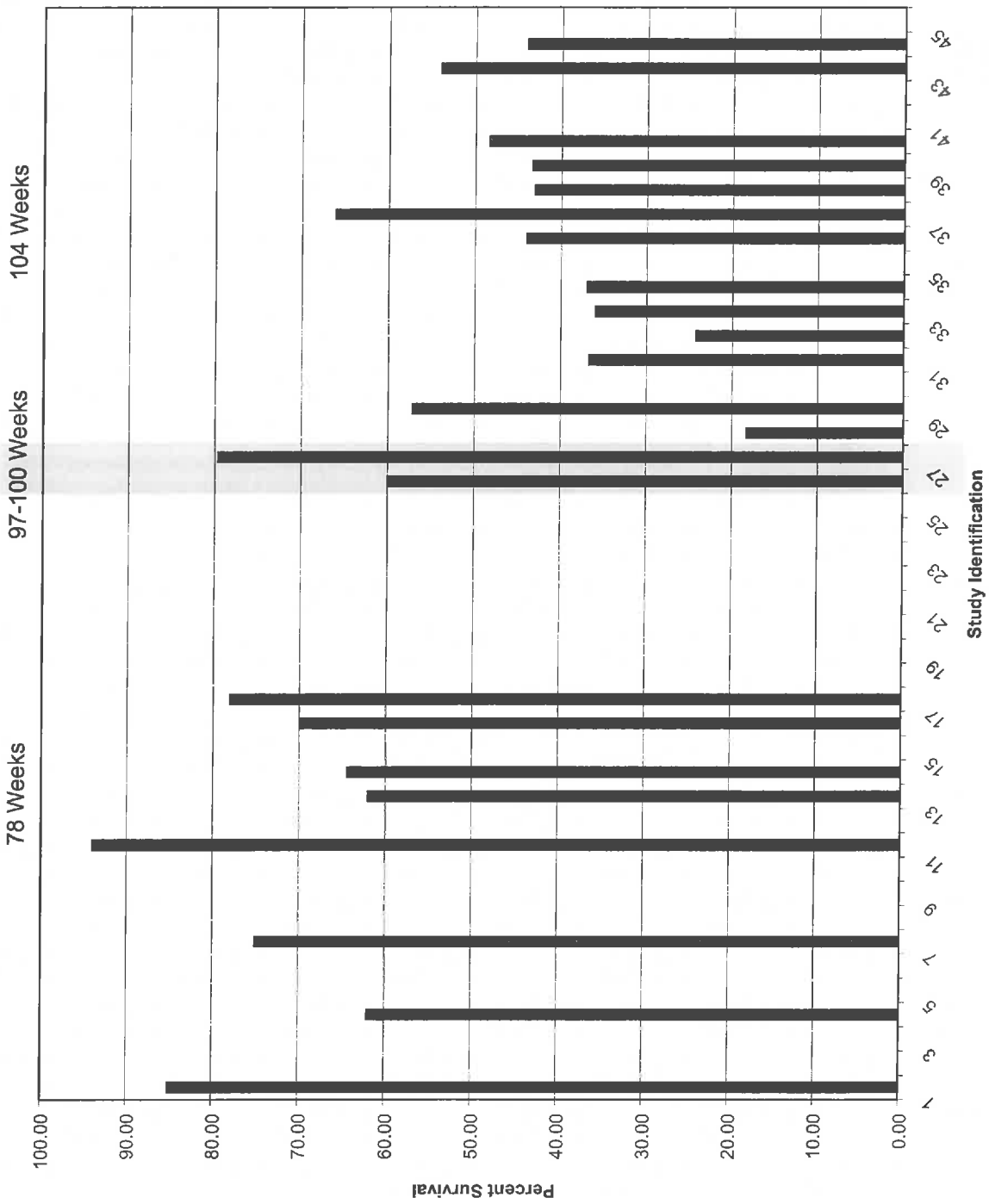
Table 2: Summary of Individual Study Information and Survival/Females

Study Identification	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Study Initiation Date	1987	1988	1988	1988	1988	1988	1989	1989	1989	1990	1990	1990	1990	1991	1991	1991
Total Number on Study	52	49	50	48	49	60	50	60	50	48	50	49	70	49	59	60
Number Surviving to Termination	NR	40	NR	NR	33	NR	NR	45	NR	NR	NR	36	NR	31	38	NR
% Survival		81.6			67.3			75.0				73.5		63.3	64.4	
Study Duration in Weeks	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78

Study Identification	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Study Initiation Date	1992	1992	1992	1993	1993	1993	1993	1994	1995	1996	1995	1995	1989	1992	1990	1991
Total Number on Study	50	50	50	50	50	59	50	50	70	116	60	75	50	50	60	70
Number Surviving to Termination	39	NR	NR	NR	NR	NR	NR	NR	NR	NR	36	47	37	39	13	31
% Survival	78.0										60.0	62.7	74.0	78.0	21.7	44.3
Study Duration in Weeks	78	78	78	78	78	78	78	78	78	91	94	94	97	100	104	104

Study Identification	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
Study Initiation Date	1991	1992	1993	1993	1993	1993	1993	1994	1994	1994	1995	1995	1995	1995	1996	1996
Total Number on Study	65	150	60	70	50	65	59	50	65	65	60	60	60	80	50	50
Number Surviving to Termination	NR	NR	21	13	16	20		22	36	28	27	23	NR	NR	21	21
% Survival			35.0	18.6	32.0	30.8		44.0	55.4	43.1	45.0	38.3			42.0	42.0
Study Duration in Weeks	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104

Graph 1: Male Survival



Graph 2: Female Survival

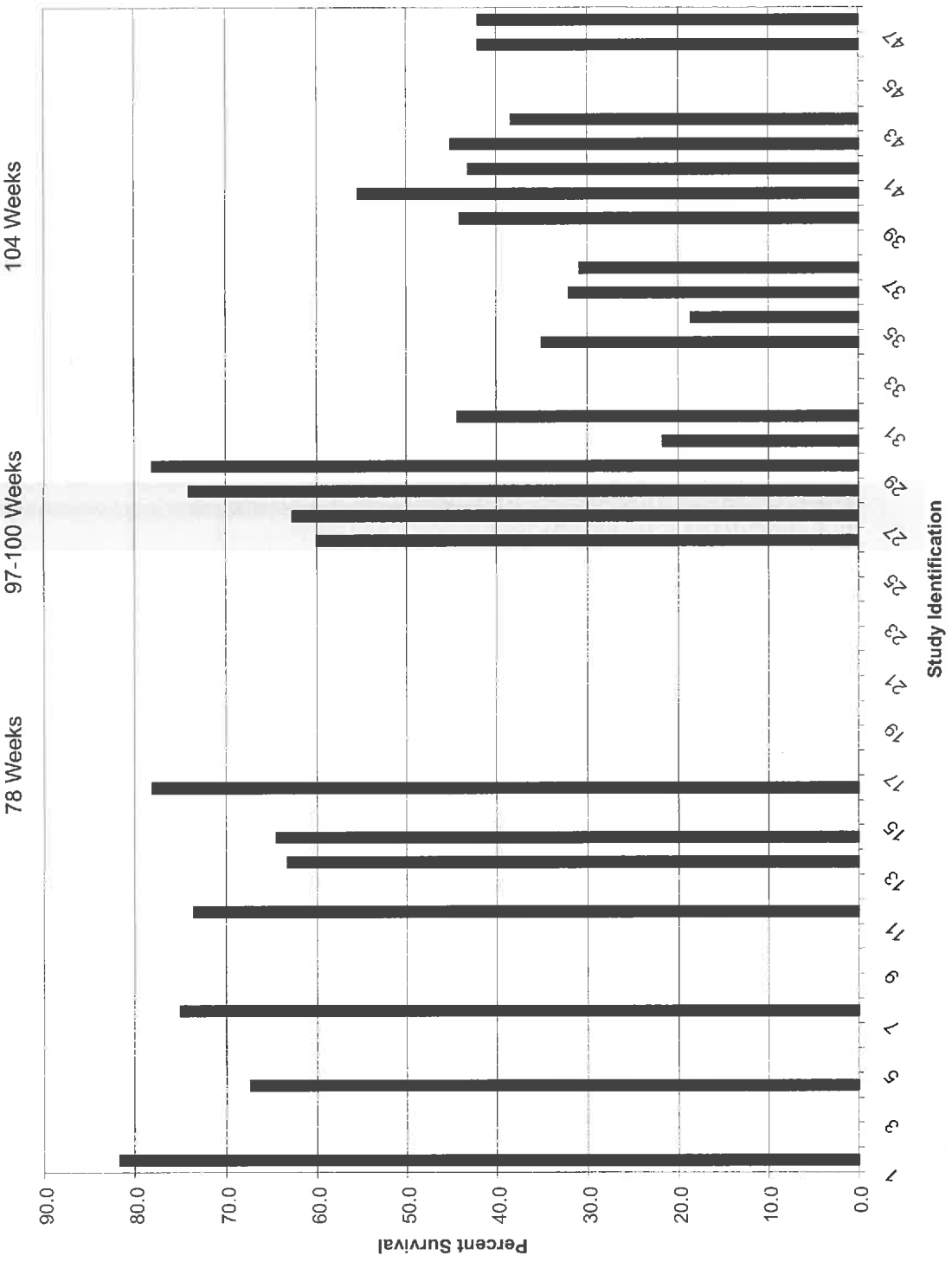


Table 3: Neoplasms/Males

		TOTAL		# STUDIES		
		# ORGANS	PERCENT	USING THIS	MINIMUM	MAXIMUM
LOCATION AND TUMOR	# STUDIES	# LESIONS	OF TOTAL	DIAGNOSIS	% FOUND	%FOUND
DIGESTIVE SYSTEM						
ORAL CAVITY	46	2577				
SALIVARY GLAND	46	2577				
STOMACH	46	2546				
Nonglandular Mucosa/Squamous Cell Papilloma		3	0.12	3	1.67	1.72
Adenocarcinoma		1	0.04	1	1.79	1.79
SMALL INTESTINE	46	2455				
Adenoma		1	0.04	1	1.72	1.72
Adenocarcinoma		5	0.20	4	1.67	2.90
LARGE INTESTINE/CECUM/ANUS	46	2482				
Adenocarcinoma		3	0.12	2	1.43	4.08
LIVER	46	2571				
Hepatocellular Adenoma		269	10.46	44	2.86	28.00
Hepatocellular Carcinoma		136	5.29	39	1.54	16.00
Hemangioma		9	0.35	7	1.54	4.00
Hemangiosarcoma		29	1.13	15	1.11	5.00
GALL BLADDER	46	2257				
Adenoma		3	0.13	3	1.69	2.00
Papilloma		6	0.27	3	2.08	5.00
PERITONEUM	46	2577				
Fibrosarcoma		1	0.04	1	1.69	1.69
Lipoma		2	0.08	2	1.43	2.00

		TOTAL		# STUDIES		
		# ORGANS	PERCENT	USING THIS	MINIMUM	MAXIMUM
LOCATION AND TUMOR	# STUDIES	# LESIONS	OF TOTAL	DIAGNOSIS	% FOUND	%FOUND
RESPIRATORY SYSTEM						
NASAL CAVITY	46	2577				
Nasal Adenocarcinoma		1	0.04	1	2.00	2.00
LUNG	46	2575				
Adenoma, Alveolar/Bronchiolar		368	14.29	43	2.00	42.00
Adenocarcinoma, Alveolar/Bronchiolar		177	6.87	37	1.43	26.00
UROGENITAL SYSTEM						
KIDNEY	46	2569				
Adenoma/Tubular Adenoma		7	0.27	5	2.00	4.00
Adenocarcinoma/Tubular Adenocarcinoma		4	0.16	4	1.43	2.00
URINARY BLADDER	46	2535				
Leiomyoma		1	0.04	1	1.67	1.67
Leiomyoblastoma, Malignant		2	0.08	2	1.45	1.67
Leiomyosarcoma		5	0.20	3	2.00	4.00
TESTIS	46	2576				
Interstitial Cell Tumor, Benign		19	0.74	15	1.43	4.00
Interstitial Cell Tumor, Malignant		2	0.08	2	1.67	2.00
Hemangioma		2	0.08	2	1.67	2.00
Hemangiosarcoma		2	0.08	2	1.43	1.67
Sertoli Cell Tumor, Benign		3	0.12	3	1.43	1.69
SEMINAL VESICLE	46	2542				
Adenocarcinoma		1	0.04	1	2.00	2.00
Leiomyosarcoma		1	0.04	1	1.67	1.67
PROSTATE	46	2565				
Adenoma		1	0.04	1	1.67	1.67
EPIDIDYMIS	46	2515				
Adenoma		1	0.04	1	2.00	2.00
Fibrosarcoma/Stromal Sarcoma		2	0.08	2	1.43	1.54
Leiomyoma		1	0.04	1	1.67	1.67

		TOTAL		# STUDIES		
		# ORGANS	PERCENT	USING THIS	MINIMUM	MAXIMUM
LOCATION AND TUMOR	# STUDIES	# LESIONS	OF TOTAL	DIAGNOSIS	% FOUND	%FOUND
SKIN						
SKIN	46	2552				
Papilloma/Squamous Cell Papilloma		4	0.16	4	1.47	2.00
Trichoepithelioma, Benign		1	0.04	1	2.63	2.63
SKIN, cont'd						
Chondroma		1	0.04	1	1.67	1.67
Fibroma		2	0.08	2	2.00	2.08
Fibrosarcoma		2	0.08	2	1.54	2.00
Hemangioma		1	0.04	1	1.54	1.54
Hemangiosarcoma		4	0.16	4	1.43	1.67
Leiomyosarcoma		1	0.04	1	1.43	1.43
Mast Cell Tumor		1	0.04	1	1.54	1.54
Nerve Sheath Tumor, Benign		1	0.04	1	1.67	1.67
Nerve Sheath Tumor, Malignant		3	0.12	3	1.43	2.00
Sarcoma		1	0.04	1	2.00	2.00
Neurofibroma		1	0.04	1	2.00	2.00
ENDOCRINE SYSTEM						
ADRENAL	46	2526				
Cortex, Adenoma		30	1.19	17	1.56	7.14
Cortex, Carcinoma		1	0.04	1	2.00	2.00
Pheochromocytoma, Benign		11	0.44	7	1.11	5.00
Spindle Cell Tumor, Benign		6	0.24	4	1.56	4.00
PANCREAS	46	2559				
Islet Cell, Adenoma		4	0.16	3	1.54	2.00
Hemangiosarcoma		1	0.04	1	1.69	1.69
PITUITARY	46	2504				
Adenoma		6	0.24	5	1.45	3.23
Carcinoma		1	0.04	1	2.04	2.04
Pars Intermedia, Adenoma		1	0.04	1	2.00	2.00
THYROID	46	2524				
C-Cell, Adenoma		1	0.04	1	2.00	2.00
Follicular Cell, Adenoma		12	0.48	12	1.11	2.00
Follicular Cell, Carcinoma		1	0.04	1	2.00	2.00

		TOTAL		# STUDIES		
		# ORGANS	PERCENT	USING THIS	MINIMUM	MAXIMUM
LOCATION AND TUMOR	**# STUDIES**	**# LESIONS**	**OF TOTAL**	**DIAGNOSIS**	**% FOUND**	**%FOUND**
PARATHYROID	46	2200				
ENDOCRINE SYSTEM						
BRAIN	46	2576				
Oligodendroglioma		1	0.04	1	2.04	2.04
BRAIN, cont'd.						
Meningioma		1	0.04	1	1.43	1.43
SPINAL CORD	46	2575				
PERIPHERAL NERVE	46	2509				
MUSCULOSKELETAL SYSTEM						
SKELETAL MUSCLE	46	2412				
BONE	46	2570				
Osteoma, Benign		1	0.04	1	1.43	1.43
Osteosarcoma		1	0.04	1	1.54	1.54
Sarcoma		1	0.04	1	1.43	1.43
CIRCULATORY SYSTEM						
HEART	46	2578				
BLOOD VESSEL	46	2554				
HEMATOPOIETIC/LYMPHOID SYSTEM						
BONE MARROW	46	2498				
Lymphoma, Malignant		1	0.04	1	2.00	2.00
SPLEEN	46	2543				
Hemangioma		8	0.31	7	1.67	4.00
Hemangiosarcoma		28	1.10	15	1.67	8.00

		TOTAL		# STUDIES		
		# ORGANS	PERCENT	USING THIS	MINIMUM	MAXIMUM
LOCATION AND TUMOR	**# STUDIES**	**# LESIONS**	**OF TOTAL**	**DIAGNOSIS**	**% FOUND**	**%FOUND**
Lymphoma, Malignant		4	0.16	1	8.00	8.00
THYMUS	46	2037				
Lymphoma, Malignant		7	0.34	1	14.89	14.89
LYMPH NODES	46	2504				
Hemangioma		3	0.12	3	1.43	2.04
Hemangiosarcoma		2	0.08	2	2.00	2.00
Lymphoma, Malignant		3	0.12	1	6.00	6.00
WHOLE BODY/MULTIPLE ORGAN	46	2565				
Lymphoma, Malignant		105	4.09	33	1.45	21.67
Lymphoma, Lymphocytic		11	0.43	8	1.69	4.08
Leukemia, Granulocytic		6	0.23	6	1.43	2.04
Leukemia, Lymphocytic		3	0.12	2	2.00	3.33
Hemangiosarcoma		29	1.13	8	1.67	12.00
Histiocytic Sarcoma		35	1.36	19	1.11	8.00
Mast Cell Tumor, Malignant		4	0.16	3	1.43	2.00
SPECIAL SENSES						
EYE	46	2539				
Harderian Gland, Adenoma		120	4.73	31	1.67	14.00
Harderian Gland, Adenocarcinoma		11	0.43	7	1.43	8.33
EAR	46	2575				
Pinna, Hemangioma		1	0.04	1	1.67	1.67
Pinna, Papilloma		1	0.04	1	1.67	1.67

Table 4: Neoplasms/Females

		TOTAL		# STUDIES		
		# ORGANS	PERCENT	USING THIS	MINIMUM	MAXIMUM
	# STUDIES	# LESIONS	OF TOTAL	DIAGNOSIS	% FOUND	%FOUND
DIGESTIVE SYSTEM						
ORAL CAVITY	48	2695				
Tongue, Papilloma		1	0.04	1	1.67	1.67
STOMACH	48	2772				
Polypoid Adenoma		2	0.07	2	1.47	2.00
Squamous Papilloma		4	0.14	4	0.79	2.04
Squamous Cell Carcinoma		1	0.04	1	2.00	2.00
Undifferentiated Carcinoma		2	0.07	2	1.56	2.00
SMALL INTESTINE	48	2667				
Adenoma		1	0.04	1	1.18	1.18
Adenocarcinoma		3	0.11	3	1.49	2.00
LARGE INTESTINE/CECUM/ANUS	48	2645				
Leiomyoma		1	0.04	1	1.72	1.72
LIVER	48	2740				
Hepatocellular Adenoma		27	0.99	20	0.85	7.84
Hepatocellular Carcinoma		18	0.66	13	1.43	4.29
Undifferentiated Carcinoma		1	0.04	1	1.54	1.54
Hemangioma		6	0.22	6	1.54	2.00
Hemangiosarcoma		17	0.62	12	1.43	4.29
GALL BLADDER	48	2513				
Papilloma		2	0.08	2	2.00	3.03
Adenoma		1	0.04	1	3.03	3.03
PERITONEUM	48	2841				

		TOTAL		# STUDIES		
		# ORGANS	PERCENT	USING THIS	MINIMUM	MAXIMUM
	# STUDIES	# LESIONS	OF TOTAL	DIAGNOSIS	% FOUND	%FOUND
RESPIRATORY SYSTEM						
NASAL CAVITY	48	2781				
LUNG	48	2773				
Adenoma, Alveolar/Bronchiolar		236	8.51	43	1.67	26.67
Adenocarcinoma, Alveolar/Bronchiolar		113	4.08	35	0.77	18.37
Mesothelioma, Benign		1	0.04	1	1.67	1.67
UROGENITAL SYSTEM						
KIDNEY	48	2857				
Adenoma/Tubular Adenoma		1	0.04	1	2.00	2.00
Adenocarcinoma/Tubular Adenocarcinoma		1	0.04	1	2.00	2.00
Transitional Cell Carcinoma		1	0.04	1	2.00	2.00
URINARY BLADDER	48	2718				
Transitional Cell Carcinoma		1	0.04	1	2.17	2.17
Leiomyosarcoma		4	0.15	4	1.75	2.44
Undifferentiated Sarcoma, Malignant		1	0.04	1	2.00	2.00
OVARY	48	2735				
Cystadenoma		18	0.66	12	1.54	6.00
Granulosa Cell Tumor, Benign		6	0.22	6	1.47	2.08
Tubular Adenoma		22	0.80	13	1.43	8.16
Luteal Cell Tumor, Benign		6	0.22	5	1.47	4.00
Luteal Cell Tumor, Malignant		1	0.04	1	1.11	1.11
Sertoliform Adenoma		2	0.07	2	2.00	2.04
Theca Cell Tumor, Benign		6	0.22	6	0.77	2.04
Theca Cell Tumor, Malignant		1	0.04	1	2.04	2.04
Hemangioma		8	0.29	7	1.11	2.90
Hemangiosarcoma		2	0.07	2	1.75	2.00
Leiomyoma		4	0.15	4	1.69	2.13
Oviduct, Fibroma		2	0.07	2	0.77	2.04
UTERUS	48	2812				
Endometrium, Adenoma		3	0.11	3	1.54	2.00
Endometrium, Adenocarcinoma		11	0.39	7	0.86	4.00
Endometrial Stromal Polyp		146	5.19	35	1.67	17.14

		TOTAL		# STUDIES		
		# ORGANS	PERCENT	USING THIS	MINIMUM	MAXIMUM
	# STUDIES	# LESIONS	OF TOTAL	DIAGNOSIS	% FOUND	%FOUND
Endometrial Stromal Sarcoma		33	1.17	19	1.43	8.00
Fibroma		2	0.07	2	1.67	2.00
Fibrosarcoma		2	0.07	2	1.54	1.69
Granular Cell Tumor		1	0.04	1	2.04	2.04
Hemangioma		15	0.53	11	1.25	4.62
UTERUS, cont'd.						
Hemangiosarcoma		14	0.50	12	0.77	4.08
Leiomyoma		40	1.42	20	1.43	7.50
Leiomyosarcoma		36	1.28	21	0.86	6.00
Nerve Sheath Tumor, Malignant		6	0.21	5	1.43	3.08
Neurofibrosarcoma		1	0.04	1	2.00	2.00
Osteosarcoma		8	0.28	4	1.54	8.00
Deciduoma		1	0.04	1	1.75	1.75
CERVIX	48	2724				
Squamous Cell Carcinoma		5	0.18	5	1.15	2.00
Endometrial Stromal Polyp		7	0.26	6	1.15	3.33
Endometrial Stromal Sarcoma		6	0.22	6	0.80	2.04
Fibrosarcoma		3	0.11	3	0.80	1.69
Hemangiopericytoma		1	0.04	1	1.75	1.75
Leiomyoma		12	0.44	10	0.80	4.17
Leiomyosarcoma		16	0.59	11	1.45	4.17
Lymphangioma		1	0.04	1	2.04	2.04
Myxoma		1	0.04	1	2.00	2.00
Nerve Sheath Tumor, Benign		1	0.04	1	2.00	2.00
VAGINA	48	2744				
Papilloma		1	0.04	1	2.04	2.04
Polyp		4	0.15	3	0.78	2.86
Adenocarcinoma		1	0.04	1	2.04	2.04
Fibrosarcoma		1	0.04	1	1.43	1.43
Leiomyoma		7	0.26	6	1.47	3.33
Leiomyosarcoma		3	0.11	2	2.08	3.33
CLITORAL GLAND	48	2771				

		TOTAL		# STUDIES		
		# ORGANS	PERCENT	USING THIS	MINIMUM	MAXIMUM
	# STUDIES	# LESIONS	OF TOTAL	DIAGNOSIS	% FOUND	%FOUND
SKIN						
SKIN	48	2803				
Basal Cell Tumor, Benign		1	0.04	1	1.67	1.67
Basal Cell Carcinoma		1	0.04	1	2.00	2.00
Squamous Cell Papilloma		4	0.14	4	1.43	2.00
Squamous Cell Carcinoma		8	0.29	7	1.43	3.33
Fibrosarcoma		10	0.36	8	1.54	4.29
Leiomyosarcoma		1	0.04	1	2.00	2.00
SKIN, cont'd.						
Liposarcoma		2	0.07	1	4.00	4.00
Rhabdomyosarcoma		1	0.04	1	1.54	1.54
Sarcoma		3	0.11	3	1.43	1.67
Nerve Sheath Tumor, Malignant		14	0.50	3	1.67	14.00
MAMMARY GLAND	48	2573				
Adenoma		2	0.08	2	2.04	2.63
Adenocarcinoma		42	1.63	22	0.78	8.33
Adenoacanthoma		1	0.04	1	1.79	1.79
Adenoacanthoma, Malignant		5	0.19	3	2.08	3.85
Fibrosarcoma		3	0.12	2	2.04	2.35
ENDOCRINE SYSTEM						
ADRENAL	48	2797				
Cortex, Adenoma		7	0.25	5	0.78	3.08
Cortex, Adenocarcinoma		1	0.04	1	2.00	2.00
Pheochromocytoma, Benign		8	0.29	5	0.78	5.00
Pheochromocytoma, Malignant		1	0.04	1	1.96	1.96
Spindle Cell Tumor, Benign		7	0.25	5	1.54	4.00
PANCREAS	48	2774				
Acinar Cell Adenoma		2	0.07	2	1.54	2.00
Islet Cell, Adenoma		6	0.22	6	1.54	2.08
PITUITARY	48	2697				
Adenoma		55	2.04	27	0.78	14.29
Carcinoma		1	0.04	1	1.69	1.69
Pars Intermedia, Adenoma		1	0.04	1	1.45	1.45

		TOTAL		# STUDIES		
		# ORGANS	PERCENT	USING THIS	MINIMUM	MAXIMUM
	# STUDIES	# LESIONS	OF TOTAL	DIAGNOSIS	% FOUND	%FOUND
THYROID	48	2733				
C-Cell, Carcinoma		2	0.07	2	2.00	2.00
Follicular Cell, Adenoma		8	0.29	8	0.77	2.08
Follicular Cell, Carcinoma		1	0.04	1	1.56	1.56
PARATHYROID	48	2340				
Adenoma		4	0.17	4	1.64	3.23
NERVOUS SYSTEM						
BRAIN	48	2784				
Ependymoma		1	0.04	1	1.43	1.43
Meningeal Sarcoma		1	0.04	1	2.04	2.04
SPINAL CORD	48	1913				
PERIPHERAL NERVE	48	2837				
MUSCULOSKELETAL SYSTEM						
SKELETAL MUSCLE	48	2630				
Rhabdomyosarcoma		5	0.19	5	1.67	2.00
Carcinoma, Squamous Cell		1	0.04	1	0.78	0.78
Sarcoma		1	0.04	1	2.00	2.00
BONE	48	2814				
Osteoma		8	0.28	6	1.43	3.08
Osteosarcoma		4	0.14	4	1.43	2.00
Fibrosarcoma		1	0.04	1	1.56	1.56
CIRCULATORY SYSTEM						
HEART	48	2789				
Hemangiosarcoma		1	0.04	1	2.00	2.00

		TOTAL		# STUDIES		
		# ORGANS	PERCENT	USING THIS	MINIMUM	MAXIMUM
	# STUDIES	# LESIONS	OF TOTAL	DIAGNOSIS	% FOUND	%FOUND
BLOOD VESSEL	48	2533				
HEMATOPOIETIC/LYMPHOID SYSTEM						
BONE MARROW	48	2817				
Fibrosarcoma		1	0.04	1	1.54	1.54
Plasmacytoma		1	0.04	1	2.04	2.04
Hemangiosarcoma		2	0.07	2	1.67	1.69
SPLEEN	48	2772				
Hemangioma		2	0.07	2	1.69	2.00
SPLEEN, cont'd.						
Hemangiosarcoma		12	0.43	11	1.43	3.85
Leiomyosarcoma		1	0.04	1	2.00	2.00
THYMUS	48	2404				
Thymoma, Malignant		2	0.08	2	1.49	2.00
Lymphoma, Thymic		1	0.04	1	1.89	1.89
LYMPH NODES	48	2742				
Hemangioma		5	0.18	4	1.43	4.17
WHOLE BODY/MULTIPLE ORGAN	48	2822				
Lymphoma, Malignant		274	9.71	41	1.67	50.00
Lymphoma, Lymphocytic		30	1.06	4	2.00	27.45
Fibrous Histiocytoma		1	0.04	1	2.00	2.00
Histiocytic Sarcoma		111	3.93	31	1.67	18.33
Lymphoma, Histiocytic		10	0.35	4	2.08	6.38
Leukemia, Lymphocytic		6	0.21	2	1.54	8.62
Leukemia, Granulocytic		7	0.25	5	0.77	4.08
Mast Cell Tumor, Malignant		1	0.04	1	2.00	2.00
Hemangioma		4	0.14	3	1.43	2.67
Hemangiosarcoma		25	0.89	9	1.67	12.00

		TOTAL		# STUDIES		
		# ORGANS	PERCENT	USING THIS	MINIMUM	MAXIMUM
	# STUDIES	# LESIONS	OF TOTAL	DIAGNOSIS	% FOUND	%FOUND
SPECIAL SENSES						
EYE	48	2733				
Harderian Gland, Adenoma		62	2.27	30	1.35	8.33
Harderian Gland, Adenocarcinoma		5	0.18	5	1.43	2.38
EAR	48	2544				
Squamous Cell Carcinoma		1	0.04	1	2.00	2.00

Table 5: Incidence of Neoplasms by Study for Selected Organs/Males

Study Identification	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
LIVER	53	47	50	49	50	59	50	60	50	47	50	50	68	50	59	60	50	50	50	49	50	50	60
Hepatocellular Adenoma	4	7	5	7	3	7	3	3	2	2	5	2	11	3	9	3	12	6	5	2	3	3	3
Hepatocellular Carcinoma	4	6	1	1	2		1	4	1	2	1	1	6	2	2	2	3	4		4	2	2	1
Hemangioma										1							1						
Hemangiosarcoma	2						2				2			1		1	2		2				
LUNG	53	47	50	49	50	58	50	60	50	48	50	50	69	50	59	60	50	50	50	49	50	50	60
Adenoma, Alveolar/Bronchiolar	6	9	9	10	1	5	6	6		10	3	8	15	6	8	3	13	7	1	2	2	2	4
Adenocarcinoma, Alveolar/Bronchiolar	1	1	3	1	4	2	5	3		3			16		1		3	5	6	3	3	3	4
Hemangiosarcoma																							
WHOLE BODY/MULTIPLE ORGAN	53	47	50	49	50	59	50	60	50	46	50	50	69	50	59	60	50	50	50	50	50	50	50
Lymphoma, Malignant	2	2	1	4	1	3	1	2	2	2		1	1	1	2		7		1		1		
Lymphoma, Lymphocytic												2	2	1	1							1	
Leukemia, Granulocytic																							1
Leukemia, Lymphocytic								2															1
Hemangiosarcoma																							
Histiocytic Sarcoma							1	1					2		1					1			
Mast Cell Tumor, Malignant	1						1																

Table 5: Incidence of Neoplasms by Study for Selected Organs/Males (cont'd.)

Study Identification	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46
LIVER	50	50	60	50	49	60	67	60	59	70	50	65	50	50	65	65	60	60	60	70	50	50	90
Hepatocellular Adenoma	6	6	8	7	3	3	4	15	4	3	8	13	8	7	3	8	8	11	5	2	14	6	7
Hepatocellular Carcinoma		1	2	3	5	4	10	2	8	4	3	1	8	2		5		2	4	6	4	5	5
Hemangioma											2	1					1	1		2			
Hemangiosarcoma				2		3	1	1	2	3			1							3			1
LUNG	50	50	60	50	49	60	69	60	60	70	50	65	50	50	65	65	60	60	60	70	50	50	90
Adenoma, Alveolar/Bronchiolar	8	9	7	14	12	5	11	2	6	8	4	6	6	13	14	17	10	11	14	15	13	21	6
Adenocarcinoma, Alveolar/Bronchiolar	3	1		13	6		6	3	6	12	7	8	6	3	7	2	4	1	4	1	3	4	10
Hemangiosarcoma																							
WHOLE BODY/MULTIPLE ORGAN	50	50	60	49	49	60	70	60	60	70	50	65	50	50	65	65	60	60	60	70	50	50	90
Lymphoma, Malignant			3	3		4	2	6	13	5		1		2	4	5	3	5	3	2	4	1	5
Lymphoma, Lymphocytic				1	2								1										
Leukemia, Granulocytic				1		1				1								1	1				
Leukemia, Lymphocytic																							
Hemangiosarcoma												3		1	5	3	4	1			6	6	
Histiocytic Sarcoma			1	2			2			2	2		1	4	1	4	2	2	1	4			1
Mast Cell Tumor, Malignant														1						1			

Table 6: Incidence of Neoplasms by Study for Selected Organs/Females

Study Identification	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
LIVER	52	49	50	47	49	60	50	57	49	47	50	49	70	48	59	60	50	49	49	50	50	59	50	50
Hepatocellular Adenoma					1	1	1											1	1	1				
Hepatocellular Carcinoma			1										1			2		1	1		1			
Undifferentiated Carcinoma																								
Hemangioma																							1	
Hemangiosarcoma	2					1					1	1					1						1	
LUNG	52	49	50	48	49	60	50	57	50	48	50	49	70	49	59	60	50	50	50	50	50	59	50	50
Adenoma, Alveolar/Bronchiolar	3	6	6	5	2	2	5	6		3	5	5	11	3	6	5	8	3	2	2	2	2	6	2
Adenocarcinoma, Alveolar/Bronchiolar		3	4	1	3	2	4	2	4	5		1	7		2		3	6	1	2		5	1	1
Mesothelioma, Benign																								
WHOLE BODY/MULTIPLE ORGAN	52	49	50	48	50	60	50	58	50	47	50	49	70	49	59	60	50	50	50	50	50	59	50	50
Lymphoma, Malignant	2	2	7	6	1	5	7	10	2	5	4	2		3		6	4	3	1	3	3	9		5
Lymphoma, Lymphocytic													9										1	
Fibrous Histiocytoma											1													
Histiocytic Sarcoma		1						1					2	2	1	2	2		2	1	1	3	1	
Lymphoma, Histiocytic			3	1						3														
Leukemia, Lymphocytic								5																
Leukemia, Granulocytic														2									2	
Mast Cell Tumor, Malignant																								
Hemangioma													1											
Hemangiosarcoma													2											

Table 6: Incidence of Neoplasms by Study for Selected Organs/Females (cont'd.)

Study Identification	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
LIVER	58	85	59	75	50	50	60	70	58	117	59	70	50	65	51	50	65	65	60	41	59	70	50	50
Hepatocellular Adenoma				1	1				1	1		1			4	1	1	1	1	3	2		2	1
Hepatocellular Carcinoma			1				2	1	2		1	3						1						
Undifferentiated Carcinoma														1										
Hemangioma					1		1							1					1					1
Hemangiosarcoma							2	1	1	2	1	3												
LUNG	60	89	59	75	49	50	60	70	60	130	60	70	50	65	51	50	65	65	60	46	60	70	50	50
Adenoma, Alveolar/Bronchiolar	1	2	3	9	6	7			2	9			5	4	2	8	8	10	16	9	7	7	9	12
Adenocarcinoma, Alveolar/Bronchiolar		3			9	3			5	1			4	6		3	3	2	5	3	3	2	1	3
Mesothelioma, Benign																			1					
WHOLE BODY/MULTIPLE ORGAN	60	116	60	75	50	50	60	70	60	130	60	70	50	65	51	50	65	65	60	60	60	75	50	50
Lymphoma, Malignant			1	6	2	3	12	35	10	11	17	13	7	3		5	8	10	5	8	6		16	6
Lymphoma, Lymphocytic						6									14									
Fibrous Histiocytoma																								
Histiocytic Sarcoma	9		2	3			5	5	1	9	11	2	3	8	2	4	5	7	4	3			3	6
Lymphoma, Histiocytic						3																		
Leukemia, Lymphocytic																	1							
Leukemia, Granulocytic									1	1							1							
Mast Cell Tumor, Malignant																1								
Hemangioma			1	2																				
Hemangiosarcoma			1										4	2		1			2	4			3	6

Spontaneous Neoplastic Lesions in the Crl:CD-1®BR Mouse

March, 1995

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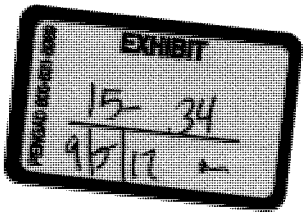
CHARLES RIVER
LABORATORIES



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SPONTANEOUS NEOPLASTIC LESIONS IN THE Crl:CD-1 ®13R MOUSE

These mouse data were obtained from clients who routinely use mice from Charles River Laboratories in product safety evaluation. Only control groups are presented here. These data were taken from studies run in thirteen different labs, including six contract toxicology labs and seven industrial labs. Starting dates ranged from November, 1981 to March, 1991, but most were begun in the late 1980s. This publication complements an earlier reference paper published by Charles River in February, 1987 with the same title. The study groups presented in the current publication are different from those in the previous publication.

The information presented here includes primary neoplastic lesion incidence from toxicology studies which ran for up to 24 months. It is divided into three groups because chronic mouse studies are terminated at times varying from 18 months to 24 months after initiation. The majority of the studies ran either 18 months or 24 months, but there were 7 groups which could not justifiably be added to either of these time points. They are presented in the 21 month group of studies. Study CV is presented under 21 months for males and 24 months for females because the sexes were sacrificed at different times.

COMMON STUDY PARAMETERS

Some of the important parameters for each study group are listed in Table 1. These include the date the in-life portion of the study was initiated, the diet fed, the cage type used (either shoebox or metal with wire mesh floor), the route of dosing, and the number of animals housed per cage. The CRL animal breeding site is also presented.

Data presented in the summary tables are grouped by organ system. Included in this summary are data from mice which died or were sacrificed moribund during the course of the study and those sacrificed at study termination. No data from animals that were part of a scheduled interim sacrifice (i.e., at 12 or 18 months of study) are included in this compilation.

All studies from which these data were obtained were run under U. S. Good Laboratory Practice Regulations promulgated by either the EPA or FDA or both. Therefore a quality assurance unit oversaw the performance of the study and reviewed the final report from which the data were taken.

SECTIONS OF REPORT

The report is divided into three sections. Section A includes several tables describing incidence of neoplastic lesions in 18 month study groups; Section B presents 21 month study groups; Section C presents 24 month study groups.

TABLES

Within each section two summary tables are presented; #1 is males and #2 is females. Also within each section three expanded tables are presented; one for liver (#3), lung (#4), lymphoreticular tissues (#5). The latter present data for both males and females in the same table by study group. This allows the reader to see the distribution of diagnoses across groups.

SUMMARY TABLE CALCULATIONS

The first column in the summary tables defines the organ and tumor evaluated. The second presents the total number of tissues which were examined for each organ. The third column shows the number of study groups in which this organ was examined. Some organs, such as the nasal turbinates, were examined routinely only in a few study groups. The fourth column shows the total number of specific tumors reported in these study groups. The fifth column reports the overall incidence of each tumor. This is obtained by dividing the total number of tumors (column 4) by the total number of organs examined (column 2) and multiplying by 100 to convert it to a percent. The sixth column shows the minimum and maximum percent in which each individual tumor was diagnosed in any of the groups in which the organ was examined. For example, in the testes of males in the 18 month studies (Table A1), the interstitial cell tumor was reported at the following incidences in the 12 study groups: none in 10 groups, 1.25% in one and 4.08% in another. Therefore the minimum presented in column 5 is 0.00% and the maximum is 4.08%. In another example, female groups from the 24 month interval show incidences of bronchiolar/alveolar adenoma of 14.0%, 18.37%, 10.00%, 9.62%, 8.00%, 9.80%, 4.00%, 8.00%, 8.16%, 12.00% and 7.04%. In Table C2 column 6 the range therefore is reported as 4.00% to 18.37%

LIVER LESIONS

The liver lesions listed in these tables are not necessarily neoplastic lesions. The altered foci and nodular proliferation are thought to possibly be pre-neoplastic lesions and are presented here because their incidence is frequently requested. The expanded tables presenting all liver lesions allow the reader to interpret the data according to need.

SURVIVAL GRAPHS

Survival data for each group of animals reported above are shown in Figures 1-6 by study code. This information is shown here for two reasons. First, the actual range of survival values for groups of mice at these three time points can be used to compare to other datasets either in-house or from the literature. Second, the distribution of animals sacrificed at study termination vs. those which died (or were sacrificed moribund) during the course of each study can be compared between groups. Also, the tumor incidence in the lungs, liver and lymphoreticular tissues in which there was good survival can be compared to that in groups with poor survival.

When fate tables were available, the data were transformed using the Kaplan-Meier procedure (Kaplan, E. and P. Meier, "Non-parametric Estimation from Incomplete Observations", Journal of the American Statistical Association, 23:1958 p. 457). This procedure handles the mice that were killed accidentally (from gavage error, bleeding procedure, etc.) during the course of the study differently than those that died or were sacrificed moribund. When individual fate tables were not available, the total number of mice surviving at study termination was reported as a percent of the total at initiation. Animals that were sacrificed prior to study termination for the purpose of evaluating health at that interval (interim sacrifice group) were not included in this calculation.

SYNONYMS

In compiling the summary tables for neoplastic lesions, it became clear that pathologists gave different names to the same tumor. In general, it was felt that the information would be more useful to the reader if identical, or similar, tumors were combined under one heading. For example, all tumors of granulosa cell origin, including tumors of luteinized cells, were combined in the category "granulosa/theca cell tumor". Recent texts used in developing lists of synonyms included "Mouse Histopathology", by J.M. Faccini, D.P. Abbott, and G.J.J. Paulus, Elsevier, 1990, and "Pathology of Laboratory Rodents and Rabbits", by D.H. Percy and S.W. Barthold, Iowa State University Press, 1993.

The synonyms which were included in the various diagnoses are presented in the synonym list which follows. Synonymous terms or diagnoses were frequently encountered in different study groups, and for utilitarian purposes were combined under a single, often broad, diagnosis, which was termed the primary diagnosis. Although some effort was made to use currently acceptable terms, it is beyond the scope of this publication to propose a system of "preferred" diagnoses. The number of lesions reported in each table include all those listed by either the primary diagnoses or the synonymous diagnoses.

SYNONYMS

Ovary:

CYSTADENOMA: tubular adenoma; papillary adenoma; papilloma; papillary cystadenoma; adenoma

GRANULOSA/ THECA CELL TUMOR: luteoma; granulosa cell tumor, luteinized

Uterus:

ENDOMETRIAL STROMAL SARCOMA: sarcoma, endometrial sarcoma, stromal sarcoma

ENDOMETRIAL STROMAL POLYP: glandular polyp, endometrial polyp, polyp (B)

ADENOCARCINOMA: endometrial adenocarcinoma

LEIOMYOSARCOMA: leiomyoma/ leiomyosarcoma

Pituitary Gland:

ADENOMA: adenoma, pars distalis; adenoma, anterior lobe

CARCINOMA: carcinoma, pars distalis

Bone:

OSTEOSARCOMA: osteogenic sarcoma

Lymphoreticular Tumors:

MALIGNANT LYMPHOMA (NOS): lymphosarcoma; malignant lymphoma undifferentiated

HISTIOCYTIC SARCOMA: malignant lymphoma histiocytic; reticulum cell sarcoma

Mammary Gland:

CARCINOMA: adenocarcinoma; adenocarcinoma, Type A (acinar pattern); adenocarcinoma, Type B (multiform)

Lung:

BRONCHIOLAR/ ALVEOLAR ADENOMA: adenoma; pulmonary adenoma

BRONCHIOLAR/ ALVEOLAR CARCINOMA: carcinoma; pulmonary carcinoma; adenocarcinoma; pulmonary adenocarcinoma

Liver:

NODULAR HEPATOCELLULAR PROLIFERATION: nodular hyperplasia

HEPATOCELLULAR ADENOMA: benign liver cell tumor

HEPATOCELLULAR CARCINOMA: malignant liver cell tumor

ACIDOPHILIC FOCUS: eosinophilic focus; hepatocellular alteration, eosinophilic

BASOPHILIC FOCUS: basophilic hepatocytes; hepatocellular alteration, basophilic

Adrenal:

CORTICAL ADENOCARCINOMA: carcinoma

Kidney:

RENAL CELL ADENOMA: tubular adenoma

RENAL CELL CARCINOMA: tubular carcinoma

Table 1
STUDY GROUP INFORMATION
18 MONTH STUDIES

Study Code	DJ	DI	DH	DL	BU	DK	AB	M	I	DF	DY	DG
Study Start Date	Mar-91	Oct-90	Jun-90	Nov-90	Dec-84	Oct-90	Sep-85	Mar-85	Oct-85	May-85	Jun-90	Feb-91
Diet	LAD # 2	LAD # 2	LAD # 1	LAD# 2	Purina	LAD # 2	Purina	Purina	Purina	Purina	LAD # 2	LAD # 2
CRL Source	UK	UK	UK	UK	Portage	UK	Kingston	Kingston	Kingston	Wilmington	UK	UK
Cage Type	box w/ bed	box w/ bed	box w/ bed	box w/ bed	wire mesh	box w/ bed	wire mesh	wire mesh	wire mesh	wire mesh	box w/ bed	box w/ bed
Route of Dosing	diet	diet	gavage[1]	diet	diet	diet	diet	diet	diet	dermal+	diet	diet
Diet Form	ground	ground	extruded	ground	ground	ground	ground	ground*	ground	pellets	ground	ground
No. per Cage	1	4	4	4	1	4	1	1	1	1	4	4

* with 0.5% corn oil
vehicle control received 5% gum arabic
\+ vehicle patched with purified water

21 MONTH STUDIES

Study Code	CT	DE	DD	CI	CJ	EF	CV
Study Start Date	Aug 85	Mar-86	Feb-85	Jun-86	Jun-86	Oct-90	Jul-83
Diet	Purina	Purina	Labsure RM M(S)	Altromin	Altromin	R/M 1	Purina
CRL Source	Kingston	Kingston	UK	Germany	Germany	UK	Kingston
Cage Type	wire mesh	wire mesh	wire mesh	box w/ bed	box w/ bed	box w/ bed	wire mesh
Route of Dosing	diet	diet	gavage	diet	diet	diet	diet
Diet Form	ground	ground	extruded	ground	ground	ground	ground
No. per Cage	1	1	4	M1, F2-4	M1, F2-4	1	1

24 MONTH STUDIES

Study Code	CX	CQ	CR	DN	DU	DZ	CP	BX	EG	CV
Study Start Date	Sep-83	Apr-85	Apr-85	Jan-88	Sep-89	Oct-90	Jul-85	Nov-81	Aug-89	Jul-83
Diet	LAD # 2	Purina	Purina	RM-1	RM-1	RM-1	RM-1	LAD # 2	RM-1	Purina
CRL Source	UK	Q	Q	UK	UK	UK	UK	UK	UK	Kingston
Cage Type	wire mesh	wire mesh	wire mesh	box/ bed	box/ bed	box/ bed	wire mesh	box/ bed	box/ bed	wire mesh
Route of Dosing	diet	diet	diet	diet	diet	diet	diet	diet	diet	diet
Diet Form	ground	ground	ground	ground	ground	ground	ground	ground	ground	ground
No. per Cage	4	1	1	1	1	1	3	4	1	1

Table A 1
NEOPLASMS
18 MONTH STUDIES
MALE CD-1® MICE

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Tumors	Mean Percent	Range Percent
HEMATOPOIETIC SYSTEM					
LYMPH NODES	718	12			
THYMUS	648	12			
SPLEEN	767	12			
hemangiosarcoma			4	0.52	0-2.53
BONE MARROW	640	10			
LYMPHORETICULAR TUMORS	770^^	12			
malignant lymphoma, (NOS)			14	1.82	0-5.77
malignant lymphoma, lymphocytic			2	0.26	0-1.25
malignant lymphoma, mixed cell			2	0.26	0-1.25
histiocytic sarcoma			5	0.65	0-5.00
INTEGUMENTARY SYSTEM					
SKIN/SUBCUTIS	741	12			
lipoma			5	0.67	0-4.00
neurofibroma			1	0.13	0-1.03
basal cell tumor			1	0.13	0-3.70
fibroma			1	0.13	0-3.70
sarcoma			3	0.40	0-3.85
adenocarcinoma			1	0.13	0-1.92
squamous cell carcinoma, footpad			1	0.13	0-1.25
MAMMARY GLAND	279	7			
MUSCULOSKELETAL SYSTEM					
SKELETAL MUSCLE	476	7			
sarcoma, musculoskeletal sys.			3*		
osteosarcoma			1	0.21	0-1.25
BONE	697	12			
sarcoma			1	0.14	0-1.92
RESPIRATORY SYSTEM					
NASAL TURBINATES	236	3			
hemangiosarcoma			1	0.42	0-1.32
TRACHEA	409	6			
LUNG	770	12			
bronchiolar/alveolar adenoma			58	7.53	1.92-12.00
bronchiolar/alveolar carcinoma			45	5.84	0-21.15
CIRCULATORY SYSTEM					
HEART	770	12			
AORTA	413	6			

Table AI (Cont.)

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Tumors	Mean Percent	Range Percent
DIGESTIVE SYSTEM					
ORAL CAVITY	+				
squamous cell papilloma			1		
squamous cell papilloma, tongue			1		
SALIVARY GLAND	720	11			
fibrosarcoma			1	0.14	0-1.92
ESOPHAGUS	509	7			
STOMACH	743	12			
adenoma			1	0.13	0-1.18
SMALL INTESTINE	716	12			
adenoma			1	0.14	0-1.89
polypoid adenoma			1	0.14	0-1.28
adenocarcinoma			1	0.14	0-1.18
COLON/ CECUM	678	11			
carcinoma, cecum			1	0.15	0-1.92
LIVER	770	12			
focus/ area of cellular alteration			3	0.39	0-2.50
acidophilic focus/ area			1	0.13	0-1.92
clear cell focus/ area			3	0.39	0-2.00
basophilic focus/ area			7	0.91	0-5.00
nodular hepatocellular proliferation			15	1.95	0-15.38
hepatocellular adenoma			83	10.78	0-19.23
hepatocellular carcinoma			38	4.94	1.25-11.54
hemangioma			3	0.39	0-2.50
hemangiosarcoma			8	1.04	0-3.85
GALL BLADDER	659	11			
papilloma (B)			1	0.15	0-2.27
PANCREAS (EXOCRINE)	763	12			
URINARY SYSTEM					
KIDNEY	770	12			
URINARY BLADDER	758	12			
leiomyoma			2	0.26	0-2.53
leiomyosarcoma			1	0.13	0-1.27
undifferentiated sarcoma			1	0.13	0-1.27
REPRODUCTIVE SYSTEM					
TESTIS	768	12			
interstitial cell tumor (B)			3	0.39	0-4.08
granular cell tumor (M)			1	0.13	0-1.92
germ cell tumor (M)			1	0.13	0-1.92
hemangioma			1	0.13	0-1.25
fibrosarcoma, epididymides			1	0.13	0-1.92
PROSTATE	660	11			
SEMINAL VESICLES	766	12			
PREPUTIAL/ CLITORAL GLAND**	91	1			
adenoma			1		1.10

Table AI (Cont.)

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Tumors	Mean Percent	Range Percent
ENDOCRINE SYSTEM					
PANCREAS (ENDOCRINE)	763	12			
islet cell adenoma			1	0.13	0-1.69
PITUITARY GLAND	607	11			
THYROID GLAND	757	12			
follicular cell adenoma			4	0.53	0-2.53
PARATHYROID GLAND	499	11			
adenoma (B)			5++	1.00	0-10.42
ADRENAL GLAND	759	12			
nodular hyperplasia			17++	2.24	0-17.17
cortical adenoma			15	1.98	0-11.67
cortical adenocarcinoma			1	0.13	0-1.01
pheochromocytoma(B)			2	0.26	0-1.92
NERVOUS SYSTEM					
SPINAL CORD	716	12			
BRAIN	637	11			
astrocytoma(B)			1	0.16	0-1.18
oligodendroglioma			1	0.16	0-1.25
PERIPHERAL NERVES	489	8			
SPECIAL SENSES					
EYE AND ADNEXA	751	12			
LACRIMAL GLAND	331	4			
adenoma			5-H-	1.51	0-5.43
HARDERIAN GLAND	239	3			
adenoma			6++	2.51	0-7.59^
papillary cystadenoma			2++	0.84	0-2.5
BODY CAVITIES					
ABDOMINAL CAVITY	+				
mesothelioma (M), mesentery			1		

* 2 found in one group, one in another: muscle tissue was not on tissue list to be examined in either study
** examined in one study only
^ 1 additional adenoma found in group in which Harderian gland not on tissue list to be examined
^^ number animals examined
+ gross lesions not reported elsewhere
++ all found in one study group

Table A2
NEOPLASMS
18 MONTH STUDIES
FEMALE CD-1 ® MICE

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Tumors	Mean Percent	Range Percent
HEMATOPOIETIC SYSTEM					
LYMPH NODES	732	12			
hemangiosarcoma			1	0.14	0-1.14
myeloid sarcoma (M)			1	0.14	0-1.14
THYMUS	693	12			
thymoma			1	0.14	0-1.41
SPLEEN	768	12			
hemangioma			1	0.13	0-1.92
hemangiosarcoma			2	0.26	0-1.92
BONE MARROW	667	10			
LYMPHORETICULAR TUMORS	770^^	12			
malignant lymphoma, (NOS)			49	6.36	0-23.08
malignant lymphoma, lymphocytic			6	0.78	0-5.00
lymphosarcoma (thymus)			16++	2.08	0-26.67
malignant lymphoma, mixed cell			1	0.13	0-1.25
histiocytic sarcoma			17	2.21	0-10.00
large granular lymphocyte leukemia			1	0.13	0-1.92
INTEGUMENTARY SYSTEM					
SKIN/SUBCUTIS	730	12			
hair matrix tumor (B)			1	0.14	0-1.04
basal cell carcinoma			1	0.14	0-1.27
adenocarcinoma			1	0.14	0-1.67
sarcoma			2	0.27	0-3.33
MAMMARY GLAND	610	10			
fibroadenoma			1	0.16	0-1.69
carcinoma (M)			13*	2.13	0-5.77
MUSCULOSKELETAL SYSTEM					
SKELETAL MUSCLE	463	7			
rhabdomyosarcoma			1**		
BONE	769	12			
osteoma			1	0.13	0-1.27
osteosarcoma			1	0.13	0-1.67
RESPIRATORY SYSTEM					
NASAL TURBINATES	239	3			
TRACHEA	454	6			
LUNG	770	12			
bronchiolar/alveolar adenoma			50	6.49	0-15.38
bronchiolar/alveolar carcinoma			31	4.03	0-9.62
leiomyosarcoma			1	0.13	0-1.00
CIRCULATORY SYSTEM					
HEART	774	12			
AORTA	402	6			

Table A2 (Cont.)

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Tumors	Mean Percent	Range Percent
DIGESTIVE SYSTEM					
SALIVARY GLAND	718	11			
carcinoma			1	0.14	0-1.92
ESOPHAGUS	504	7			
STOMACH	747	12			
squamous cell carcinoma			1	0.13	0-1.67
SMALL INTESTINE	731	12			
COLON/CECUM	649	11			
leiomyoma, cecum			1	0.15	0-1.25
LIVER	769	12			
acidophilic focus/area			2	0.26	0-1.92
basophilic focus/area			3	0.39	0-3.85
nodular hepatocellular proliferation			1	0.13	0-1.67
hepatocellularadenoma			5	0.65	0-2.00
hepatocellular carcinoma			3	0.39	0-2.00
hemangioma			3	0.39	0-2.50
hemangiosarcoma			6	0.78	0-2.50
GALL BLADDER	686	11			
PANCREAS (EXOCRINE)	769	12			
URINARY SYSTEM					
KIDNEY	770	12			
URINARY BLADDER	726	12			
transitional cell carcinoma			2	0.28	0-1.72
REPRODUCTIVE SYSTEM					
OVARY	761	12			
cystadenoma			9	1.18	0-3.85
granulosa/theca cell tumor			6	0.79	0-2.53
fibroma			1	0.13	0-1.69
hemangioma			3	0.39	0-1.96
hemangiosarcoma			1	0.13	0-1.67
UTERUS/CERVIX	766	12			
adenocarcinoma(M)			1	0.13	0-1.92
endometrial stromal polyp			24	3.13	0-13.92
endometrial stromal sarcoma			4	0.52	0-6.00
leiomyoma			13	1.70	0-3.85
leiomyoma, cervical			1	0.13	0-2.00
leiomyosarcoma			8	1.04	0-8.00
hemangioma (B)			2	0.26	0-1.92

Table A2 (Cont.)

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Tumors	Mean Percent	Range Percent
ENDOCRINE SYSTEM					
PANCREAS (ENDOCRINE)	769	12			
PITUITARY GLAND	651	11			
adenoma			5	0.77	0-2.08
THYROID GLAND	757	12			
adenoma			1	0.52	0-1.92
C-cell adenoma			1	0.13	0-1.67
PARATHYROID GLAND	489	11			
adenoma(B)			2	0.41	0-3.08
ADRENAL GLAND	762	12			
nodular hyperplasia			2++	0.26	0-2.02
cortical adenocarcinoma			1	0.13	0-1.25
pheochromocytoma(B)			1	0.13	0-1.01
pheochromocytoma (M)			1	0.13	0-1.01
NERVOUS SYSTEM					
SPINAL CORD	732	12			
BRAIN	631	11			
PERIPHERAL NERVES	514	8			
SPECIAL SENSES					
EYE AND ADNEXA	757	12			
LACRIMAL GLAND	323	4			
adenoma			3++	0.93	0-3.33
HARDERIAN GLAND	239	3			
adenoma			10	4.18	0-8.75[A]
carcinoma			1**		
OTHER	+				
hemangioma, tail (M)			1		

* 2 additional carcinomas found in study group in which mammary not on tissue list to be examined
** found in group in which tissue was not on list to be examined
[A] 1 additional adenoma found in group in which Harderian gland not on tissue list to be examined
[AA] number animals examined
+ gross lesions not reported elsewhere
++ all found in one study group

Table A3
LIVER NEOPLASMS BY STUDY GROUP
18 MONTH STUDIES
MALE

Study Code	DJ	DI	DH	ED	DL	DK	AB	DY	I	M	DG	DF
No. tissues examined	50	52	60	100	52	52	80	52	80	80	52	60
focus/area of cellular alteration									1	2		
%									1.25	2.50		
acidophilic focus/area											1	
%											1.92	
clear cell focus/area	1				1						1	
%	2.00				1.92						1.92	
basophilic focus/area		1	1		2							3
%		1.92	1.67		3.85							5.00
nodular hepatocellular proliferation	2		4			8					1	
%	4.00		6.67			15.38					1.92	
hepatocellular adenoma	4	10		16	10	2	9	3	4	11	8	6
%	8.00	19.23		16.00	19.23	3.85	11.25	5.77	5.00	13.75	15.38	10.00
hepatocellular carcinoma	1	1	2	6	4	6	3	6	4	1	2	2
%	2.00	1.92	3.33	6.00	7.69	11.54	3.75	11.54	5.00	1.25	3.85	3.33
hemangioma				1					2			
%				1.00					2.50			
hemangiosarcoma	1				1	2	1			3		
%	2.00				1.92	3.85	1.25			3.75		

FEMALE

Study Code	DJ	DI	DH	ED	DL	DK	AB	DY	I	M	DG	DF
No. tissues examined	50	52	60	100	52	52	80	52	80	80	51	60
acidophilic focus/area		1		1								
%		1.92		1.00								
basophilic focus/area				1	2							
%				1.00	3.85							
nodular hepatocellular proliferation			1									
%			1.67									
hepatocellular adenoma	1			2			1			1		
%	2.00			2.00			1.25			1.25		
hepatocellular carcinoma	1					1				1		
%	2.00					1.92				1.25		
hemangioma		1							2			
%		1.92							2.50			
hemangiosarcoma	1		1				2			1	1	
%	2.00		1.67				2.50			1.25	1.96	

Table A4
LUNG NEOPLASMS BY STUDY GROUP
18 MONTH STUDIES
MALE

Study Code	DJ	DI	DH	ED	DL	DK	AB	DY	I	M	DG	DF
No. tissues examined	50	52	60	100	52	52	80	52	80	80	52	60
bronchiolar/ alveolar adenoma	6	4	5	12	5	4	3	5	5	4	1	4
%	12.00	7.69	8.33	12.00	9.62	7.69	3.75	9.62	6.25	5.00	1.92	6.67
bronchiolar/ alveolar carcinoma	4	4	9	2	3	6		5		1	11	
%	8.00	7.69	15.00	2.00	5.77	11.54		9.62		1.25	21.15	

FEMALE

Study Code	DJ	DI	DH	ED	DL	DK	AB	DY	I	M	DG	DF
No. tissues examined	50	52	60	100	52	52	80	52	80	80	52	60
bronchiolar/ alveolar adenoma		3		14	1	8	8	3	3	4	3	3
%		5.77		14.00	1.92	15.38	10.00	5.77	3.75	5.00	5.77	5.00
bronchiolar/ alveolar carcinoma	3	5	2	6	5	2		1	1	2	3	1
%	6.00	9.62	3.33	6.00	9.62	3.85		1.92	1.25	2.50	5.77	1.67
leiomyosarcoma				1								
%				1.00								

Table AS
LYMPHORETICULAR NEOPLASMS BY STUDY GROUP
18 MONTH STUDIES
MALE

Study Code	DJ	DI	DH	ED	DL	DK	AB	DY	I	M	DG	DF
No. animals examined	50	52	60	100	52	52	80	52	80	80	52	60
malignant lymphoma, (NOS)	2	2		1		3	1	1	1		1	2
%	4.00	3.85		1.00		5.77	1.25	1.92	1.25		1.92	3.33
malignant lymphoma, lymphocytic									1	1		
%									1.25	1.25		
malignant lymphoma, mixed cell									1	1		
%									1.25	1.25		
histiocytic sarcoma		1	3								1	
%		1.92	5.00								1.92	

FEMALE

Study Code	DJ	DI	DH	ED	DL	DK	AB	DY	I	M	DG	DF
No. animals examined	50	52	60	100	52	52	80	52	80	80	52	60
malignant lymphoma, (NOS)	1	3	5	9	5	12	6	5	2		1	
%	2.00	5.77	8.33	9.00	9.62	23.08	7.50	9.62	2.50		1.92	
malignant lymphoma, lymphocytic									4	2		
%									5.00	2.50		
lymphosarcoma (thymus)												16
%												26.67
malignant lymphoma, mixed cell										1		
%										1.25		
histiocytic sarcoma	5		1		1	1	1	1	2	4	1	
%	10.00		1.67		1.92	1.92	1.25	1.92	2.50	5.00	1.92	
large granular lymphocyte,leukemia											1	
%											1.92	

Table B 1
NEOPLASMS
21 MONTH STUDIES
MALE CD-1® MICE

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Lesions	Mean Percent	Range Percent
HEMATOPOIETIC SYSTEM					
LYMPH NODES	358	7			
hemangioma			1	0.28	0-1.89
THYMUS	287	7			
SPLEEN	369	7			
hemangiosarcoma			3	0.81	0-2.00
BONE MARROW	368	7			
hemangiosarcoma			1	0.27	0-2.00
LYMPHORETICULAR TUMORS	160^^	3			
malignant lymphoma (NOS)			2	1.25	0-2.00
malignant lymphoma, lymphocytic			3++	1.88	0-6.00
malignant lymphoma, mixed			1	0.63	0-2.00
histiocytic sarcoma			2	1.25	0-2.00
INTEGUMENTARY SYSTEM					
SKIN/ SUBCUTIS	368	7			
sarcoma			1	0.27	0-2.00
lipoma			1	0.27	0-2.00
hemangioma			1	0.27	0-1.72
MAMMARY GLAND	167	4			
MUSCULOSKELETAL SYSTEM					
SKELETAL MUSCLE	310	6			
BONE	318	6			
RESPIRATORY SYSTEM					
TRACHEA	270	5			
NASAL TURBINATES	51	1			
LUNG	370	7			
bronchiolar/ alveolar adenoma			43	11.62	0-26.00
bronchiolar/ alveolar carcinoma			18	4.86	0-16.67
CIRCULATORY SYSTEM					
VASCULAR SYSTEM	+				
hemangiosarcoma			2		
HEART	370	7			
AORTA	156	3			

Table B 1 (Cont.)

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Lesions	Mean Percent	Range Percent
DIGESTIVE SYSTEM					
ESOPHAGUS	270	5			
GALL BLADDER	339	7			
STOMACH	368	7			
SALIVARY GLAND	369	7			
mixed tumor, (M)			1	0.27	0-2.00
SMALL INTESTINE	365	7			
LIVER	370	7			
basophilic focus/area			3	0.81	0-5.00
nodular hepatocellular proliferation			1	0.27	0-2.00
hepatocellular adenoma			28	7.57	0-12.00
hepatocellular carcinoma			20	5.41	0-12.00
hemangioma			3	0.81	0-3.33
hemangiosarcoma			10	2.70	0-6.00
COLON/CECUM	363	7			
PANCREAS (EXOCRINE)	369	7			
URINARY SYSTEM					
KIDNEY	370	7			
URINARY BLADDER	370	7			
REPRODUCTIVE SYSTEM					
TESTIS	369	7			
interstitial cell tumor (NOS)			2	0.54	0-2.00
interstitial cell adenoma			1	0.27	0-2.00
sarcoma, epididymides, (NOS)			1	0.27	0-1.69
sarcoma, undifferentiated			1	0.27	0-1.67
PROSTATE	367	7			
SEMINAL VESICLES	309	7			
ENDOCRINE SYSTEM					
PANCREAS (ENDOCRINE)	369	7			
PITUITARY GLAND	325	7			
THYROID GLAND	369	7			
follicular cell adenoma			2++	0.54	0-3.33
PARATHYROID GLAND	307	7			
ADRENAL GLAND	368	7			
cortical adenoma			5	1.36	0-6.00
pheochromocytoma(B)			1	0.27	0-1.67

Table B 1 (Cont.)

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Lesions	Mean Percent	Range Percent
NERVOUS SYSTEM					
SPINAL CORD	310	6			
BRAIN	369	7			
PERIPHERAL NERVES	272	6			
SPECIAL SENSES					
EYE AND ADNEXA	260	5			
HARDERIAN GLAND	151	3			
adenoma			3	1.99	0-3.45
LACRIMAL GLAND	127	3			
BODY CAVITIES					
ABDOMINAL CAVITY	+				
sarcoma (M)			1		

^ 1 additional adenoma was found in a group in which Harderian gland not on the tissue list to be examined
+ gross lesions not reported elsewhere
++ all found in one study group
^^ number animals examined

Table B2
NEOPLASMS
21 MONTH STUDIES
FEMALE CD-1® MICE

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Lesions	Mean Percent	Range Percent
HEMATOPOIETIC SYSTEM					
LYMPH NODES	312	6			
leiomyosarcoma			1	0.32	0-1.85
THYMUS	278	6			
carcinoma			1	0.36	0-3.33
BONE MARROW	319	6			
SPLEEN	317	6			
hemangiosarcoma			2++	0.63	0-4.00
LYMPHORETICULAR TUMORS	180**	3			
malignant lymphoma (NOS)			12	7.50	0-14.00
malignant lymphoma, lymphocytic			9++	5.63	0-18.00
malignant lymphoma, mixed			2++	1.25	0-4.00
histiocytic sarcoma			6	3.75	0-6.00
INTEGUMENTARY SYSTEM					
SKIN/SUBCUTIS	320	6			
myxoma			1	0.31	0-2.00
MAMMARY GLAND	303	6			
carcinoma (M)			7	2.31	0-4.08
MUSCULOSKELETAL SYSTEM					
SKELETAL MUSCLE	266	5			
BONE	249	5			
osteogenic sarcoma			1	0.37	0-1.69
RESPIRATORY SYSTEM					
NASAL TURBINATES	56	1			
TRACHEA	220	4			
LUNG	320	6			
bronchiolar/alveolar adenoma			20	6.25	0-10.00
bronchiolar/alveolar carcinoma			10	3.13	0-10.00
CIRCULATORY SYSTEM					
VASCULAR SYSTEM	+				
hemangioma			1		
hemangiosarcoma			4++		
HEART	320	6			
AORTA	149	3			

Table B2 (Cont.)

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Lesions	Mean Percent	Range Percent
DIGESTIVE SYSTEM					
SALIVARY GLAND	319	6			
ESOPHAGUS	214	4			
STOMACH	315	6			
sarcoma			1	0.32	0-2.00
SMALL INTESTINE	310	6			
COLON/CECUM	309	6			
LIVER	318	6			
focus/area of cellular alteration			1	0.31	0-2.00
hepatocellularadenoma			4	1.26	0-2.00
hepatocellular carcinoma			1	0.31	0-1.72
hemangiosarcoma			4	1.26	0-2.00
GALL BLADDER	280	6			
PANCREAS (EXOCRINE)	318	6			
leiomyosarcoma			1	0.31	0-1.72
URINARY SYSTEM					
KIDNEY	318	6			
leiomyosarcoma			1	0.31	0-1.72
URINARY BLADDER	314	6			
carcinosarcoma			1	0.32	0-2.00
carcinoma			1	0.32	0-2.00
REPRODUCTIVE SYSTEM					
OVARY	317	6			
cystadenoma			3	0.95	0-4.00
granulosa/theca cell tumor			7	2.21	0-6.67
fibroma			1	0.32	0-2.00
leiomyosarcoma			1	0.32	0-1.75
UTERUS/CERVIX	318	6			
adenocarcinoma			1	0.31	0-2.00
endometrial stromal polyp			17	5.35	1.67-10.00
endometrial stromal sarcoma			6	1.89	0-4.02
fibroma			2++	0.63	0-4.00
leiomyoma			3	0.94	0-4.01
leiomyosarcoma			5	1.57	0-4.03
hemangiosarcoma			1	0.31	0-2.00

Table B2 (Cont.)

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Lesions	Mean Percent	Range Percent
ENDOCRINE SYSTEM					
PANCREAS (ENDOCRINE)	318	6			
islet cell adenoma			1	0.31	0-2.00
PITUITARY GLAND	316	6			
adenoma			3	0.95	0-3.57
carcinoma			1	0.32	0-2.00
meningioma			1	0.32	0-1.79
THYROID GLAND	319	6			
PARATHYROID GLAND	282	6			
adenoma			1	0.35	0-3.13
ADRENAL GLAND	317	6			
cortical adenoma			11++	3.47	0-22.45
leiomyosarcoma			1	0.32	0-1.72
NERVOUS SYSTEM					
SPINAL CORD	260	5			
BRAIN	319	6			
PERIPHERAL NERVES	260	5			
SPECIAL SENSES					
EYE AND ADNEXA	210	4			
LACRIMAL GLAND	126	3			
HARDERIAN GLAND	108	2			
adenoma			2	1.85	0-2.08
BODY CAVITIES					
ABDOMINAL CAVITY	+				
hemangiosarcoma			1		
sarcoma			1		

+ gross lesions not reported elsewhere
AA number animals examined
++ all found in one study group

Table B3
LIVER NEOPLASMS BY STUDY GROUP
21 MONTH STUDIES
MALE

Study Code	CT	DE	DD	CI	CJ	EF	CV*
No. tissues examined	50	60	60	50	50	50	50
basophilic focus/area		3					
%		5.00					
nodular hepatocellular proliferation				1			
%				2.00			
hepatocellular adenoma	4	7		3	3	6	5
%	8.00	11.67		6.00	6.00	12.00	10.00
hepatocellular carcinoma	2	2	6		2	2	6
%	4.00	3.33	10.00		4.00	4.00	12.00
hemangioma		2					1
%		3.33					2.00
hemangiosarcoma	1	1	1	1	3		3
%	2.00	1.67	1.67	2.00	6.00		6.00

FEMALE

Study Code	CT	DE	DD	CI	CJ	EF
No. tissues examined	50	58	60	50	50	50
focus !area of cellular alteration				1		
%				2.00		
hepatocellular adenoma	1	1			1	1
%	2.00	1.72			2.00	2.00
hepatocellular carcinoma		1				
%		1.72				
hemangiosarcoma	1	1		1	1	
%	2.00	1.72		2.00	2.00	

* Data on females are found in 24 month study tables.

Table B4
LUNG NEOPLASMS BY STUDY GROUP
18 MONTH STUDIES
MALE

Study Code	CT	DE	DD	CI	CJ	EF	CV*
No. tissues examined	50	60	60	50	50	50	50
bronchiolar/ alveolar adenoma	8	13		2	3	13	4
%	16.00	21.67		4.00	6.00	26.00	8.00
bronchiolar/ alveolar carcinoma	2	3	10		1	2	
%	4.00	5.00	16.67		2.00	4.00	

FEMALE

Study Code	CT	DE	DD	CI	CJ	EF
No. tissues examined	50	60	60	50	50	50
bronchiolar/ alveolar adenoma	5	3		3	4	5
%	10.00	5.00		6.00	8.00	10.00
bronchiolar/ alveolar carcinoma	1	1	6			2
%	2.00	1.67	10.00			4.00

* Data on females found in 24 month study tables.

Table B5
LYMPHORETICULAR NEOPLASMS BY STUDY GROUP
21 MONTH STUDIES
MALE

Study Code	CT	DE	DD	CI	CJ	EF	CV*
No. animals examined	50	60		---		50	
malignant lymphoma (NOS)		1				1	
%		1.67				2.00	
malignant lymphoma,							
lymphocytic	3						
%	6.00						
malignant lymphoma, mixed	1						
%	2.00						
histiocytic sarcoma	1					1	
%	2.00					2.00	

FEMALE

Study Code	CT	DE	DD	CI	CJ	EF
No. animals examined	50	60				50
malignant lymphoma (NOS)		5				7
%		8.33				14.00
malignant lymphoma,						
lymphocytic	9					
%	18.00					
malignant lymphoma, mixed	2					
%	4.00					
histiocytic sarcoma	3	1				2
%	6.00	1.67				4.00

* Data on females are found in 24 month study tables.

Table C1
NEOPLASMS
24 MONTH STUDIES
MALE CD-1® MICE

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Tumors	Mean Percent	Range Percent
HEMATOPOIETIC SYSTEM					
LYMPH NODES	488	10			
hemangiosarcoma			1	0.20	0-2.04
THYMUS	406	10			
thymic lymphoma			1	0.25	0-1.64
SPLEEN	519	10			
hemangiosarcoma			3	0.58	0-2.08
BONE MARROW	259	6			
LYMPHORETICULAR TUMORS	423**	8			
malignant lymphoma (NOS)			25	5.91	0-12.00
malignant lymphoma, lymphocytic			2++	0.47	0-4.00
malignant lymphoma, mixed			1	0.24	0-2.00
histiocytic sarcoma			8	1.89	0-7.69
mast cell tumor			1	0.24	0-2.04
INTEGUMENTARY SYSTEM					
SKIN/SUBCUTIS	523	10			
squamous cell carcinoma			2	0.38	0-2.00
sarcoma			4	0.76	0-4.23
hemangiosarcoma			1	0.19	0-2.04
subcutaneous fibrosarcoma (M)			2	0.38	0-3.85
MAMMARY GLAND	364	9			
MUSCULOSKELETAL SYSTEM					
SKELETAL MUSCLE	417	9			
BONE	324	6			
RESPIRATORY SYSTEM					
TRACHEA	519	8			
LUNG	524	10			
bronchiolar/alveolar adenoma			94	17.94	9.72-28.00
bronchiolar/alveolar carcinoma			58	11.07	1.92-20.00
sarcoma (unknown origin)			1	0.19	0-1.39
pleural mesothelioma			1	0.19	0-1.92
CIRCULATORY SYSTEM					
HEART	522	10			
AORTA	416	8			
hemangiosarcoma			1	0.24	0-2.00

Table C 1 (Cont.)

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Tumors	Mean Percent	Range Percent
DIGESTIVE SYSTEM					
SALIVARY GLAND	523	10			
ESOPHAGUS	518	10			
STOMACH	515	10			
squamous cell carcinoma			1	0.19	0-2.00
SMALL INTESTINE	386	8			
polyp (B)			1	0.26	0-2.17
COLON/ CECUM	501	10			
intestinal carcinoma			1	0.20	0-1.41
LIVER	521	10			
acidophilic focus/ area			7	1.34	0-4.08
basophilic focus/ area			21	4.03	0-10.00
focus of alteration, mixed cell			1	0.19	0-2.00
clear cell focus/ area			5	0.96	0-6.00
bile duct proliferation			1	0.19	0-1.39
nodular hepatocellular proliferation			6	1.15	0-6.00
hepatocellular adenoma			97	18.62	4.08-37.5
hepatocellular carcinoma			68	13.05	0-28.00
carcinoma/ adenoma			3++	0.58	0-6.00
hemangioma			5	0.96	0-4.00
hemangiosarcoma			11	2.11	0-8.0
cholangioma			8++	1.54	0-16.00
GALL BLADDER	421	9			
papilloma (B)			1	0.24	0-2.13
PANCREAS (EXOCRINE)	517	10			
URINARY SYSTEM					
KIDNEY	521	10			
renal cell adenoma			7	1.34	0-4.26
renal cell carcinoma			5	0.96	0-2.13
URINARY BLADDER	514	10			
REPRODUCTIVE SYSTEM					
TESTIS	524	10			
Rete Testis papilloma			2++	0.38	0-4.00
interstitial cell tumor (B)			10	1.91	0-6.12
interstitial cell tumor (NOS)			3++	0.57	0-5.77
papillary adenoma (B)			2++	0.38	0-4.08
mesothelioma (NOS)			1	0.19	0-1.92
PROSTATE	505	10			
SEMINAL VESICLES	431	10			
sarcoma			1	0.23	0-2.08
fibrosarcoma			1	0.23	0-2.00

Table CI (Cont.)

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Tumors	Mean Percent	Range Percent
ENDOCRINE SYSTEM					
PANCREAS (ENDOCRINE)	517	10			
islet cell adenoma			2	0.39	0-2.08
pancreatic duct adenocarcinoma			1	0.19	0-2.00
PITUITARY GLAND	479	10			
adenoma			4	0.84	0-4.55
carcinoma			1	0.21	0-2.27
THYROID GLAND	511	10			
follicular cell adenoma			3	0.59	0-4.08
PARATHYROID GLAND	353	10			0-6.00
ADRENAL GLAND	509	10			
cortical adenoma			8	1.57	0-4.00
pheochromocytoma (NOS)			1	0.20	0-1.92
pheochromocytoma (B)			1	0.20	0-2.22
subcapsular cell adenoma			1	0.20	0-2.22
spindle cell fibroma			1	0.20	0-2.13
NERVOUS SYSTEM					
SPINAL CORD	350	7			
oligodendroglioma			1	0.29	0-2.00
ganglioneuroma			1	0.29	0-2.00
schwannoma (M)			1	0.29	0-2.04
BRAIN	518	10			
ependymoma (M)			1	0.21	0-2.00
PERIPHERAL NERVES	516	10			
SPECIAL SENSES					
EYE AND ADNEXA*	409	8			
adenoma, accessory			5	1.22	0-8.16
HARDERIAN GLAND	172	3			
adenoma			22	12.79	0-18.06^
BODY CAVITIES					
THORACIC CAVITY	+				
mesothesioma (M)			1		

* accessory gland could be Harderian or lacrimal; all found in groups in which gland was not on tissue list to be examined

^ 5 additional adenomas were found in study groups in which Harderian gland not on tissue list to be examined

^^ number animals examined

+ gross lesions not reported elsewhere

++ all found in one study group

Table C2
NEOPLASMS
24 MONTH STUDIES
FEMALE CD-1® MICE

Location & Tumor	No. Tissues Examined	No. Study Groups	Total No. Tumors	Mean Percent	Range Percent
LOCATION & TUMOR					
HEMATOPOIETIC SYSTEM					
LYMPH NODES	553	11			
hemangiosarcoma			1	0.18	0-1.92
THYMUS	505	11			
thymic lymphoma			2++	0.40	0-2.99
hemangiosarcoma			6	1.19	0-6.82
BONE MARROW	338	7			
SPLEEN	573	11			
hemangioma			2	0.35	0-1.96
hemangiosarcoma			8	1.40	0-6.00
LYMPHORETICULAR TUMORS	425^^	8			
malignant lymphoma (NOS)			57	13.41	0-28.00
malignant lymphoma, lymphocytic			10++	2.35	0-19.61
malignant lymphoma, mixed			2++	0.47	0-3.92
myeloid leukemia			1	0.24	0-1.92
histiocytic sarcoma			16	3.76	0-10.00
INTEGUMENTARY SYSTEM					
SKIN/SUBCUTIS	575	11			
papilloma			1	0.17	0-2.00
sarcoma			7	1.22	0-3.92
hemangioma			1	0.17	0-1.96
hemangiosarcoma			4	0.70	0-4.00
chondrosarcoma			1	0.17	0-1.39
myxoma (B)			1	0.17	0-2.00
subcutaneous osteosarcoma			1	0.17	0-2.00
MAMMARY GLAND	549	11			
adenoacanthoma			3++	0.55	0-4.23
adenoma			1	0.18	0-2.00
carcinoma			25	4.55	0-12.20
MUSCULOSKELETAL SYSTEM					
SKELETAL MUSCLE	496	10			
BONE	374	7			
osteoma			2	0.45	0-2.00
osteosarcoma			3	0.60	0-4.00
RESPIRATORY SYSTEM					
TRACHEA	464	9			
LUNG	572	11			
bronchiolar/alveolar adenoma			56	9.79	4.00-18.37
bronchiolar/alveolar carcinoma			38	6.64	0-13.46
hemangiosarcoma			1	0.17	0-2.00

Table C2 (Cont.)

Location & Tumor	No. Tissues Examined	No. Study Groups	Total No. Tumors	Mean Percent	Range Percent
CIRCULATORY SYSTEM					
VASCULAR SYSTEM	7				
hemangiosarcoma			1		
hemangioma			1		
intercostal hemangiosarcoma			1		
HEART	574	11			
hemangiosarcoma			1	0.17	0-1.92
AORTA	415	8			
hemangioma			1	0.29	0-2.04
hemangiosarcoma			2	0.58	0-4.08
DIGESTIVE SYSTEM					
SALIVARY GLAND	572	11			
ESOPHAGUS	570	11			
STOMACH	568	11			
squamous cell papilloma			1	0.18	0-2.00
SMALL INTESTINE	456	9			
adenomatous polyp			1	0.22	0-2.08
adenocarcinoma			2	0.44	0-2.08
hemangiosarcoma			1	0.22	0-2.13
COLON/CECTUM	484	11			
leiomyoma, cecum			1	0.21	0-2.08
LIVER	573	11			
acidophilic focus/area			4	0.70	0-2.00
focus of alteration-mixed cell			1	0.18	0-2.00
basophilic focus/area			2	0.35	0-2.04
hepatocellular adenoma			18	3.15	0-11.27
hepatocellular carcinoma			9	1.58	0-4.00
hemangioma			4	0.70	0-2.04
hemangiosarcoma			3	0.53	0-2.00
GALL BLADDER	488	10			
PANCREAS (EXOCRINE)	523	11			
URINARY SYSTEM					
KIDNEY	582	11			
renal cell adenoma			3	0.52	0-4.00
renal cell carcinoma			1	0.17	0-2.00
URINARY BLADDER	560	11			
REPRODUCTIVE SYSTEM					
OVARY	568	11			
cystadenoma			11	1.94	0-6.12
granulosa/theca cell tumor			11	1.94	0-6.00
granulosa cell tumor (M)			2	0.35	0-2.00
adenoma, fallopian tube (69 exam.)			2	0.35	0-2.00
interstitial cell tumor (B)			1	0.18	0-2.08
hemangiosarcoma			2	0.35	0-2.04
Sertoli cell tumor (B)			1	0.18	0-2.04
mesothelioma			1	0.18	0-1.92
stromal cell tumor			1	0.18	0-0.44

Table C2 (Cont.)

Location & Tumor	No. Tissues Examined	No. Study Groups	Total No. Tumors	Mean Percent	Range Percent
REPRODUCTIVE SYSTEM (Cont.)					
UTERUS/CERVIX	572	11			
endometrial adenoma			1	0.17	0-1.41
adenocarcinoma			7	1.22	0-6.00
endometrial stromal polyp			35	6.12	0-22.00
endometrial stromal sarcoma			14	2.45	0-14.00
fibroma			2	0.35	0-2.00
leiomyoma			13	2.27	0-8.00
leiomyosarcoma			12	2.10	0-9.80
hemangioma			2	0.35	0-2.00
hemangiosarcoma			9	1.57	0-6.00
ENDOCRINE SYSTEM					
PANCREAS (ENDOCRINE)	573	11			
islet cell adenoma			2	0.35	0-2.00
PITUITARY GLAND	544	11			
adenoma			21	3.86	0-8.00
craniopharyngeal cyst carcinoma			1	0.18	0-2.04
THYROID GLAND	565	11			
follicular cell adenoma			2	0.35	0-2.00
follicular cell carcinoma			2	0.35	0-2.08
PARATHYROID GLAND	359	11			
ADRENAL GLAND	569	11			
cortical adenoma			3	0.53	0-2.00
pheochromocytoma (B)			2	0.35	0-2.08
NERVOUS SYSTEM					
SPINAL CORD	431	8			
BRAIN	575	11			
PERIPHERAL NERVES	517	10			
schwannoma			1	0.19	0-2.08
SPECIAL SENSES					
EYE AND ADNEXA	468	9			
cataract			25	5.34	0-28.00
adenoma, accessory gland			6*		
HARDERIAN GLAND	222	4			
adenoma			11	4.95	0-6.94[A]
adenocarcinoma			1	0.45	0-2.04

* accessory gland could be Harderian or lacrimal If Harderian, they were found in groups in which gland was not on tissue list to be examined
\+ gross lesions not reported elsewhere
++ all found in one study group
[A] 2 additional found in group in which Harderian gland not on tissue list to be examined not on tissue list to be examined
[AA] number animals examined

Table C3
LIVER NEOPLASMS BY STUDY GROUP
24 MONTH STUDIES
MALE

Study Code	CQ	CR	DZ	CP	BX	DN	DX	CX	DU	EG
No. tissues examined	50	50	49	50	52	48	50	72	50	50
acidophilic focus/area		2	2		1				2	
%		4.00	4.08		1.92				4.00	
focus of alteration, mixed cell									1	
%									2.00	
clear cell focus/area							3	2		
%							6.00	2.78		
basophilic focus/area	2	3	1		3	2	3	1	5	1
%	4.00	6.00	2.04		5.77	4.17	6.00	1.39	10.00	2.00
nodular hepatocellular proliferation	3	2		1						
%	6.00	4.00		2.00						
hepatocellular adenoma	9	7	2	9	6	10	9	27	9	9
%	18.00	14.00	4.08	18.00	11.54	20.83	18.00	37.50	18.00	18.00
hepatocellular carcinoma	14		8	1	9	4	8	12	7	5
%	28.00		16.33	2.00	17.31	8.33	16.00	16.67	14.00	10.00
carcinoma/adenoma				3						
%				6.00						
hemangioma	2			1	1				1	
%	4.00			2.00	1.92				2.00	
hemangiosarcoma	2	4				3			2	
%	4.00	8.00				6.25			4.00	
cholangioma		8								
%		16.00								

FEMALE

Study Code	**CQ**	**CR**	DZ	CP	BX	DN	DX	CX	DU	EG	CV
No. tissues examined	50	50	49	51	52	49	50	71	50	49	50
eosinophilic focus	1	1		1	1						
%	2.00	2.00		1.96	1.92						
focus of alteration-mixed cell									1		
%									2.00		
basophilic focus					1	1					
%					1.92	2.04					
hepatocellular adenoma	1	1			2	1	1	8		3	1
%	2.00	2.00			3.85	2.04	2.00	11.27		6.12	2.00
hepatocellular carcinoma	1	2		1	1		1		2	1	
%	2.00	4.00		1.96	1.92		2.00		4.00	2.04	
hemangioma					1	1			1		1
%					1.92	2.04			2.00		2.00
hemangiosarcoma	1							1			1
%	2.00							1.41			2.00

Table C4
LUNG NEOPLASMS BY STUDY GROUP
24 MONTH STUDIES
MALE

Study Code	CQ	CR	DZ	CP	BX	DN	DX	CX	DU	EG
No. tissues examined	50	50	50	51	52	49	50	72	50	50
bronchiolar/alveolar adenoma	8	8	9	7	12	9	9	7	11	14
%	16.00	16.00	18.00	13.73	23.08	18.37	18.00	9.72	22.00	28.00
bronchiolar/alveolar carcinoma	5	4	8	1	1	6	10	10	8	5
%	10.00	8.00	16.00	1.96	1.92	12.24	20.00	13.89	16.00	10.00
sarcoma (unknown origin)								1		
%								1.39		
pleural mesothelioma					1					
%					1.92					

FEMALE

Study Code	CQ	CR	DZ	CP	BX	DN	DX	CX	DU	EG	CV
No. tissues examined	50	49	50	51	52	49	50	71	50	50	50
bronchiolar/alveolar adenoma	6	4	2	5	5	9	7	5	4	5	4
%	12.00	8.16	4.00	9.80	9.62	18.37	14.00	7.04	8.00	10.00	8.00
bronchiolar/alveolar carcinoma		2	5	3	7	2	3	7	5	1	3
%		4.08	10.00	5.88	13.46	4.08	6.00	9.86	10.00	2.00	6.00
hemangiosarcoma	1										
%	2.00										

Table C5
LYMPHORETICULAR NEOPLASMS BY STUDY GROUP
24 MONTH STUDIES
MALE

Study Code	CQ	CR	DZ	CP	BX	DN	DX	CX	DU	EG
No. animals examined	---		50	50	52	49	50	72	50	50
malignant lymphoma (NOS)			6	1	2	3	4	6	3	
%			12.00	2.00	3.85	6.12	8.00	8.33	6.00	
malignant lymphoma, lymphocytic				2						
%				4.00						
malignant lymphoma, mixed				1						
%				2.00						
histiocytic sarcoma				3	4	1				
%				6.00	7.69	2.04				
mast cell tumor						1				
%						2.04				

FEMALE

Study Code	CQ	CR	DZ	CP	BX	DN	DX	CX	DU	EG	CV
No. tissues examined	---	---	50	51	52	50	50	72	50	50	---
malignant lymphoma			6	1	4	12	14	12	5	3	
%			12.00	1.96	7.69	24.00	28.00	16.67	10.00	6.00	
malignant lymphoma, lymphocytic				10							
%				19.61							
malignant lymphoma, mixed				2							
%				3.92							
myeloid leukemia					1						
%					1.92						
histiocytic sarcoma				2	2	3			5	4	
%				3.92	3.85	6.00			10.00	8.00	

FIGURE A1
MALE - SURVIVAL AT 18 MONTHS

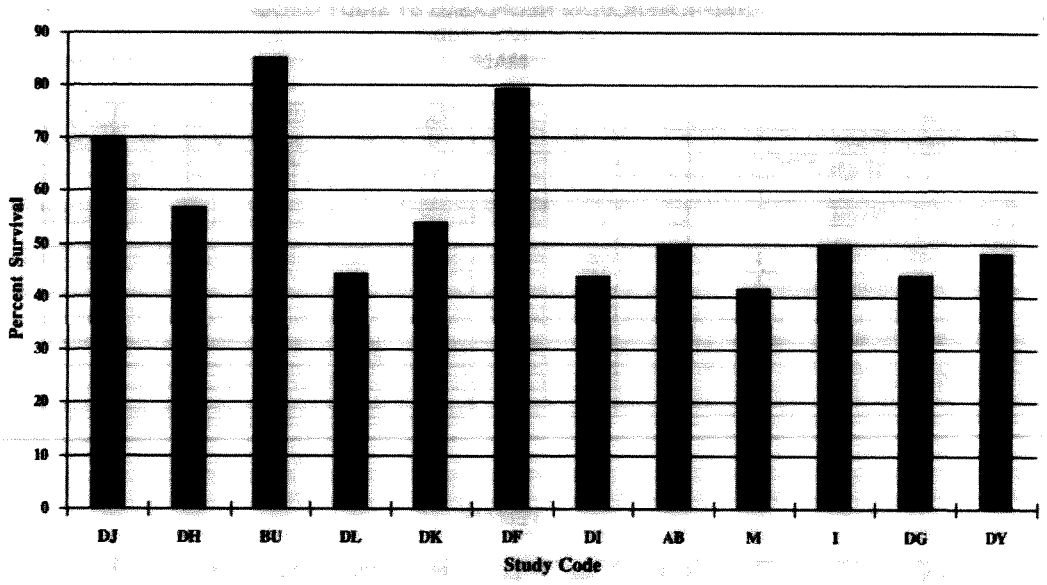


FIGURE A2
FEMALE - SURVIVAL AT 18 MONTHS

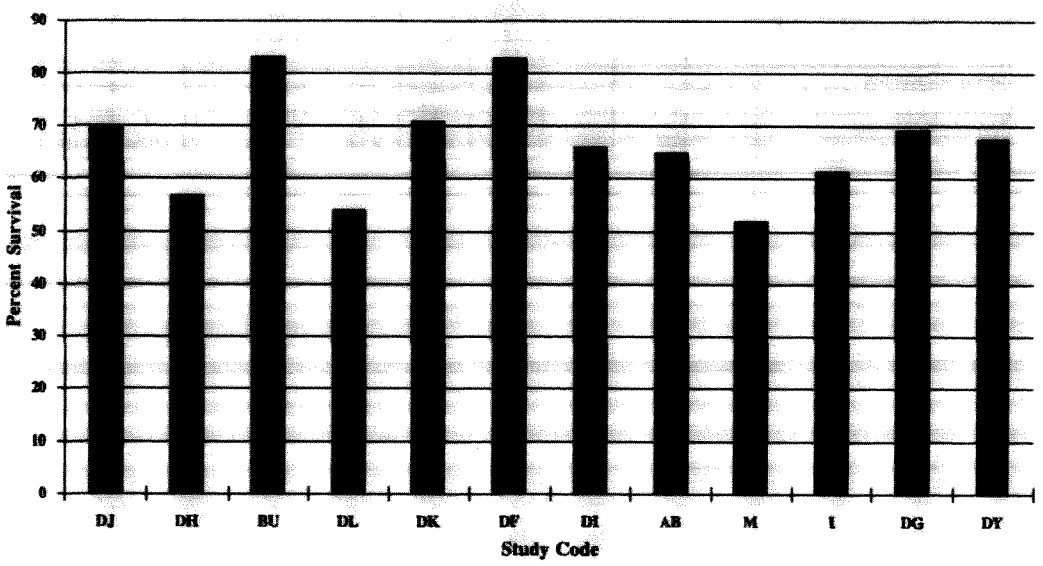


FIGURE B1
MALE - SURVIVAL AT 21 MONTHS

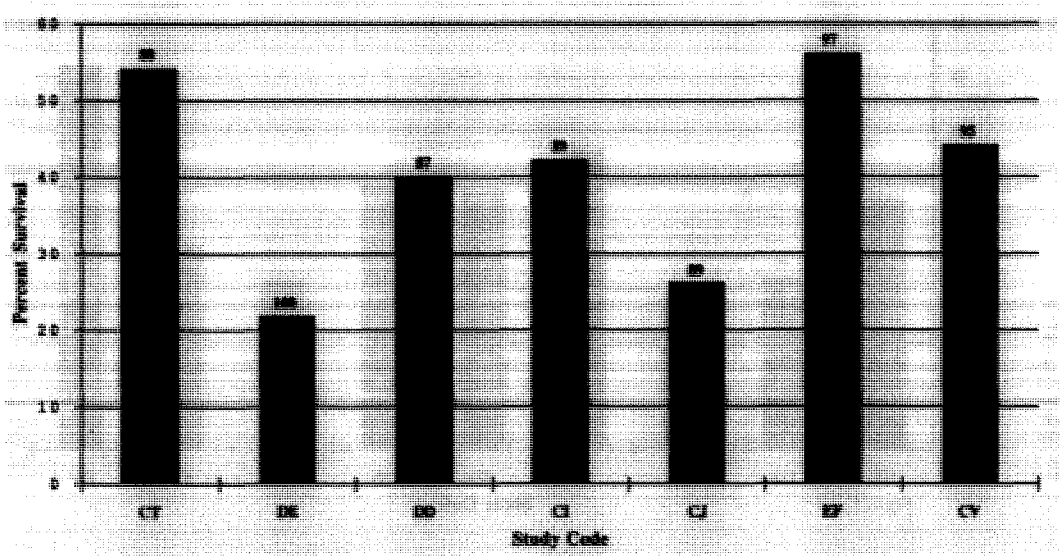
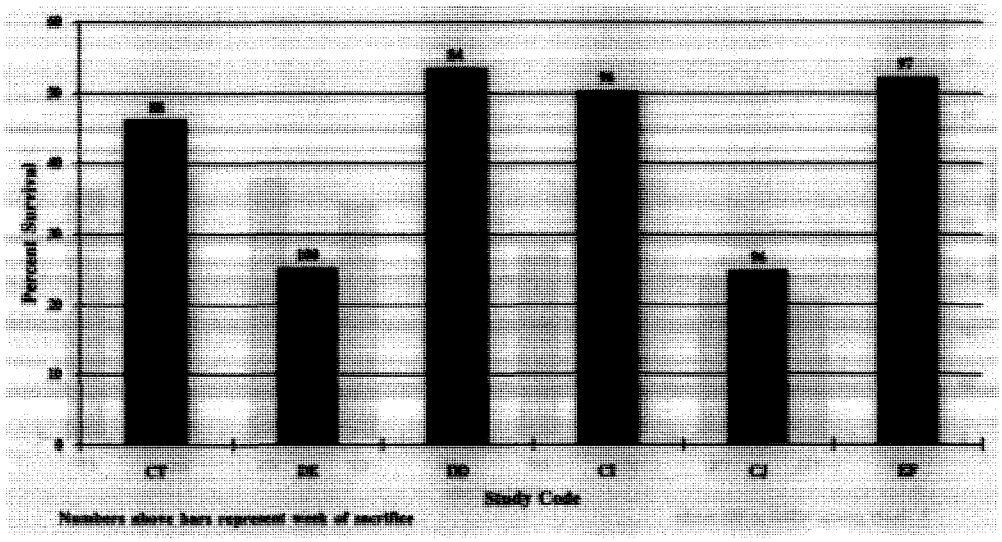


FIGURE B2
FEMALE - SURVIVAL AT 21 MONTHS



C1 FIGURE
MALE - SURVIVAL AT 24 MONTHS

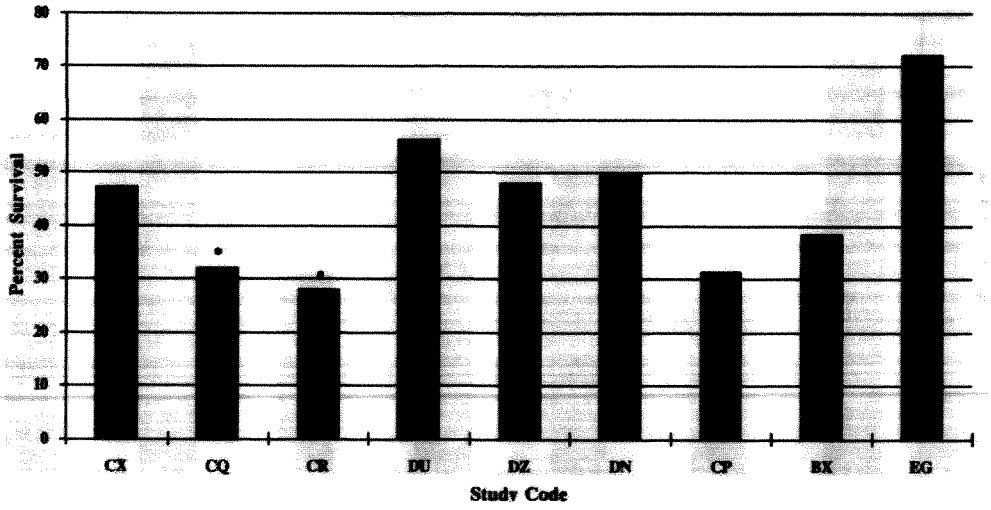
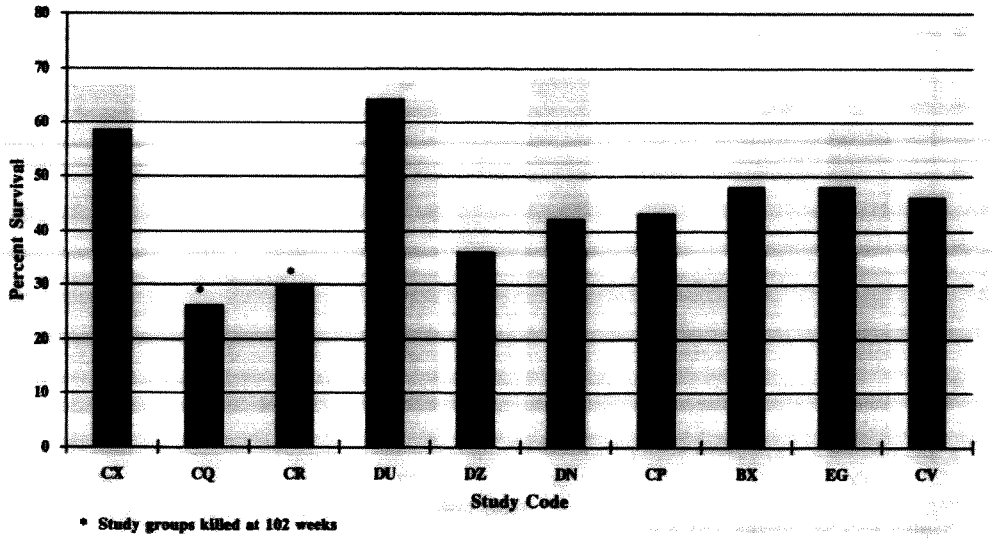


FIGURE C2
FEMALE - SURVIVAL AT 24 MONTHS



From: Carey Gillam <careygillamnewsnow@gmail.com>
Subject: Re: CD-1 mouse study
Date: June 7, 2017 at 6:11:14 PM GMT+2
To: Chris Portier <[redacted]>

One quick quote perhaps? I'm writing about Monsanto's manipulation of the kidney study results, or their efforts to convince regulators of their industry-friendly "interpretation." I see dog studies, rats, mice, rabbits, etc..that show tumors, reduced pregnancy rates, other negative impacts, and yet the data all eventually are discounted by regulators as not statistically significant. Can you offer a reader-friendly quote addressing this?
Carey

On Mon, Jun 5, 2017 at 9:32 PM, Chris Portier <[redacted]> wrote:
The kidney tumors in the 1983 study are definitely important. When the two 24 month mouse studies are combined, the kidney tumors are statistically significant. Individually, when historical controls are used against the rates seen in the 1983 study, the finiding is highly statistically significant. The argument used by the regulatory agencies that these tumors fall within the range of historical controls is an incorrect statistical comparison and a mor rigorous approach needs to be used - this leads to significance as noted by IARC. In general, all four mouse studies in CD-1 mice showed some positive trend in kidney tumors that, when combined, is highly significant. The same is true for hemangiosarcomas in male mice and malignant lymphoma in male mice in the 18-month studies. They are all important.

C.

On Jun 6, 2017, at 4:37 AM, Carey Gillam <careygillamnewsnow@gmail.com> wrote:

Hello again - I'm writing up a piece about the twisted path of the 1983 CD-1 mouse study that has appeared fairly pivotal when it comes to glyphosate carcinogenicity classifications. You know the saga of the non-existent tumor in the control group that then appeared after Monsanto enlisted an outside pathologist to review tissue slides.
I'm wondering how you view this study and how much weight it carries, or

does not carry, in your evaluations of the research surrounding glyphosate and cancer.
You are aware, I believe, that the plaintiffs' attorneys in the Roundup cancer litigation in San Francisco received court approval to review the tissue slides. I'd be most interested in your view on that study. This is the one prepared by BioDynamics for Monsanto's submission to EPA.

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Best regards,
Carey Gillam
913-526-6190
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www.careygillam.com
https://twitter.com/careygillam

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Carey Gillam
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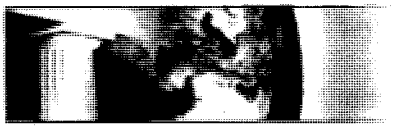
https://twitter.com/careygillam



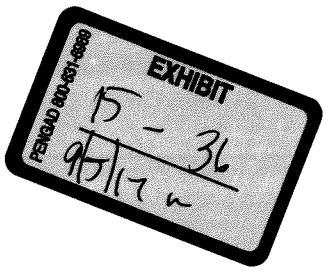
National Toxicology Program
Department of Health and Human Services

NTP Historical Controls Report

All Routes and Vehicles

Wistar-Han RATS

August 2016



REPORT DESCRIPTION

This report shows the tumor rates of control group animals from selected studies. The studies used are shown on the Study Summary page.

The report combines all the data from all of the historical control studies into one section. To see this data broken up by route and vehicle you must run the "By Route And Vehicle" report.

The individual tumor rates shown on the data pages of the report relate to the Study Summary page as follows: the tumor rates are shown in the same order as the Study Summary page, except that they are grouped horizontally in sets of three, with the males in the first set of three and the females in the second set. For example if the study summary showed the studies like this:

Male
M1
M2
M3
M4
M5
Female
F1
F2
F3
F4
F5

the data would be shown as:

Male			Female		
M1	M2	M3	F1	F2	F3
M4	M5		F4	F5	

Directly beneath the individual tumor rates on the data pages are the overall totals for that tumor/site combination. This includes the total tumors/animals, the overall mean (in parentheses), the mean of the study means, and the standard deviation of the study means.

Studies with no control animals of a particular gender are listed on the summary page with the Number of Animals shown as zero and the Start Date and Length of Study shown as "N/A". On the data pages there are blank spaces where tumor rates for these studies would normally be found, so that the male and female rates for the remaining studies can be easily compared.

Study Summary

Laboratory Name	Study Number	Study Start Date	Length of Study in Days	Number of Animals Total and (#/Cage)	Number Surviving and (Mean Life Span)	Maximum Mean Weekly Body Weight	Chemical
				Male			
Battelle Northwest	052060103	09/22/08	729	50(5)	30(672)	606.7	Antimony trioxide
Battelle Northwest	052072503	08/17/09	729	50(5)	36(692)	615.2	2,3-Butanedione
Battelle Columbus Laboratory	052020303	07/18/07	727	50(3)	35(687)	632.7	Green Tea Extract
Battelle Northwest	052051503	04/14/08	729	50(5)	33(688)	602.8	Metal Working Fluids: CIMSTAR 3800
Battelle Northwest	052052303	07/20/09	729	50(5)	36(696)	622.2	Metal Working Fluids: TRIM VX
Southern Research Institute	052020903	08/26/08	729	49(3)	36(671)	673.4	Pentabromodiphenyl Ether Mixture [DE-71 (Technical Grade)]
Battelle Columbus Laboratory	052032003	07/25/07	727	50(3)	33(642)	662.9	Tetrabromobisphenol A
				Female			
Battelle Northwest	052060103	09/22/08	730	50(5)	39(704)	395.6	Antimony trioxide
Battelle Northwest	052072503	08/17/09	731	50(5)	34(688)	400.0	2,3-Butanedione
Battelle Columbus Laboratory	052020303	07/19/07	729	50(5)	26(671)	369.7	Green Tea Extract
Battelle Northwest	052051503	04/14/08	731	50(5)	35(700)	384.9	Metal Working Fluids: CIMSTAR 3800
Battelle Northwest	052052303	07/20/09	731	50(5)	30(681)	391.1	Metal Working Fluids: TRIM VX
Southern Research Institute	052020903	08/26/08	732	50(5)	37(678)	389.6	Pentabromodiphenyl Ether Mixture [DE-71 (Technical Grade)]
Battelle Columbus Laboratory	052032003	07/26/07	728	50(5)	34(678)	375.2	Tetrabromobisphenol A

NOTE: The text on page 2 ("Report Description") describes how the studies listed here are displayed on the data pages that follow.

		Male				Female		
#All Organs:								
Benign Tumors								
		34/50 (68%)	27/50 (54%)	26/50 (52%)		33/50 (66%)	39/50 (78%)	38/50 (76%)
		32/50 (64%)	24/50 (48%)	33/49 (67%)		42/50 (84%)	42/50 (84%)	37/50 (74%)
		30/50 (60%)				38/50 (76%)		
Overall Incidence	Total	206/349 (59.03%)	Mean 59.05%	SD 7.87%	Total	269/350 (76.86%)	Mean 76.86%	SD 6.2%
#All Organs:								
Malignant Tumors								
		6/50 (12%)	13/50 (26%)	12/50 (24%)		17/50 (34%)	12/50 (24%)	16/50 (32%)
		13/50 (26%)	4/50 (8%)	13/49 (27%)		11/50 (22%)	13/50 (26%)	10/50 (20%)
		8/50 (16%)				10/50 (20%)		
Overall Incidence	Total	69/349 (19.77%)	Mean 19.79%	SD 7.68%	Total	89/350 (25.43%)	Mean 25.43%	SD 5.62%
#All Organs:								
Malignant and Benign Tumors								
		36/50 (72%)	35/50 (70%)	36/50 (72%)		40/50 (80%)	40/50 (80%)	43/50 (86%)
		37/50 (74%)	26/50 (52%)	36/49 (73%)		43/50 (86%)	47/50 (94%)	40/50 (80%)
		34/50 (68%)				40/50 (80%)		
Overall Incidence	Total	240/349 (68.77%)	Mean 68.78%	SD 7.68%	Total	293/350 (83.71%)	Mean 83.71%	SD 5.35%
#All Organs:								
Hemangioma								
		1/50 (2%)	1/50 (2%)	0/50 (0%)		0/50 (0%)	1/50 (2%)	0/50 (0%)
		0/50 (0%)	1/50 (2%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		1/50 (2%)				0/50 (0%)		
Overall Incidence	Total	5/349 (1.43%)	Mean 1.43%	SD 0.98%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female		
#All Organs:								
Hemangiosarcoma								
		3/50 (6%)	3/50 (6%)	0/50 (0%)		1/50 (2%)	2/50 (4%)	2/50 (4%)
		3/50 (6%)	0/50 (0%)	8/49 (16%)		1/50 (2%)	0/50 (0%)	2/50 (4%)
		3/50 (6%)				2/50 (4%)		
Overall Incidence	Total	20/349 (5.73%)	Mean 5.76%	SD 5.45%	Total	10/350 (2.86%)	Mean 2.86%	SD 1.57%
#All Organs:								
Hemangiosarcoma or Hemangioma								
		4/50 (8%)	4/50 (8%)	0/50 (0%)		1/50 (2%)	3/50 (6%)	2/50 (4%)
		3/50 (6%)	1/50 (2%)	9/49 (18%)		1/50 (2%)	0/50 (0%)	2/50 (4%)
		4/50 (8%)				2/50 (4%)		
Overall Incidence	Total	25/349 (7.16%)	Mean 7.2%	SD 5.87%	Total	11/350 (3.14%)	Mean 3.14%	SD 1.95%
#All Organs:								
Histiocytic Sarcoma								
		0/50 (0%)	1/50 (2%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	2/50 (4%)	0/50 (0%)
		0/50 (0%)				0/50 (0%)		
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	2/350 (0.57%)	Mean 0.57%	SD 1.51%
#All Organs:								
Leukemia: Lymphocytic, Monocytic, Mononuclear, or Undifferentiated								
		1/50 (2%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		1/50 (2%)				0/50 (0%)		
Overall Incidence	Total	3/349 (0.86%)	Mean 0.86%	SD 1.08%	Total	0/350 (0%)	Mean 0%	SD 0%

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
#All Organs:									
Malignant Lymphoma: Histiocytic, Lymphocytic, Mixed, NOS, or Undifferentiated Cell Type									
		0/50 (0%)	3/50 (6%)	0/50 (0%)		0/50 (0%)	1/50 (2%)	1/50 (2%)	
		0/50 (0%)	1/50 (2%)	0/49 (0%)		2/50 (4%)	1/50 (2%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	4/349 (1.15%)	Mean 1.14%	SD 2.27%	Total	5/350 (1.43%)	Mean 1.43%	SD 1.51%	
#All Organs:									
Mesothelioma: Benign, Malignant, NOS									
		0/50 (0%)	1/50 (2%)	2/50 (4%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	2/50 (4%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	6/349 (1.72%)	Mean 1.71%	SD 1.8%	Total	0/350 (0%)	Mean 0%	SD 0%	
#All Organs:									
Mesothelioma: Malignant									
		0/50 (0%)	1/50 (2%)	2/50 (4%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	1/50 (2%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	5/349 (1.43%)	Mean 1.43%	SD 1.51%	Total	0/350 (0%)	Mean 0%	SD 0%	
#All Organs:									
Osteoma									
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
#All Organs:									
Osteosarcoma									
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 0.98%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#All Organs:									
Osteosarcoma or Osteoma									
		0/50 (0%)	0/50 (0%)	2/50 (4%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	3/349 (0.86%)	Mean 0.86%	SD 1.57%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
***Adrenal Cortex:**									
Adenoma									
		3/50 (6%)	2/50 (4%)	1/50 (2%)		0/50 (0%)	1/50 (2%)	0/50 (0%)	
		2/50 (4%)	1/50 (2%)	0/49 (0%)		2/50 (4%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)				1/50 (2%)			
Overall Incidence	Total	9/349 (2.58%)	Mean 2.57%	SD 2.23%	Total	5/350 (1.43%)	Mean 1.43%	SD 1.51%	
***Adrenal Cortex:**									
Carcinoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				1/50 (2%)			
Overall Incidence	Total	2/349 (0.57%)	Mean 0.58%	SD 0.99%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
***Adrenal Medulla:**									
Pheochromocytoma Benign									
		1/49 (2%)	1/50 (2%)	1/50 (2%)		0/49 (0%)	3/50 (6%)	1/50 (2%)	
		4/50 (8%)	0/50 (0%)	0/49 (0%)		1/49 (2%)	0/50 (0%)	1/50 (2%)	
		0/49 (0%)				2/49 (4%)			
Overall Incidence	Total	7/347 (2.02%)	Mean 2.01%	SD 2.83%	Total	8/347 (2.31%)	Mean 2.3%	SD 2.15%	
***Adrenal Medulla:**									
Pheochromocytoma Complex									
		1/49 (2%)	0/50 (0%)	0/50 (0%)		0/49 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/49 (0%)	0/50 (0%)	1/50 (2%)	
		0/49 (0%)				0/49 (0%)			
Overall Incidence	Total	1/347 (0.29%)	Mean 0.29%	SD 0.77%	Total	1/347 (0.29%)	Mean 0.29%	SD 0.76%	
***Adrenal Medulla:**									
Pheochromocytoma Malignant									
		0/49 (0%)	0/50 (0%)	0/50 (0%)		0/49 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		1/49 (2%)	0/50 (0%)	0/50 (0%)	
		0/49 (0%)				0/49 (0%)			
Overall Incidence	Total	1/347 (0.29%)	Mean 0.29%	SD 0.77%	Total	1/347 (0.29%)	Mean 0.29%	SD 0.77%	
***Adrenal Medulla:**									
Pheochromocytoma: Benign, Complex, Malignant, NOS									
		2/49 (4%)	1/50 (2%)	1/50 (2%)		0/49 (0%)	3/50 (6%)	1/50 (2%)	
		4/50 (8%)	0/50 (0%)	1/49 (2%)		2/49 (4%)	0/50 (0%)	2/50 (4%)	
		0/49 (0%)				2/49 (4%)			
Overall Incidence	Total	9/347 (2.59%)	Mean 2.59%	SD 2.77%	Total	10/347 (2.88%)	Mean 2.88%	SD 2.28%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
#Blood Vessel:									
Hemangiosarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
***Bone Marrow:**									
Hemangiosarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Bone:									
Osteoma									
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Bone:									
Osteosarcoma									
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 0.98%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
#Bone:									
Osteosarcoma or Osteoma									
		0/50 (0%)	0/50 (0%)	2/50 (4%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	3/349 (0.86%)	Mean 0.86%	SD 1.57%		Total 1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Bone:									
Sarcoma									
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%		Total 0/350 (0%)	Mean 0%	SD 0%	
***Brain:**									
Glioma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		2/50 (4%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 1.51%		Total 0/350 (0%)	Mean 0%	SD 0%	
***Brain:**									
Glioma Malignant									
		0/50 (0%)	1/50 (2%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	3/349 (0.86%)	Mean 0.86%	SD 1.08%		Total 0/350 (0%)	Mean 0%	SD 0%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
***Brain:**									
Granular Cell Tumor Benign									
		1/50 (2%)	3/50 (6%)	2/50 (4%)		1/50 (2%)	1/50 (2%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		2/50 (4%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)				0/50 (0%)			
Overall Incidence	Total	8/349 (2.29%)	Mean 2.29%	SD 2.14%	Total	4/350 (1.14%)	Mean 1.14%	SD 1.57%	
***Brain:**									
Granular Cell Tumor Malignant									
		0/50 (0%)	1/50 (2%)	0/50 (0%)		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
***Brain:**									
Meningioma Malignant									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
***Brain:**									
Meningioma: Benign, Malignant, NOS									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
***Brain:**									
Oligodendroglioma Benign									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	1/50 (2%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%		Total 1/350 (0.29%)	Mean 0.29%	SD 0.76%	
***Brain:**									
Oligodendroglioma, Glioma, or Astrocytoma									
		0/50 (0%)	1/50 (2%)	1/50 (2%)		0/50 (0%)	1/50 (2%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	3/349 (0.86%)	Mean 0.86%	SD 1.08%		Total 1/350 (0.29%)	Mean 0.29%	SD 0.76%	
***Clitoral/Preputial Gland:**									
Carcinoma									
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/49 (0%)	0/49 (0%)	
		0/50 (0%)	0/49 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/49 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	2/348 (0.57%)	Mean 0.58%	SD 0.99%		Total 0/347 (0%)	Mean 0%	SD 0%	
***Clitoral/Preputial Gland:**									
Carcinoma or Adenoma									
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/49 (0%)	0/49 (0%)	
		0/50 (0%)	0/49 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/49 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	2/348 (0.57%)	Mean 0.58%	SD 0.99%		Total 0/347 (0%)	Mean 0%	SD 0%	

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#: Denominator is number of animals necropsied

		Male				Female			
***Heart:**									
Schwannoma Benign									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				1/50 (2%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
***Heart:**									
Schwannoma NOS									
		1/50 (2%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Intestine Small: Duodenum:									
Fibroma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.77%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Intestine Small: Duodenum:									
Leiomyosarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				1/50 (2%)			
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	

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#: Denominator is number of animals necropsied

		Male				Female			
#Intestine Small: Jejunum: Leiomyoma									
		0/50 (0%)	1/50 (2%)	0/50 (0%)		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Intestine Small: Jejunum: Leiomyosarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Intestine Small: Site Unspecified: Fibroma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.77%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Intestine Small: Site Unspecified: Leiomyoma									
		0/50 (0%)	1/50 (2%)	0/50 (0%)		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	

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		Male				Female		
#Intestine Small: Site Unspecified:								
Leiomyosarcoma								
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	1/50 (2%)
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		0/50 (0%)				1/50 (2%)		
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%	Total	2/350 (0.57%)	Mean 0.57%	SD 0.98%
***Islets, Pancreatic:**								
Adenoma								
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		0/50 (0%)	5/50 (10%)	4/49 (8%)		1/49 (2%)	0/50 (0%)	0/50 (0%)
		1/50 (2%)				0/50 (0%)		
Overall Incidence	Total	10/349 (2.87%)	Mean 2.88%	SD 4.33%	Total	1/349 (0.29%)	Mean 0.29%	SD 0.77%
***Islets, Pancreatic:**								
Carcinoma								
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		0/50 (0%)	0/50 (0%)	2/49 (4%)		0/49 (0%)	0/50 (0%)	0/50 (0%)
		0/50 (0%)				0/50 (0%)		
Overall Incidence	Total	2/349 (0.57%)	Mean 0.58%	SD 1.54%	Total	0/349 (0%)	Mean 0%	SD 0%
***Islets, Pancreatic:**								
Carcinoma or Adenoma								
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		0/50 (0%)	5/50 (10%)	6/49 (12%)		1/49 (2%)	0/50 (0%)	0/50 (0%)
		1/50 (2%)				0/50 (0%)		
Overall Incidence	Total	12/349 (3.44%)	Mean 3.46%	SD 5.32%	Total	1/349 (0.29%)	Mean 0.29%	SD 0.77%

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		Male				Female			
***Kidney: Pelvis and Transitional Epithelium:**									
Papilloma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
***Kidney: Renal Tubule:**									
Adenoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
***Kidney: Renal Tubule:**									
Carcinoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	1/50 (2%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
***Kidney: Renal Tubule:**									
Carcinoma or Adenoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	1/50 (2%)	0/49 (0%)		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	

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		Male				Female			
***Kidney: Renal Tubule: Lipoma**									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%		Total 1/350 (0.29%)	Mean 0.29%	SD 0.76%	
***Kidney: Renal Tubule: Liposarcoma**									
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%		Total 0/350 (0%)	Mean 0%	SD 0%	
***Liver: Cholangioma**									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	3/50 (6%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%		Total 3/350 (0.86%)	Mean 0.86%	SD 2.27%	
***Liver: Hemangioma**									
		0/50 (0%)	1/50 (2%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%		Total 0/350 (0%)	Mean 0%	SD 0%	

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#: Denominator is number of animals necropsied

		Male				Female			
***Liver:**									
Hepatocellular Adenoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		1/50 (2%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)	1/50 (2%)	3/49 (6%)		0/50 (0%)	0/50 (0%)	3/50 (6%)	
		0/50 (0%)				1/50 (2%)			
Overall Incidence	Total	4/349 (1.15%)	Mean 1.16%	SD 2.31%	Total	6/350 (1.71%)	Mean 1.71%	SD 2.14%	
***Liver:**									
Hepatocellular Carcinoma or Hepatocellular Adenoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		1/50 (2%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)	1/50 (2%)	3/49 (6%)		0/50 (0%)	0/50 (0%)	3/50 (6%)	
		0/50 (0%)				1/50 (2%)			
Overall Incidence	Total	4/349 (1.15%)	Mean 1.16%	SD 2.31%	Total	6/350 (1.71%)	Mean 1.71%	SD 2.14%	
***Liver:**									
Hepatocellular Carcinoma, Hepatocellular Adenoma, or Hepatoblastoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		1/50 (2%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)	1/50 (2%)	3/49 (6%)		0/50 (0%)	0/50 (0%)	3/50 (6%)	
		0/50 (0%)				1/50 (2%)			
Overall Incidence	Total	4/349 (1.15%)	Mean 1.16%	SD 2.31%	Total	6/350 (1.71%)	Mean 1.71%	SD 2.14%	
***Lung:**									
Alveolar/Bronchiolar Adenoma									
		3/50 (6%)	1/50 (2%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	5/349 (1.43%)	Mean 1.43%	SD 2.23%	Total	0/350 (0%)	Mean 0%	SD 0%	

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		Male				Female			
***Lung:**									
Alveolar/Bronchiolar Carcinoma or Alveolar/Bronchiolar Adenoma									
		3/50 (6%)	1/50 (2%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	5/349 (1.43%)	Mean 1.43%	SD 2.23%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Lymph Node:									
Hemangioma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	1/50 (2%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Lymph Node, Mandibular:									
Hemangioma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	1/50 (2%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Lymph Node, Mesenteric:									
Hemangioma									
		1/50 (2%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)				0/50 (0%)			
Overall Incidence	Total	3/349 (0.86%)	Mean 0.86%	SD 1.08%	Total	0/350 (0%)	Mean 0%	SD 0%	

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#: Denominator is number of animals necropsied

		Male				Female		
#Lymph Node, Mesenteric:								
Hemangiosarcoma								
		2/50 (4%)	2/50 (4%)	0/50 (0%)		0/50 (0%)	2/50 (4%)	1/50 (2%)
		3/50 (6%)	0/50 (0%)	7/49 (14%)		1/50 (2%)	0/50 (0%)	2/50 (4%)
		1/50 (2%)				1/50 (2%)		
Overall Incidence	Total	15/349 (4.3%)	Mean 4.33%	SD 4.92%	Total	7/350 (2%)	Mean 2%	SD 1.63%
#Mammary Gland:								
Adenoma								
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	5/50 (10%)	2/50 (4%)
		0/50 (0%)	0/50 (0%)	0/49 (0%)		2/50 (4%)	4/50 (8%)	0/50 (0%)
		0/50 (0%)				4/50 (8%)		
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%	Total	17/350 (4.86%)	Mean 4.86%	SD 3.98%
#Mammary Gland:								
Carcinoma								
		0/50 (0%)	1/50 (2%)	0/50 (0%)		5/50 (10%)	4/50 (8%)	6/50 (12%)
		0/50 (0%)	0/50 (0%)	0/49 (0%)		4/50 (8%)	4/50 (8%)	1/50 (2%)
		0/50 (0%)				1/50 (2%)		
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	25/350 (7.14%)	Mean 7.14%	SD 3.8%
#Mammary Gland:								
Carcinoma or Adenoma								
		0/50 (0%)	1/50 (2%)	0/50 (0%)		5/50 (10%)	8/50 (16%)	8/50 (16%)
		0/50 (0%)	0/50 (0%)	0/49 (0%)		6/50 (12%)	8/50 (16%)	1/50 (2%)
		0/50 (0%)				4/50 (8%)		
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	40/350 (11.43%)	Mean 11.43%	SD 5.26%

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		Male				Female		
#Mammary Gland:								
Fibroadenoma								
		0/50 (0%)	0/50 (0%)	0/50 (0%)		7/50 (14%)	13/50 (26%)	11/50 (22%)
		0/50 (0%)	0/50 (0%)	0/49 (0%)		9/50 (18%)	2/50 (4%)	9/50 (18%)
		1/50 (2%)				8/50 (16%)		
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	59/350 (16.86%)	Mean 16.86%	SD 6.91%
#Mammary Gland:								
Fibroma, Fibroadenoma or Adenoma								
		0/50 (0%)	0/50 (0%)	0/50 (0%)		7/50 (14%)	15/50 (30%)	11/50 (22%)
		0/50 (0%)	0/50 (0%)	0/49 (0%)		11/50 (22%)	6/50 (12%)	9/50 (18%)
		1/50 (2%)				12/50 (24%)		
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	71/350 (20.29%)	Mean 20.29%	SD 6.16%
#Mammary Gland:								
Fibroma, Fibroadenoma, Carcinoma, or Adenoma								
		0/50 (0%)	1/50 (2%)	0/50 (0%)		10/50 (20%)	15/50 (30%)	15/50 (30%)
		0/50 (0%)	0/50 (0%)	0/49 (0%)		13/50 (26%)	9/50 (18%)	10/50 (20%)
		1/50 (2%)				12/50 (24%)		
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 0.98%	Total	84/350 (24%)	Mean 24%	SD 4.9%
#Mesentery:								
Hemangiosarcoma								
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	1/50 (2%)
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		0/50 (0%)				0/50 (0%)		
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
#Mesentery:									
Lipoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.77%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Mesentery:									
Schwannoma Malignant									
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
***Nose:**									
Adenoma									
		0/50 (0%)	1/50 (2%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/49 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/349 (0%)	Mean 0%	SD 0%	
***Nose:**									
Chondroma									
		1/50 (2%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/49 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
***Nose:**									
Olfactory Neuroblastoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/49 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				1/50 (2%)			
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%		Total 1/349 (0.29%)	Mean 0.29%	SD 0.76%	
#Oral Cavity (Oral Mucosa, Tongue, Pharynx, Tooth, Gingiva):									
Squamous Cell Carcinoma									
		0/50 (0%)	1/50 (2%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 0.98%		Total 1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Oral Cavity (Oral Mucosa, Tongue, Pharynx, Tooth, Gingiva):									
Squamous Cell Carcinoma, Papilloma Squamous, or Papilloma									
		0/50 (0%)	1/50 (2%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 0.98%		Total 1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Oral Mucosa:									
Squamous Cell Carcinoma									
		0/50 (0%)	1/50 (2%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 0.98%		Total 1/350 (0.29%)	Mean 0.29%	SD 0.76%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male		Female	
***Ovary:**					
Adenoma					
		2/50 (4%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)			
Overall Incidence	Total	2/350 (0.57%)	Mean 0.57%	SD 1.51%	
***Ovary:**					
Cystadenoma					
		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)			
Overall Incidence	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
***Ovary:**					
Granulosa Cell Tumor Benign					
		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)			
Overall Incidence	Total	2/350 (0.57%)	Mean 0.57%	SD 0.98%	
***Ovary:**					
Granulosa Cell Tumor Malignant					
		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	1/50 (2%)	1/50 (2%)	
		1/50 (2%)			
Overall Incidence	Total	3/350 (0.86%)	Mean 0.86%	SD 1.07%	

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		Male		Female	
***Ovary:**					
Granulosa Cell Tumor: Benign, Malignant, NOS					
		0/50 (0%)		0/50 (0%)	0/50 (0%)
		1/50 (2%)		1/50 (2%)	2/50 (4%)
		1/50 (2%)			
Overall Incidence	Total	5/350 (1.43%)		Mean 1.43%	SD 1.51%
***Ovary:**					
Granulosa-Theca Tumor Malignant					
		0/50 (0%)		1/50 (2%)	0/50 (0%)
		0/50 (0%)		0/50 (0%)	0/50 (0%)
		0/50 (0%)			
Overall Incidence	Total	1/350 (0.29%)		Mean 0.29%	SD 0.76%
***Ovary:**					
Sex Cord Stromal Tumor, Benign					
		0/50 (0%)		0/50 (0%)	0/50 (0%)
		0/50 (0%)		0/50 (0%)	0/50 (0%)
		2/50 (4%)			
Overall Incidence	Total	2/350 (0.57%)		Mean 0.57%	SD 1.51%
***Ovary:**					
Tubulostromal Adenoma					
		2/50 (4%)		1/50 (2%)	0/50 (0%)
		0/50 (0%)		0/50 (0%)	0/50 (0%)
		0/50 (0%)			
Overall Incidence	Total	3/350 (0.86%)		Mean 0.86%	SD 1.57%

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		Male				Female		
***Pancreas:**								
Adenoma								
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		1/50 (2%)	1/50 (2%)	1/46 (2%)		0/49 (0%)	0/50 (0%)	0/50 (0%)
		1/50 (2%)				0/50 (0%)		
Overall Incidence	Total	4/346 (1.16%)	Mean 1.17%	SD 1.09%	Total	0/349 (0%)	Mean 0%	SD 0%
***Pancreas:**								
Carcinoma or Adenoma								
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		1/50 (2%)	1/50 (2%)	1/46 (2%)		0/49 (0%)	0/50 (0%)	0/50 (0%)
		1/50 (2%)				0/50 (0%)		
Overall Incidence	Total	4/346 (1.16%)	Mean 1.17%	SD 1.09%	Total	0/349 (0%)	Mean 0%	SD 0%
***Parathyroid Gland:**								
Adenoma								
		0/44 (0%)	1/49 (2%)	0/47 (0%)		0/39 (0%)	0/46 (0%)	0/47 (0%)
		0/43 (0%)	0/39 (0%)	2/47 (4%)		0/47 (0%)	1/42 (2%)	1/49 (2%)
		0/45 (0%)				0/48 (0%)		
Overall Incidence	Total	3/314 (0.96%)	Mean 0.9%	SD 1.66%	Total	2/318 (0.63%)	Mean 0.63%	SD 1.08%
***Pituitary Gland: Pars Distalis or Unspecified Site:**								
Adenoma								
		14/50 (28%)	9/50 (18%)	17/50 (34%)		19/50 (38%)	26/50 (52%)	32/50 (64%)
		16/49 (33%)	14/50 (28%)	19/49 (39%)		35/50 (70%)	34/50 (68%)	23/50 (46%)
		21/50 (42%)				21/50 (42%)		
Overall Incidence	Total	110/348 (31.61%)	Mean 31.63%	SD 7.93%	Total	190/350 (54.29%)	Mean 54.29%	SD 13.03%

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		Male				Female		
***Pituitary Gland: Pars Distalis or Unspecified Site: Carcinoma**								
		0/50 (0%)	0/50 (0%)	0/50 (0%)		1/50 (2%)	0/50 (0%)	0/50 (0%)
		0/49 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		0/50 (0%)				0/50 (0%)		
Overall Incidence	Total	0/348 (0%)	Mean 0%	SD 0%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%
***Pituitary Gland: Pars Distalis or Unspecified Site: Carcinoma or Adenoma**								
		14/50 (28%)	9/50 (18%)	17/50 (34%)		20/50 (40%)	26/50 (52%)	32/50 (64%)
		16/49 (33%)	14/50 (28%)	19/49 (39%)		35/50 (70%)	34/50 (68%)	23/50 (46%)
		21/50 (42%)				21/50 (42%)		
Overall Incidence	Total	110/348 (31.61%)	Mean 31.63%	SD 7.93%	Total	191/350 (54.57%)	Mean 54.57%	SD 12.63%
***Pituitary Gland: Pars Intermedia: Adenoma**								
		1/50 (2%)	2/50 (4%)	1/50 (2%)		0/50 (0%)	1/50 (2%)	2/50 (4%)
		2/49 (4%)	1/50 (2%)	0/49 (0%)		1/50 (2%)	1/50 (2%)	1/50 (2%)
		2/50 (4%)				4/50 (8%)		
Overall Incidence	Total	9/348 (2.59%)	Mean 2.58%	SD 1.52%	Total	10/350 (2.86%)	Mean 2.86%	SD 2.54%
***Pituitary Gland: Pars Intermedia: Carcinoma or Adenoma**								
		1/50 (2%)	2/50 (4%)	1/50 (2%)		0/50 (0%)	1/50 (2%)	2/50 (4%)
		2/49 (4%)	1/50 (2%)	0/49 (0%)		1/50 (2%)	1/50 (2%)	1/50 (2%)
		2/50 (4%)				4/50 (8%)		
Overall Incidence	Total	9/348 (2.59%)	Mean 2.58%	SD 1.52%	Total	10/350 (2.86%)	Mean 2.86%	SD 2.54%

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#: Denominator is number of animals necropsied

		Male			Female		
***Prostate:**							
Adenoma							
		1/50 (2%)	0/50 (0%)	0/50 (0%)			
		1/50 (2%)	0/50 (0%)	0/49 (0%)			
		0/50 (0%)					
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 0.98%			
***Prostate:**							
Carcinoma							
		0/50 (0%)	1/50 (2%)	0/50 (0%)			
		0/50 (0%)	0/50 (0%)	0/49 (0%)			
		0/50 (0%)					
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%			
***Prostate:**							
Carcinoma or Adenoma							
		1/50 (2%)	1/50 (2%)	0/50 (0%)			
		1/50 (2%)	0/50 (0%)	0/49 (0%)			
		0/50 (0%)					
Overall Incidence	Total	3/349 (0.86%)	Mean 0.86%	SD 1.07%			
***Salivary Glands:**							
Adenoma							
		0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/49 (0%)
		0/50 (0%)	0/50 (0%)	1/46 (2%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
		0/50 (0%)			0/50 (0%)		
Overall Incidence	Total	1/346 (0.29%)	Mean 0.31%	SD 0.82%	Total 0/349 (0%)	Mean 0%	SD 0%

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#: Denominator is number of animals necropsied

		Male				Female			
***Salivary Glands: Carcinoma**									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/49 (0%)	
		0/50 (0%)	0/50 (0%)	0/46 (0%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	0/346 (0%)	Mean 0%	SD 0%	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	
***Salivary Glands: Carcinoma or Adenoma**									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/49 (0%)	
		0/50 (0%)	0/50 (0%)	1/46 (2%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/346 (0.29%)	Mean 0.31%	SD 0.82%	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	
***Salivary Glands: Myoepithelioma**									
		1/50 (2%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/49 (0%)	
		0/50 (0%)	0/50 (0%)	0/46 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)				0/50 (0%)			
Overall Incidence	Total	2/346 (0.58%)	Mean 0.57%	SD 0.98%	Total	0/349 (0%)	Mean 0%	SD 0%	
***Salivary Glands: Schwannoma Malignant**									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/49 (0%)	
		1/50 (2%)	0/50 (0%)	0/46 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/346 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/349 (0%)	Mean 0%	SD 0%	

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#: Denominator is number of animals necropsied

		Male				Female			
#Seminal Vesicle:									
Adenoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)					
		1/50 (2%)	0/50 (0%)	0/49 (0%)					
		0/50 (0%)							
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%					
#Skeletal Muscle:									
Hemangiosarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.77%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Skeletal Muscle:									
Sarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Skin:									
Basal Cell Adenoma									
		0/50 (0%)	0/50 (0%)	2/50 (4%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		2/50 (4%)				0/50 (0%)			
Overall Incidence	Total	5/349 (1.43%)	Mean 1.43%	SD 1.9%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	

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		Male				Female			
#Skin:									
Basal Cell Adenoma or Basosquamous Tumor Benign									
		0/50 (0%)	0/50 (0%)	2/50 (4%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		2/50 (4%)				0/50 (0%)			
Overall Incidence	Total	5/349 (1.43%)	Mean 1.43%	SD 1.9%		Total 1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Skin:									
Basal Cell Adenoma, Basosquemous Tumor Benign, or Trichoepithelioma									
		0/50 (0%)	0/50 (0%)	2/50 (4%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		2/50 (4%)				0/50 (0%)			
Overall Incidence	Total	5/349 (1.43%)	Mean 1.43%	SD 1.9%		Total 1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Skin:									
Basal Cell Carcinoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)				0/50 (0%)			
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 0.98%		Total 0/350 (0%)	Mean 0%	SD 0%	
#Skin:									
Basal Cell Carcinoma or Basosquamous Tumor (malignant or NOS)									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)				0/50 (0%)			
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 0.98%		Total 0/350 (0%)	Mean 0%	SD 0%	

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#: Denominator is number of animals necropsied

		Male				Female			
#Skin:									
Basal Cell Carcinoma, Basal Cell Adenoma, Basosquamous Tumor (benign, malignant or NOS), or Trichoepithelioma									
		0/50 (0%)	0/50 (0%)	2/50 (4%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		2/50 (4%)				0/50 (0%)			
Overall Incidence	Total	6/349 (1.72%)	Mean 1.72%	SD 1.8%		Total 1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Skin:									
Basal or Sq. Cell Carcinoma, Carcinoma, Basosq. Tumor (M or B), Basal Cell Adenoma, Adenoma, Papilloma, Sq Papilloma, Keratoacanthoma, Trichoepithelioma									
		1/50 (2%)	3/50 (6%)	6/50 (12%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		2/50 (4%)	1/50 (2%)	3/49 (6%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		7/50 (14%)				0/50 (0%)			
Overall Incidence	Total	23/349 (6.59%)	Mean 6.59%	SD 4.72%		Total 1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Skin:									
Fibroma									
		2/50 (4%)	0/50 (0%)	1/50 (2%)		2/50 (4%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	1/50 (2%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	6/349 (1.72%)	Mean 1.72%	SD 1.38%		Total 2/350 (0.57%)	Mean 0.57%	SD 1.51%	
#Skin:									
Fibroma, Fibrosarcoma, Sarcoma, Myxoma, Myxosarcoma, or Fibrous Histiocytoma									
		2/50 (4%)	2/50 (4%)	1/50 (2%)		2/50 (4%)	0/50 (0%)	0/50 (0%)	
		2/50 (4%)	1/50 (2%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	9/349 (2.58%)	Mean 2.58%	SD 1.51%		Total 2/350 (0.57%)	Mean 0.57%	SD 1.51%	

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#: Denominator is number of animals necropsied

		Male				Female			
#Skin:									
Fibrosarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Skin:									
Fibrosarcoma, Sarcoma, Myxosarcoma, or Fibrous Histiocytoma									
		0/50 (0%)	1/50 (2%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 0.98%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Skin:									
Fibrous Histiocytoma									
		0/50 (0%)	1/50 (2%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Skin:									
Hamartoma									
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
#Skin:									
Hemangiosarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				1/50 (2%)			
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Skin:									
Keratoacanthoma									
		1/50 (2%)	3/50 (6%)	2/50 (4%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	1/50 (2%)	2/49 (4%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		4/50 (8%)				0/50 (0%)			
Overall Incidence	Total	14/349 (4.01%)	Mean 4.01%	SD 2.31%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Skin:									
Lipoma									
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 0.98%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Skin:									
Liposarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
#Skin:									
Myxoma									
		0/50 (0%)	1/50 (2%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Skin:									
Neurofibrosarcoma or Schwannoma (malignant or NOS)									
		0/50 (0%)	0/50 (0%)	2/50 (4%)		0/50 (0%)	0/50 (0%)	2/50 (4%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		2/50 (4%)				0/50 (0%)			
Overall Incidence	Total	4/349 (1.15%)	Mean 1.14%	SD 1.95%	Total	2/350 (0.57%)	Mean 0.57%	SD 1.51%	
#Skin:									
Neurofibrosarcoma, Neurofibroma, or Schwannoma (benign, malignant or NOS)									
		0/50 (0%)	0/50 (0%)	2/50 (4%)		0/50 (0%)	0/50 (0%)	2/50 (4%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		2/50 (4%)				0/50 (0%)			
Overall Incidence	Total	4/349 (1.15%)	Mean 1.14%	SD 1.95%	Total	2/350 (0.57%)	Mean 0.57%	SD 1.51%	
#Skin:									
Schwannoma Malignant									
		0/50 (0%)	0/50 (0%)	2/50 (4%)		0/50 (0%)	0/50 (0%)	2/50 (4%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		2/50 (4%)				0/50 (0%)			
Overall Incidence	Total	4/349 (1.15%)	Mean 1.14%	SD 1.95%	Total	2/350 (0.57%)	Mean 0.57%	SD 1.51%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male					Female				
#Skin:											
Squamous Cell Carcinoma											
		0/50 (0%)	0/50 (0%)	1/50 (2%)			0/50 (0%)	0/50 (0%)	0/50 (0%)		
		0/50 (0%)	0/50 (0%)	0/49 (0%)			0/50 (0%)	0/50 (0%)	0/50 (0%)		
		0/50 (0%)					0/50 (0%)				
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%		Total	0/350 (0%)	Mean 0%	SD 0%		
#Skin:											
Squamous Cell Carcinoma, Basal Cell Carcinoma, Basosquamous Tumor (malignant or NOS), or Carcinoma											
		0/50 (0%)	0/50 (0%)	1/50 (2%)			0/50 (0%)	0/50 (0%)	0/50 (0%)		
		1/50 (2%)	0/50 (0%)	0/49 (0%)			0/50 (0%)	0/50 (0%)	0/50 (0%)		
		1/50 (2%)					0/50 (0%)				
Overall Incidence	Total	3/349 (0.86%)	Mean 0.86%	SD 1.07%		Total	0/350 (0%)	Mean 0%	SD 0%		
#Skin:											
Squamous Cell Papilloma											
		0/50 (0%)	0/50 (0%)	1/50 (2%)			0/50 (0%)	0/50 (0%)	0/50 (0%)		
		0/50 (0%)	0/50 (0%)	0/49 (0%)			0/50 (0%)	0/50 (0%)	0/50 (0%)		
		1/50 (2%)					0/50 (0%)				
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 0.98%		Total	0/350 (0%)	Mean 0%	SD 0%		
#Skin:											
Squamous Cell Papilloma or Papilloma											
		0/50 (0%)	0/50 (0%)	1/50 (2%)			0/50 (0%)	0/50 (0%)	0/50 (0%)		
		0/50 (0%)	0/50 (0%)	0/49 (0%)			0/50 (0%)	0/50 (0%)	0/50 (0%)		
		1/50 (2%)					0/50 (0%)				
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 0.98%		Total	0/350 (0%)	Mean 0%	SD 0%		

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
#Skin:									
Squamous Cell Papilloma, Papilloma, Squamous Cell Carcinoma or Keratoacanthoma									
		1/50 (2%)	3/50 (6%)	4/50 (8%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	1/50 (2%)	2/49 (4%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		5/50 (10%)				0/50 (0%)			
Overall Incidence	Total	17/349 (4.87%)	Mean 4.87%	SD 3.23%		Total 0/350 (0%)	Mean 0%	SD 0%	
#Skin:									
Squamous Cell Papilloma, Papilloma, or Keratoacanthoma									
		1/50 (2%)	3/50 (6%)	3/50 (6%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	1/50 (2%)	2/49 (4%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		5/50 (10%)				0/50 (0%)			
Overall Incidence	Total	16/349 (4.58%)	Mean 4.58%	SD 2.99%		Total 0/350 (0%)	Mean 0%	SD 0%	
#Skin: Sebaceous Gland:									
Adenoma									
		0/50 (0%)	1/50 (2%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	1/50 (2%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	3/349 (0.86%)	Mean 0.86%	SD 1.07%		Total 0/350 (0%)	Mean 0%	SD 0%	
#Skin: Sebaceous Gland:									
Carcinoma or Adenoma									
		0/50 (0%)	1/50 (2%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	1/50 (2%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	3/349 (0.86%)	Mean 0.86%	SD 1.07%		Total 0/350 (0%)	Mean 0%	SD 0%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
***Spleen:**									
Hemangiosarcoma									
		0/50 (0%)	1/50 (2%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/47 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)				0/50 (0%)			
Overall Incidence	Total	3/347 (0.86%)	Mean 0.88%	SD 1.09%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Stomach, Forestomach:									
Fibrosarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.77%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Stomach, Forestomach:									
Leiomyoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Stomach, Forestomach:									
Leiomyosarcoma									
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
#Stomach, Forestomach:									
Sarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Stomach, Forestomach:									
Squamous Cell Carcinoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Stomach, Forestomach:									
Squamous Cell Carcinoma or Papilloma Squamous									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	1/50 (2%)	1/50 (2%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.77%	Total	2/350 (0.57%)	Mean 0.57%	SD 0.98%	
#Stomach, Forestomach:									
Squamous Cell Papilloma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	1/50 (2%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.77%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
#Stomach, Glandular:									
Fibrosarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.77%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Stomach, Glandular:									
Leiomyosarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				1/50 (2%)			
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%	Total	2/350 (0.57%)	Mean 0.57%	SD 0.98%	
#Stomach, Glandular:									
Sarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
***Testes:**									
Adenoma									
		6/50 (12%)	3/50 (6%)	2/50 (4%)					
		2/50 (4%)	0/50 (0%)	2/49 (4%)					
		0/50 (0%)							
Overall Incidence	Total	15/349 (4.3%)	Mean 4.3%	SD 4.07%					

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male			Female		
***Testes:**							
Hemangiosarcoma							
		1/50 (2%)	0/50 (0%)	0/50 (0%)			
		0/50 (0%)	0/50 (0%)	0/49 (0%)			
		0/50 (0%)					
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%			
***Thymus:**							
Sarcoma							
		0/41 (0%)	0/47 (0%)	0/49 (0%)	0/46 (0%)	0/49 (0%)	0/49 (0%)
		0/40 (0%)	0/48 (0%)	0/45 (0%)	0/48 (0%)	0/48 (0%)	0/50 (0%)
		0/49 (0%)			1/50 (2%)		
Overall Incidence	Total	0/319 (0%)	Mean 0%	SD 0%	Total 1/340 (0.29%)	Mean 0.29%	SD 0.76%
***Thymus:**							
Thymoma Benign							
		3/41 (7%)	1/47 (2%)	2/49 (4%)	6/46 (13%)	0/49 (0%)	3/49 (6%)
		1/40 (3%)	3/48 (6%)	0/45 (0%)	5/48 (10%)	8/48 (17%)	0/50 (0%)
		1/49 (2%)			1/50 (2%)		
Overall Incidence	Total	11/319 (3.45%)	Mean 3.47%	SD 2.57%	Total 23/340 (6.76%)	Mean 6.89%	SD 6.65%
***Thymus:**							
Thymoma: Benign, Malignant, NOS							
		3/41 (7%)	1/47 (2%)	2/49 (4%)	6/46 (13%)	0/49 (0%)	3/49 (6%)
		1/40 (3%)	3/48 (6%)	0/45 (0%)	5/48 (10%)	8/48 (17%)	0/50 (0%)
		1/49 (2%)			1/50 (2%)		
Overall Incidence	Total	11/319 (3.45%)	Mean 3.47%	SD 2.57%	Total 23/340 (6.76%)	Mean 6.89%	SD 6.65%

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female		
***Thyroid Gland: Carcinoma**								
		0/50 (0%)	0/50 (0%)	0/50 (0%)		1/50 (2%)	0/50 (0%)	0/50 (0%)
		0/50 (0%)	0/50 (0%)	0/45 (0%)		0/50 (0%)	0/49 (0%)	0/45 (0%)
		0/50 (0%)				0/50 (0%)		
Overall Incidence	Total	0/345 (0%)	Mean 0%	SD 0%	Total	1/344 (0.29%)	Mean 0.29%	SD 0.76%
***Thyroid Gland: C-Cell: Adenoma**								
		5/50 (10%)	6/50 (12%)	4/50 (8%)		4/50 (8%)	2/50 (4%)	3/50 (6%)
		7/50 (14%)	3/50 (6%)	11/45 (24%)		3/50 (6%)	7/49 (14%)	7/45 (16%)
		5/50 (10%)				7/50 (14%)		
Overall Incidence	Total	41/345 (11.88%)	Mean 12.06%	SD 6.04%	Total	33/344 (9.59%)	Mean 9.69%	SD 4.77%
***Thyroid Gland: C-Cell: Carcinoma**								
		1/50 (2%)	0/50 (0%)	0/50 (0%)		1/50 (2%)	1/50 (2%)	1/50 (2%)
		0/50 (0%)	0/50 (0%)	0/45 (0%)		0/50 (0%)	0/49 (0%)	0/45 (0%)
		0/50 (0%)				0/50 (0%)		
Overall Incidence	Total	1/345 (0.29%)	Mean 0.29%	SD 0.76%	Total	3/344 (0.87%)	Mean 0.86%	SD 1.07%
***Thyroid Gland: C-Cell: Carcinoma or Adenoma**								
		6/50 (12%)	6/50 (12%)	4/50 (8%)		5/50 (10%)	3/50 (6%)	4/50 (8%)
		7/50 (14%)	3/50 (6%)	11/45 (24%)		3/50 (6%)	7/49 (14%)	7/45 (16%)
		5/50 (10%)				7/50 (14%)		
Overall Incidence	Total	42/345 (12.17%)	Mean 12.35%	SD 5.97%	Total	36/344 (10.47%)	Mean 10.55%	SD 4.06%

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
***Thyroid Gland: Follicular Cell: Adenoma**									
		0/50 (0%)	2/50 (4%)	0/50 (0%)		1/50 (2%)	2/50 (4%)	1/50 (2%)	
		1/50 (2%)	0/50 (0%)	1/45 (2%)		1/50 (2%)	0/49 (0%)	1/45 (2%)	
		3/50 (6%)				3/50 (6%)			
Overall Incidence	Total	7/345 (2.03%)	Mean 2.03%	SD 2.31%	Total	9/344 (2.62%)	Mean 2.6%	SD 1.89%	
***Thyroid Gland: Follicular Cell: Carcinoma**									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/45 (0%)		1/50 (2%)	1/49 (2%)	0/45 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	0/345 (0%)	Mean 0%	SD 0%	Total	3/344 (0.87%)	Mean 0.86%	SD 1.08%	
***Thyroid Gland: Follicular Cell: Carcinoma or Adenoma**									
		0/50 (0%)	2/50 (4%)	0/50 (0%)		2/50 (4%)	2/50 (4%)	1/50 (2%)	
		1/50 (2%)	0/50 (0%)	1/45 (2%)		2/50 (4%)	1/49 (2%)	1/45 (2%)	
		3/50 (6%)				3/50 (6%)			
Overall Incidence	Total	7/345 (2.03%)	Mean 2.03%	SD 2.31%	Total	12/344 (3.49%)	Mean 3.47%	SD 1.47%	
***Urinary Bladder: Carcinoma or Papilloma**									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/49 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)				1/50 (2%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female		
***Urinary Bladder:**								
Papilloma								
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/49 (0%)
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		1/50 (2%)				1/50 (2%)		
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%
#Uterus:								
Adenoma								
						0/50 (0%)	0/50 (0%)	0/50 (0%)
						0/50 (0%)	1/50 (2%)	1/50 (2%)
						0/50 (0%)		
Overall Incidence					Total	2/350 (0.57%)	Mean 0.57%	SD 0.98%
#Uterus:								
Carcinoma								
						3/50 (6%)	2/50 (4%)	3/50 (6%)
						1/50 (2%)	1/50 (2%)	1/50 (2%)
						3/50 (6%)		
Overall Incidence					Total	14/350 (4%)	Mean 4%	SD 2%
#Uterus:								
Granular Cell Tumor Benign								
						0/50 (0%)	0/50 (0%)	0/50 (0%)
						0/50 (0%)	1/50 (2%)	1/50 (2%)
						0/50 (0%)		
Overall Incidence					Total	2/350 (0.57%)	Mean 0.57%	SD 0.98%

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male		Female	
#Uterus:					
Hemangiosarcoma					
		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)			
Overall Incidence	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Uterus:					
Leiomyosarcoma					
		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)			
Overall Incidence	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Uterus:					
Malignant Mixed Mullerian Tumor					
		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)			
Overall Incidence	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Uterus:					
Polyp Stromal					
		2/50 (4%)	9/50 (18%)	3/50 (6%)	
		5/50 (10%)	6/50 (12%)	3/50 (6%)	
		2/50 (4%)			
Overall Incidence	Total	30/350 (8.57%)	Mean 8.57%	SD 5.13%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male		Female	
#Uterus:					
Sarcoma Stromal					
		1/50 (2%)	1/50 (2%)	1/50 (2%)	
		2/50 (4%)	1/50 (2%)	0/50 (0%)	
		0/50 (0%)			
Overall Incidence	Total	6/350 (1.71%)	Mean 1.71%	SD 1.38%	
#Uterus:					
Sarcoma Stromal or Polyp Stromal					
		3/50 (6%)	10/50 (20%)	4/50 (8%)	
		6/50 (12%)	7/50 (14%)	3/50 (6%)	
		2/50 (4%)			
Overall Incidence	Total	35/350 (10%)	Mean 10%	SD 5.66%	
#Uterus:					
Schwannoma Malignant					
		0/50 (0%)	1/50 (2%)	1/50 (2%)	
		0/50 (0%)	2/50 (4%)	1/50 (2%)	
		0/50 (0%)			
Overall Incidence	Total	5/350 (1.43%)	Mean 1.43%	SD 1.51%	
#Uterus:					
Squamous Cell Papilloma					
		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)			
Overall Incidence	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female		
#Vagina:								
Fibrosarcoma								
						0/50 (0%)	0/50 (0%)	0/50 (0%)
						0/50 (0%)	1/50 (2%)	0/50 (0%)
						0/50 (0%)		
Overall Incidence					Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%
#Vagina:								
Leiomyoma								
						0/50 (0%)	0/50 (0%)	0/50 (0%)
						0/50 (0%)	0/50 (0%)	0/50 (0%)
						1/50 (2%)		
Overall Incidence					Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%
#Vagina:								
Polyp								
						0/50 (0%)	0/50 (0%)	1/50 (2%)
						0/50 (0%)	0/50 (0%)	0/50 (0%)
						0/50 (0%)		
Overall Incidence					Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%
#Zymbal's Gland:								
Carcinoma								
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		2/50 (4%)	1/50 (2%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		0/50 (0%)				0/50 (0%)		
Overall Incidence	Total	4/349 (1.15%)	Mean 1.14%	SD 1.57%	Total	0/350 (0%)	Mean 0%	SD 0%

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
#Zymbal's Gland:									
Carcinoma or Adenoma									
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		2/50 (4%)	1/50 (2%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	4/349 (1.15%)	Mean 1.14%	SD 1.57%	Total	0/350 (0%)	Mean 0%	SD 0%	

*: Denominetor is number of animals with tissues examined microscopically
#: Denominetor is number of animals necropsied

Glyphosat – Auf Kosten der Menschen

19/07/2017 NPR

Glyphosat: EU-Bewertung hat gravierende Mängel – US-Experte Christopher Portier rügt EU-Behörden: Bei der Risikobewertung von Glyphosat wurde schlampig und fehlerhaft gearbeitet.

Die zur Weltgesundheitsorganisation WHO gehörende Agentur für Krebsforschung IARC hat den Unkrautvernichter Glyphosat im Jahr 2015 als «wahrscheinlich krebserregend» eingestuft. Vor Kurzem hat sich die kalifornische Behörde für Gesundheit und Umwelt dieser Beurteilung angeschlossen. Seit dem 7. Juli 2017 gilt der Unkrautvernichter in Kalifornien als «krebserregende Substanz». Monsanto ficht den Entscheid an.

Die Europäische Behörde für Lebensmittelsicherheit EFSA und das deutsche Bundesinstitut für Risikobewertung (BfR) hingegen stuften Glyphosat 2016 als «ungefährlich» ein. Es gebe keine Hinweise auf eine krebserzeugende oder erbgutschädigende Wirkung durch Glyphosat, so ihre Bewertung. Auch die Europäische Chemikalienagentur (ECHA) gab Mitte März Entwarnung: Glyphosat sei nicht krebserregend, heisst es im Gutachten der ECHA. Gestützt auf die Bewertung der europäischen Behörden will die EU-Kommission Glyphosat für weitere zehn Jahre zulassen. Erfahrungsgemäss wird sich die Schweiz stark an die Massnahmen der EU anlehnen.

Widerspruch gegen die Risikobewertung der EU-Behörden kommt von Christopher Portier, Experte für Chemikaliensicherheit in den USA. Er hat die Krebsrisiken von Glyphosat im Auftrag der IARC untersucht und bewertet. Portier und weitere 93 WissenschaftlerInnen kritisieren die europäischen Zulassungsbehörden scharf: Die EU-Bewertung weise schwere wissenschaftliche Mängel auf1, die «eine ernsthafte Gefährdung der öffentlichen Gesundheit bedeuten können».

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Das Interview mit Christopher Portier ist in der Fachzeitschrift «Oekoskop» 2/17 der Ärztinnen und Ärzte für Umweltschutz erschienen.

«Oekoskop»: Christopher Portier, Sie tragen den Entscheid der IARC mit, Glyphosat sei als «wahrscheinlich krebsfördernd» einzustufen, und kritisieren die gegenteilige Einschätzung durch die EFSA und die ECHA scharf. Weshalb sollten wir der IARC mehr vertrauen als den europäischen Behörden?

Christopher Portier: Es gibt ein paar grundsätzliche Unterschiede, wie die IARC bzw. die EFSA und die ECHA zu ihren Einschätzungen kommen. Die IARC verwendet ausschliesslich öffentlich verfügbare Studiendaten. Denn sie überprüft auch die Rohdaten der Studien, um sicher zu gehen, dass alle Angaben und Zahlen richtig sind. Viele der Studien zu Tierkrebs und Genotoxizität[2] sind jedoch im Besitz der Industrie. Sie sind weder für die IARC noch für sonst jemanden öffentlich einsehbar.

Es scheint, dass die EFSA und die ECHA die Rohdaten nicht überprüfen. Wenn sie nur die Berichte überprüfen, die ihnen die Industrie einreicht, so kann es sein, dass die Behörden wichtige Studienresultate übersehen.

Woraus schliessen Sie, dass die Behörden das nicht tun?

Die EFSA hat in ihrem Bericht zur Glyphosat-Einschätzung acht positive Tumorbefunde in Tierstudien übersehen. Das BfR lieferte die Grundlage für diesen EFSA-Bericht. Die entsprechende Kritik von zahlreichen Wissenschaftlern haben BfR-Mitarbeitende bestätigt. Wäre ich Chef des BfR, würde ich mich unter diesen Umständen sofort fragen: Haben wir noch andere Tumore übersehen? An diesem Punkt liesse ich das gesamte Datenmaterial durch meine Mitarbeitenden nochmals evaluieren und jeden Tumor-Typ auf seine statistische Signifikanz hin neu bewerten. Das ist die einfachste und offensichtlichste Sache, die sie in einer Krebs-Evaluation tun können. Trotzdem hat dies das BfR nicht getan.

Warum überprüfen EFSA und ECHA nicht genauer?
Ich kann nicht für sie sprechen, aber ich kann von meiner Funktion innerhalb einer Regulierungsbehörde berichten. Nicht nur beim BfR, der EFSA und der ECHA sind alle mit Arbeit überlastet. Zudem stehen die Behörden unter Druck, sehr schnell Resultate zu liefern. Denn wird Glyphosat über längere Zeit nicht genehmigt oder verliert Monsanto gar die Zulassung in Europa, entgeht dem Konzern viel Geld. Die Behörden stehen also unter starkem Druck und haben keine Zeit.

Zulassungsprozess muss unabhängig und transparent seinNach Ansicht von Christopher Portier gibt es bei der Zulassung von chemischen Substanzen einiges zu verbessern. Seine Forderungen:

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- Unternehmen sollen ihre Unterlagen elektronisch einreichen, damit die Daten nicht mehr mühsam digitalisiert werden müssen, um sie zu prüfen.
- Die Industrie muss die Rohdaten ihrer Studien öffentlich zugänglich machen, damit alle die gleichen Überprüfungsmöglichkeiten haben. Alle positiven und negativen Befunde sollten aufgelistet werden, damit eine schnelle Reevaluation möglich ist.
- Der Zulassungsprozess muss unabhängig sein. Heute bestimmt die Regierung, wer in der ECHA sitzt und wer den EFSA-Bericht evaluiert. Eine unabhängige Institution sollte Wissenschaftler nominieren, die dafür qualifiziert sind und aus Universitäten und Institutionen stammen, die weder mit der Industrie noch mit Behörden verbandelt sind. Eine hohes Mass an Unabhängigkeit könnte so gewährleistet werden, auch wenn die Regierung am Ende aus den Nominierten auswählt.
- Es braucht strenge Gesetze über mögliche Interessenkonflikte. Die fehlen z B. in der EU weitgehend. Es müsste unter anderem auch definiert sein, was ein Interessenkonflikt ist.

Welche weiteren Unterschiede sehen Sie zwischen IARC und EFSA/ECHA?

Die Regeln, nach welchen sowohl IARC wie auch EFSA und ECHA arbeiten, um die wissenschaftliche Evidenz für Krebs zu evaluieren, sind identisch. Also sollte man meinen, dass auch die Schlüsse, die gezogen werden, identisch sind. Dem ist aber nicht so. Die IARC fand bei der Überprüfung einer epidemiologischen Studie einen plausiblen Zusammenhang zwischen der Glyphosat-Exposition und Non-Hodgkin-Lymphom-Erkrankungen. Deshalb kam die IARC zum Schluss, dass eine limitierte Evidenz für Krebserkrankungen beim Menschen besteht. EFSA und ECHA hingegen wiesen dem Befund eine «sehr limitierte Evidenz» zu. Das ist eine Kategorie, die es offiziell gar nicht gibt. Es ist nicht nachvollziehbar, was sie damit meinen.

Die Gegenseite wirft der IARC genauso vor, sie würde unwissenschaftlich arbeiten: Nicht nur EFSA und ECHA. Auch die US-amerikanische Umweltbehörde EPA und andere Behörden sagen, bei Glyphosat liege die IARC falsch.

Wenn zwei positive Tierstudien vorliegen muss die Evidenz als ausreichend kategorisiert werden. Beim Glyphosat fand die IARC vier Tierstudien mit positivem Krebsbefund. Es gab keinen Grund, sie anzuzweifeln. Die Befunde waren plausibel und statistisch signifikant gegenüber den Kontrollgruppen. Die Behörden hingegen gaben immer wieder andere Gründe an, weshalb die Befunde dennoch nicht taugen würden.

Bundesrat Josef Schneider-Amman schrieb uns kürzlich: «Die Schlussfolgerungen der IARC basieren nicht auf neuen Studien, sondern auf einer anderen Beurteilungsmethode, welche die Exposition, d.h. die Menge und Dosis, der ein Anwender und/oder Konsument ausgesetzt ist, nicht berücksichtigt».[3] Was sagen Sie dazu?

Das ist richtig. Ich kenne das Schweizer Gesetz nicht, aber in der EU ist es sehr klar: Das Dosis-Wirkung-Prinzip wird bei nicht genotoxischen Substanzen angewandt. Ist eine Substanz aber genotoxisch, dann spielt die Dosis der Exposition keine Rolle und die Substanz muss gemäss EU-Recht verboten werden. Deshalb ist die Aussage des Bundesrates zumindest bezüglich EU-Recht für Glyphosat kein statthaftes Argument.

Die meisten Behörden auf der Welt haben festgelegt: Ist eine Substanz genotoxisch und handelt es sich um ein Karzinogen, dann wird sie verboten.

Ist Glyphosat genotoxisch?

Wir wissen es nicht genau: Die Daten von 50 Prozent der Studien sprechen für eine Genotoxizität, 50 Prozent dagegen. Im Interesse der öffentlichen Gesundheit sollten wir Glyphosat deshalb meiner Meinung nach als genotoxisch klassieren.

Die Zulassungsbehörden wurden in den 1970er-Jahren aufgebaut, um einen zweiten «Fall DDT» zu verhindern. Mit Blick auf die Pestizide Glyphosat, Triclosan oder die Neonicotinoide: Wurde dieses Ziel erreicht?

Das ist schwer zu beantworten. Seitdem chemische Substanzen verboten wurden, wissen wir nicht, ob wir damit tatsächlich präventiv Krebsfälle verhindert haben. Aber ganz klar, seit DDT haben wir Fehler gemacht. Viele Substanzen haben wir falsch angegangen; z. B. Blei im Benzin, es dauerte lange, bis es verboten wurde. Es hiess zwar, Blei ist ein Problem, aber nur ein kleines. Dann zeigten Studien, dass das Problem doch grösser sein könnte...

...ist das nicht immer so?

Es ist oft so, dass die Behörden bei einer Substanz einen Grenzwert festlegen, um später festzustellen, dass dieser zu hoch war. Sie senken ihn, um danach erneut zu bemerken, dass er noch immer zu hoch ist. So wiederholte es sich bei zahlreichen Substanzen, etwa bei den Dioxinen, den Dibenzofuranen, den PCBs und auch bei den bromierten Brandschutzchemikalien.

Anders aber scheint es bei den klassischen Pestiziden abzulaufen. Sind sie einmal zugelassen, so verfolgt kaum jemand mehr ihre gesundheitlichen Konsequenzen. Wer geht der Frage nach, ob zugelassene Pestizide Krebs auslösen oder nicht? Beim Glyphosat stammen einige der Studien, die wir überprüft haben, aus dem Jahre 1981. Darin tauchen Tumore auf, obwohl meist nur rund 200 Menschen berücksichtigt wurden. Während 36 Jahren will weltweit keine Zulassungsbehörde diese Tumor-Befunde erkannt haben, obwohl die Literatur nur neun Studien zum Krebsrisiko durch Glyphosat beim Menschen umfasst. Stellen Sie sich vor, schon 1981 hätte jemand dieses Versehen entdeckt und es korrigiert. Das hätte wohl zu einer geringeren Akzeptanz von Glyphosat geführt.

Nehmen wir die grosse US-Umweltbehörde EPA: Warum hat sie diese Tumore nicht erkannt?

Das überraschte mich auch. Die EPA betont, sie würde Pestizide ständig reevaluieren. Dasselbe sagt die EFSA. Offensichtlich tun sie es nicht richtig. Bei richtigem Vorgehen sind diese Tumor-Befunde schwerlich zu übersehen.

Heute stehen wir auch vor dem Problem der neuartigen Neonicotinoide, also Insektiziden, die systemisch in die Pflanzen eindringen. Waren sich die Behörden der neuen Dimension bewusst, als sie diese neue Art von Pestiziden zuliessen?

Früher wurde das sehr giftige Nikotin als Insektizid verwendet. Die Neonicotinoide sind viel weniger giftig, bestanden die Tests und wurden zugelassen. Der Zulassungsprozess war aber nicht speziell an die neuen Substanzen angepasst worden. Inzwischen wissen wir, dass Neonicotinoide ökotoxikologisch ein Problem sind. Ich bin überzeugt, dass die Evidenz gegeben ist, dass sie Bienen töten. Ich denke, sie werden verboten und durch ein neues Produkt ersetzt, welches dann möglicherweise wiederum problematisch ist.

Die Bienen starben schon in den 1940er-Jahren durch DDT und danach bei allen neuen Insektiziden, die auf den Markt kamen. Die Bienenverträglichkeit müsste doch zumindest heute getestet werden...

...das gehört in den USA auch heute nicht zum Zulassungsprozedere.

Warum nicht?

Das ist eine sehr gute Frage, die Sie den Zulassungsbehörden stellen sollten. In den USA werden Insektizide an Schmetterlingen getestet, nicht aber an Bienen, obwohl deren Biologie verschieden ist. Auch bei den Schmetterlingen ist die Beurteilung mehr als fragwürdig: Sterben 20 Prozent auf Grund eines Insektizids, gilt das als okay. Sterben über 20 Prozent, schauen sie genauer hin. Sind es mehr als 50 Prozent, wird die Substanz verboten.

Wie sehen Sie die Zukunft von Glyphosat?

Ich war lange Zeit in Zulassungsbehörden tätig und hatte die Möglichkeit, Substanzen zu verbieten. Darum antworte ich als Wissenschaftler und ehemaliger Funktionär: Die EFSA und die ECHA haben ihren Job nicht gemacht. Die Informationen, die sie den gesetzgebenden Politikern geliefert haben, sind wissenschaftlich nicht haltbar und qualitativ schlecht. Mir geht es nicht vordringlich darum, dass Glyphosat verboten wird. Mir geht es grundsätzlich um die wissenschaftliche Beurteilung des Krebspotenzials von Substanzen. Dafür bestehen Regeln, welche die Behörden streng befolgen müssen. Das ist bei Glyphosat momentan nicht der Fall. Folgen die Politiker der Empfehlung ihrer Behörden, wird beim Glyphosat der öffentliche Gesundheitsschutz scheitern. Deshalb habe ich den EU-Kommissionspräsidenten Jean-Claude Juncker in einem Brief auf die fehlerhaften Grundlagen aufmerksam gemacht, die er von seinen Behörden erhalten hat.

1. Christopher Portier et al.: Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA), J Epidemiol Community Health Month, JECH Online First, published on March 3, 2016 as 10.1136/jech-2015-207005.

2. Chemische Stoffe werden als genotoxisch bezeichnet, wenn sie das genetische Material von Zellen verändern.

3. E-Mail von Bundesrat Schneider-Ammann vom 22.05.2017 als Antwort auf ein Schreiben von Bernadette Scherrer (Genkritisches Forum GenAu) und Dr. med. Peter Kälin (AefU) betreffend «Unzulässige Öko-Fördergelder für Glyphosat».

Quelle: Glyphosat: EU-Bewertung hat gravierende Mängel

Video, Wirtschaft Christopher Portier, EFSA, Glyphosat, IARC, Krebs, WHO

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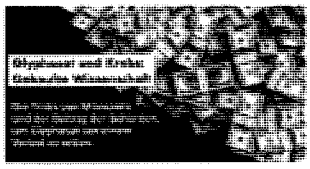

27/03/2017 NPR 0

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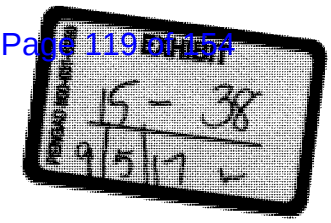

Glyphosate: EU assessment has serious flaws

Martin Forter/Stephanie Fuchs / July 18, 2017 - **US expert Christopher Portier reprimanded the EU authorities: During the risk assessment of glyphosate work had been performed sloppy and flawed.**

Red. * The agency for research on cancer IARC, which belongs to the World Health Organization WHO, has classified the herbicide glyphosate as "probably carcinogenic" in 2015. The California authority for health and environment has recently joint this assessment. Since July 7, 2017 the herbicide is classified as a "carcinogenic substance" in California. Monsanto contests the decision.

On the other hand the European Food Safety Authority EFSA and the German Federal Institute for Risk Assessment (BfR) classified glyphosate as "harmless" in 2016. There is no evidence for a carcinogenic or mutagenic effect of glyphosate, they assessed. The European Chemicals Agency (ECHA) also gave an all-clear in mid-March: According to the expert opinion of ECHA glyphosate is not carcinogenic. Supported by the assessment of the European authorities the EU commission wants to approve glyphosate for another ten years. Experience has shown that Switzerland will strongly follow the measures of the EU.

Objection against the risk assessment of the EU authorities is voiced by Christopher Portier, an expert for chemical security in the US. He has investigated and assessed cancer risks of glyphosate on behalf of the IARC. Portier and other 93 researchers excoriate the European regulatory authority: The assessments of the EU show severe scientific flaws[1], which could mean a "serious danger to public health".

The Interview with Christopher Portier appeared in the professional journal "Oeskop" 2/17 of Ärztinnen und Ärzte für Umweltschutz.

Encountering hostility by the glyphosate lobby

Christopher Portier (PhD) is a mathematician and biostatistician. He was director of the US National Center for Environmental Health, Centers for Disease Control and Prevention, and the US Agency for Toxic Substances and Disease Registry from 2010 - 2013.

Portier has been involved as an external advisor of the assessment of glyphosate at the agency for research on cancer (IARC) of the WHO among others. At that time he worked already for the US environmental fund. To exclude conflicts of interest he was allowed to contribute his expertise but had no voting right. Portier neither wrote assessments nor was he admitted to final assessments. His analysis has, however, contributed to WHO's classification of glyphosate as

* Translators note: Red. Most likely refers to "Redaktion/Redakteur" (English: editorial office/editor)

I, Susanna Weerth, hereby declare that I am fluent in English and German. I hereby certify that I have translated the attached document and, to the best of my knowledge, it is a true, accurate and complete translation of the original text.

Susanna Weerth

SANDRA H. MILLER
NOTARY PUBLIC OF MARYLAND
MY COMMISSION EXPIRES FEBRUARY 17, 202

2/17/21

"probably carcinogenic". After the vote of IARC Portier encountered hostility on the internet and also partially in the media by the glyphosate lobby. To protect the work of researchers from such attacks Portier does no longer perform any function at IARC. Today Portier is, among others, an independent advisor of government authorities for several countries.

"Oekoskop": Christopher Portier, you supported the decision of the IARC that glyphosate is to be classified as "probably carcinogenic" and excoriate the contrary assessment by EFSA and ECHA. Why should we trust IARC more than the European authorities?

Christopher Portier: There are a few fundamental differences how IARC or rather EFSA and ECHA arrive at their assessments. The IARC uses solely publicly available study data. It also reviews the raw data of the studies to make sure that all data and numbers are correct. Many studies regarding animal cancer and genotoxicity[2] are, however, property of the industry. They are neither for IARC nor for anyone else publicly available.

It seems that EFSA and ECHA don't review the raw data. If they only review the reports, which the industry submits, it could be that the authorities miss important study results.

From what do you conclude that the authorities don't do this?

The EFSA has missed in their report of the glyphosate assessment eight positive tumor findings in animal studies. The BfR provided the background for this EFSA report. BfR employees confirmed the appropriate critic of numerous researchers. If I would be the head of BfR I would immediately ask myself under these circumstances: Have we missed still other tumors? At this point I would let my employees re-assess the entire data and newly assess the statistical significance of each tumor type. This is the simplest and most obvious thing you can do at a cancer assessment. Nevertheless the BfR did not do this

Why aren't EFSA and ECHA reviewing more accurately?

I cannot speak for them but I can report about my function at a regulatory authority. Everyone is overburdened with work not only at BfR, EFSA and ECHA. In addition the authorities are more and more under pressure to deliver fast results. If glyphosate is not approved for a longer period or even Monsanto looses its approval in Europe, the corporate group looses a lot of money. Thus the authorities are under severe pressure and don't have time.

The approval process has to be independent and transparent

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From Christopher Portier's point of view there is some room for improvement for approval of chemical substances. His requests:

- Companies should submit their documents electronically so that the data need no longer be tediously digitized to review them.
- The industry has to make the raw data of their studies publicly available that everyone has the same possibilities to review. All positive and negative findings should be listed that a faster re-assessment is possible.
- The approval process has to be independent. Today the government decides, who is sitting in the ECHA and who assesses the EFSA report. An independent institution should nominate researchers, who are qualified and come from universities and institutions, which have neither a relationship with the industry nor the authorities. A high degree of independence could so be guaranteed even if the government chooses the nominees in the end.
- Stronger laws about possible conflicts of interests are needed. They are for instance largely absent in the EU. It should also be defined, among others, what a conflict of interest is.
- **Which other differences do you see between IARC and EFSA/ECHA?**
- The regulations by which the IARC as well as the EFSA and ECHA work to assess the scientific evidence for cancer are identical. Therefore you would think that also the conclusions that are drawn are identical. This is not the case. The IARC has found a probable association between glyphosate exposure and non-Hodkin's disease at a review of an epidemiological study. Thus the IARC came to the conclusion that there is limited evidence for cancer diseases in humans. EFSA and ECHA, however, allotted the finding "very limited evidence". This is a category, which does not exist officially. It is not comprehensible what they mean by this.
- **The opposite site accuses IARC just as well that they would work nonscientific: Not only EFSA and ECHA. Also the US environmental protection agency EPA and other authorities say that IARC is wrong concerning glyphosate.**
- If two positive animal studies are on hand the evidence has to be sufficiently categorized. The IARC found with glyphosate four animal studies with positive cancer findings. There was no reason to question them. The findings were feasible and statistically significant compared to control groups. The authorities, however, stated consistently other reasons why the findings would be

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nonetheless no good.

- **The Swiss Federal Councilor Josef Schneider-Amman wrote to us recently: "The conclusions of IARC are not based on new studies but on another assessment method, which does not consider the exposure, i.e. the amount and doses, which an operator and/or user is exposed."[3] What is your position on this?**

- This is right. I don't know the Swiss law but in the EU it is very clear: The dose-response principle is applied to non-genotoxic substances. However if a substance is genotoxic than the dose of the exposure does not play a role and the substance has to be banned according to EU law. Therefore the statement of the Swiss Federal Councilor is no permissible argument at least with regard to EU law for glyphosate.

- Most authorities in the world have determined: If a substance is genotoxic and if it concerns a carcinogen than it is banned.

- **Is glyphosate genotoxic?**

- We don't know for sure: The data of 50 percent of the studies argue for genotixicity, 50 percent against it. In the interest of public health we should therefore classify glyphosate as genotoxic, in my opinion.

- **The regulatory authorities were established in the 1970s to prevent a second "DDT case". In view of the pesticides glyphosate, triclosan or the neonicotinoids: Has this goal been achieved?**

- This is difficult to answer. Since chemical substances were banned we don't know if we actually prevented cancer cases in a preventive manner with this. But it is quiet clear that we have made mistakes since DDT. We have wrongly approached many substances: for instance lead in gas, it has taken long until it was banned. Although it was said lead is a problem, however, only a small one. Then studies showed that the problem could be bigger after all...

- **... is this not always the case?**

- It often happens that the authorities determine a threshold limit value of a substance to realize later that it was too high. They lower it to notice again thereafter that it is still too high. This repeatedly happened with many substances, for example dioxins, dibenzofurans, PCBs and also with the brominated fire-control chemicals.

- It seems, however, to proceed differently with the classical pesticides. Once they are approved, hardly anybody tracks anymore their health consequences. Who explores the question if approved pesticides trigger cancer or not? Some studies with glyphosate, which we reviewed, dated back to the year 1981. Therein tumors emerged even though only about 200 people were considered in most

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cases. During 36 years no regulatory authority worldwide supposedly identified these tumor findings even though the literature includes only nine studies for cancer risk in humans with glyphosate. Imagine already 1981 someone would have discovered this accidental slip and corrected it. This would have resulted in a lower acceptance of glyphosate

- **Take the big US environmental protection agency EPA: Why didn't it detect these tumors?**
- This also surprises me. The EPA stresses that it would re-assess pesticides constantly. EFSA states the same. Obviously they don't do it right. At the right approach these tumor findings are hard to miss.
- **Today we are also facing the problem of novel neonicotinoids, thus insecticides, which are systematically invading our plants. Where the authorities aware of the new dimensions when they approved this new type of pesticides?**
- In former times the very toxic nicotine was used as an insecticide. The neonicotinoids are a lot less toxic, passed the tests and were approved. The approval process had not been specifically adjusted to the new substances. In the meantime we know that neonicotinoide are ecotoxicologically a problem. I am convinced that the evidence exists that they kill bees. I think they are banned and replaced by a new product, which is probably again problematic after that.
- **Bees died already in the 1940s through DDT and then thereafter by all new insecticides that came on the market. The bee tolerance needed to be tested at least today…**
- …this also does not belong to the approval procedure in the US today.
- **Why not?**
- This is an excellent question you should ask the regulatory authorities. In the US insecticides are tested on butterflies but not on bees even though their biology is different. The assessment with butterflies is also very questionable: If 20 percent die due to an insecticide this is deemed to be okay. If more than 20 percent die they look closer. If these are more than 50 percent the substance is banned.
- **How do you see the future of glyphosate?**
- I worked for a long time at regulatory authorities and had the possibility to ban substances. Therefore I answer as a scientist and former official: The EFSA and ECHA have not done their jobs. The information that they delivered to the legislative politicians is not scientifically tenable and qualitatively poor. My priority is not to ban glyphosate. I am basically concerned about the scientific assessment of cancer-causing potentials of substances. For this regulations, with which the authorities have to strictly comply with, exist. This is currently not the

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case with glyphosate. If the politicians follow the advise of their authorities the public health protection will fail with glyphosate. Therefore I have pointed out in a letter to the president of the European Commission, Jean-Claude Juncker, the faulty principles he had received from his authorities.

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Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis

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Background: A recent review by the International Agency for Research on Cancer (IARC) updated the assessments of the > 100 agents classified as Group 1, carcinogenic to humans (IARC Monographs Volume 100, parts A–F). This exercise was complicated by the absence of a broadly accepted, systematic method for evaluating mechanistic data to support conclusions regarding human hazard from exposure to carcinogens.

Objectives and Methods: IARC therefore convened two workshops in which an international Working Group of experts identified 10 key characteristics, one or more of which are commonly exhibited by established human carcinogens.

Discussion: These characteristics provide the basis for an objective approach to identifying and organizing results from pertinent mechanistic studies. The 10 characteristics are the abilities of an agent to *1*) act as an electrophile either directly or after metabolic activation; *2*) be genotoxic; *3*) alter DNA repair or cause genomic instability; *4*) induce epigenetic alterations; *5*) induce oxidative stress; *6*) induce chronic inflammation; *7*) be immunosuppressive; *8*) modulate receptor-mediated effects; *9*) cause immortalization; and *10*) alter cell proliferation, cell death, or nutrient supply.

Conclusion: We describe the use of the 10 key characteristics to conduct a systematic literature search focused on relevant end points and construct a graphical representation of the identified mechanistic information. Next, we use benzene and polychlorinated biphenyls as examples to illustrate how this approach may work in practice. The approach described is similar in many respects to those currently being implemented by the U.S. EPA's Integrated Risk Information System Program and the U.S. National Toxicology Program.

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Introduction

Recently, the International Agency for Research on Cancer (IARC) completed a review of all its Group 1 human carcinogens and updated information on tumor sites and mechanisms of carcinogenesis (IARC Monograph Volume 100A–F) (http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php). About half of the agents classified in Group 1 had been last reviewed > 25 years ago, before mechanistic studies became prominent in evaluations of carcinogenicity. In addition, more recent studies have demonstrated that many cancer hazards reported in earlier studies were later observed to also cause cancer in other organs or through different exposure scenarios (Cogliano et al. 2011).

In compiling and updating the information for Volume 100A–F, two overarching issues became apparent. First, no broadly accepted systematic method for identifying, organizing, and summarizing mechanistic data for the purpose of decision making in cancer hazard identification was readily available. Second, the agents documented and listed as human carcinogens showed a number of characteristics that are shared among many carcinogenic agents. Many human carcinogens act via multiple mechanisms causing various biological changes in the multistage process of carcinogenesis. Indeed, cancer was once described by reference to causative agents, with multistage development of tumors being characterized through the impact of particular chemicals described as initiators and promoters of cancer. Subsequently, multistage development of cancer was identified with morphological change being correlated with genetic alterations. The more recent description by Hanahan and Weinberg of hallmarks of cancer is predicated not on morphology or the impact of carcinogens, but on changes in gene expression and cell signaling (Hanahan and Weinberg 2011). These hallmarks are the properties of cancer cells and neoplasms, and are not characteristic of the agents that cause cancer. Tumors attributable to chemical carcinogens may be distinct by mutational analysis (Westcott et al. 2015), but all neoplasms exhibit the hallmarks. A recent computational toxicology study has shown that chemicals that alter the targets or pathways among the hallmarks of cancer are likely to be carcinogenic (Kleinstreuer et al. 2013). In addition, a series of reviews

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in *Carcinogenesis* by members of the Halifax Project Task Force used the hallmarks framework to identify the carcinogenic potential of low doses and mixtures of chemicals (Harris 2015).

In 2012, participants at two workshops convened by the IARC in Lyon, France, extensively debated the mechanisms by which agents identified as human carcinogens (Group 1) produce cancer. The participants concluded that these carcinogens frequently exhibit ≥ 1 of 10 key characteristics (Table 1). Herein we describe these 10 key characteristics and discuss their importance in carcinogenesis. These characteristics are properties that human carcinogens commonly show and can encompass many different types of mechanistic end points. They are not mechanisms in and of themselves nor are they adverse outcome pathways.

Further, we describe how the 10 key characteristics can provide a basis for systematically identifying, organizing, and summarizing mechanistic information as part of the carcinogen evaluation process. The U.S. Environmental Protection Agency (EPA) and the National Toxicology Program (NTP) in the United States, as well as the IARC internationally, have recognized a need for such an approach (Rooney et al. 2014). The U.S. National Research Council (NRC) emphasized the need for consistent, transparent, systematic approaches for the identification, evaluation, and integration of data in the U.S. EPA's Integrated Risk Information System (IRIS) assessments of carcinogens and elsewhere in human health hazard assessments (NRC 2014).

Progress in the systematic evaluation of published evidence on the adverse health effects of environmental agents has been made through application of methods developed by evidence-based medicine (Koustas et al. 2014). However, mechanistic study databases present a challenge to systematic reviews in that the studies are typically both numerous and diverse, reporting on a multitude of end points and toxicity pathways. One recent example of a systematic approach searched for studies on end points relevant to nine cancer-related mechanistic categories in identifying and presenting mechanistic evidence on di(2-ethylhexyl) phthalate, a chemical with a complex database of > 3,000 research papers (Kushman et al. 2013). In this publication, the categories of mechanistic evidence were identified from a compendium of published reviews. This approach may be difficult to translate to agents with controversial or limited mechanistic evidence. It also would not permit comparisons across agents, including attempts to understand similarities or differences with human carcinogens. Further, it may be biased against the most recent mechanistic and molecular epidemiology studies that have not been the subject of a prior expert review.

To facilitate a systematic and uniform approach to organizing mechanistic data relevant to carcinogens, we propose use of the 10 key characteristics of human carcinogens as a basis for identifying and categorizing scientific findings relevant to cancer mechanisms when assessing whether an agent is a potential human carcinogen. A significant advantage of this approach is that it would encompass a wide range of end points of known relevance to carcinogenesis as identified through examination of the IARC Monographs on Group 1 carcinogens. Mechanistic topics can be included regardless of whether they have been the subject of prior expert reviews of any particular chemical. This should introduce objectivity that could reduce reliance on expert opinion, as well as facilitate comparisons across agents. Moreover, at its essence, the approach may afford a broad consideration of the mechanistic evidence rather than focusing narrowly on independent mechanistic hypotheses or pathways in isolation.

Herein, we demonstrate the applicability of this proposed systematic strategy for searching and organizing the literature using benzene and polychlorinated biphenyls (PCBs) as examples. The mechanistic study database for both of these chemicals is large, comprising > 1,800 studies for benzene and almost 3,900 for PCBs, many with multiple mechanistic end points. We conducted systematic literature searches for end points pertinent to the 10 key characteristics of human carcinogens, using literature trees to indicate the human and experimental animal studies that reported end points relevant to each characteristic. To further indicate their potential contribution to benzene and PCB carcinogenesis, we organized the characteristics into a graphical network representative of an overall mechanistic pathway.

Several recent IARC Monographs (e.g., Guyton et al. 2015; Loomis et al. 2015) have applied the 10 key characteristics described here for a variety of agents and organized the literature search results into flow diagrams. Overall, this categorization facilitated objective consideration of the relevant mechanistic information, thereby advancing analyses of hypothesized mechanisms and toxicity pathways. Because mechanistic data may provide evidence of carcinogenicity, and can play a role in up- or downgrading an evaluation based on cancer findings in animals, we suggest that this systematic approach to organizing the available data will assist future IARC Working Groups and other agencies in evaluating agents as potential human carcinogens, especially in the absence of convincing epidemiological data on cancer in humans.

Description of the Key Characteristics of Carcinogens

The number of ways by which agents contribute to carcinogenesis can be extensive if all biochemical or molecular end points are considered. However, these mechanisms can be grouped into a limited number of categories (e.g., genotoxicity, immunosuppression). Guyton et al. (2009) described 15 types of "key events" associated with human carcinogens that collectively represented many carcinogenic mechanisms. The experts present at the first of the IARC meetings in 2012 originally identified 24 mechanistic end points with several subcategories in each. This number of end points was considered too impractical as a guide for categorizing the literature, and the Working Group merged

Table 1. Key characteristics of carcinogens.

Characteristic	Examples of relevant evidence
1. Is electrophilic or can be metabolically activated	Parent compound or metabolite with an electrophilic structure (e.g., epoxide, quinone), formation of DNA and protein adducts
2. Is genotoxic	DNA damage (DNA strand breaks, DNA–protein cross-links, unscheduled DNA synthesis), intercalation, gene mutations, cytogenetic changes (e.g., chromosome aberrations, micronuclei)
3. Alters DNA repair or causes genomic instability	Alterations of DNA replication or repair (e.g., topoisomerase II, base-excision or double-strand break repair)
4. Induces epigenetic alterations	DNA methylation, histone modification, microRNA expression
5. Induces oxidative stress	Oxygen radicals, oxidative stress, oxidative damage to macromolecules (e.g., DNA, lipids)
6. Induces chronic inflammation	Elevated white blood cells, myeloperoxidase activity, altered cytokine and/or chemokine production
7. Is immunosuppressive	Decreased immunosurveillance, immune system dysfunction
8. Modulates receptor-mediated effects	Receptor in/activation (e.g., ER, PPAR, AhR) or modulation of endogenous ligands (including hormones)
9. Causes immortalization	Inhibition of senescence, cell transformation
10. Alters cell proliferation, cell death or nutrient supply	Increased proliferation, decreased apoptosis, changes in growth factors, energetics and signaling pathways related to cellular replication or cell cycle control, angiogenesis

Abbreviations: AhR, aryl hydrocarbon receptor; ER, estrogen receptor; PPAR, peroxisome proliferator–activated receptor. Any of the 10 characteristics in this table could interact with any other (e.g., oxidative stress, DNA damage, and chronic inflammation), which when combined provides stronger evidence for a cancer mechanism than would oxidative stress alone.

these categories into 10 at the second meeting in 2012, concluding that human carcinogens commonly show ≥ 1 of the 10 key characteristic properties listed in Table 1. These represent the majority of established properties of human carcinogens as described below.

Characteristic 1: Is Electrophilic or Can Be Metabolically Activated to Electrophiles

Electrophiles are electron-seeking molecules that commonly form addition products, commonly referred to as adducts, with cellular macromolecules including DNA, RNA, lipids, and proteins. Some chemical carcinogens are direct-acting electrophiles, whereas others require chemical conversion within the body (Salnikow and Zhitkovich 2008) or biotransformation by enzymes in a process termed metabolic activation (Miller 1970). Examples of direct-acting electrophilic carcinogens include sulfur mustards and ethylene oxide (Batal et al. 2014; Grosse et al. 2007; IARC 2008; Rusyn et al. 2005). The classic examples of chemical agents that require metabolic activation to become carcinogenic include polycyclic aromatic hydrocarbons, aromatic amines, *N*-nitrosamines, aflatoxins, and benzene, which by themselves are relatively inert (Slaga et al. 1980; Smith 1996). A number of enzymes, including cytochrome P450s, flavin monooxygenase, prostaglandin synthase, and various peroxidases, can biotransform relatively inert chemical compounds to potent toxic and carcinogenic metabolites or reactive intermediates (Hecht 2012; O'Brien 2000). The ability to form adducts on nucleic acids and proteins is a common property of these inherently electrophilic and/or metabolically activated human carcinogens (Ehrenberg 1984).

Characteristic 2: Is Genotoxic

The term "genotoxic" (Ehrenberg et al. 1973) refers to an agent that induces DNA damage, mutation, or both. DNA damage can be spontaneous in origin through errors of nucleic acid metabolism or can be induced by endogenous or exogenous agents. In some cases the exogenous agents may also be generated endogenously, such as formaldehyde and acetaldehyde, producing a background level of DNA damage. Examples of DNA damage include DNA adducts (a molecule bound covalently to DNA), DNA strand breaks (breaks in the phosphodiester bonds), DNA crosslinks, and DNA alkylation. DNA damage by itself is not a mutation and generally does not alter the linear sequence of nucleotides (or bases) in the DNA, whereas a mutation is a change in the DNA sequence and usually arises as the cell attempts to repair the DNA damage (Shaughnessy and DeMarini 2009).

Mutations can be classified into three groups based on their location or involvement in the genome. Gene or point mutations are changes in nucleotide sequence within a gene (e.g., base substitutions, frameshifts, and small deletions/duplications). Chromosomal mutations are changes in nucleotide sequence that extend over multiple genes (e.g., chromosome aberrations, translocations, large deletions, duplications, insertions, inversions, or micronuclei due to chromosome breakage). Genomic mutations involve the duplication or deletion of nucleotide sequences of an entire chromosome, an example of which is aneuploidy or formation of micronuclei that contain a centromere. A large proportion of Group 1 carcinogens are genotoxic, as documented in IARC Monographs Volume 100 A–F.

Characteristic 3: Alters DNA Repair or Causes Genomic Instability

Normal cells avoid deleterious mutations by replicating their genomes with high accuracy. However, the fidelity of DNA replication can vary widely depending on the DNA polymerase involved, introducing the possibility of error. Indeed, most spontaneous mutations are caused by polymerase error (Preston et al. 2010). The nature of the error, the flanking sequence, the presence of DNA damage, and the ability to correct errors all affect the outcome of this process (Arana and Kunkel 2010). As a consequence, defects in processes that determine DNA-replication fidelity can confer strong mutator phenotypes that result in genomic instability. Thus, carcinogens may act not only by producing DNA damage directly, but also by altering the processes that control normal DNA replication or repair of DNA damage. Examples include the inhibition of DNA repair by cadmium (Candéias et al. 2010) and formaldehyde (Luch et al. 2014).

Genomic instabiliry is a well-recognized feature of many cancers (Bielas et al. 2006) and is considered to be one of the enabling characteristics of cancer (Hanahan and Weinberg 2011). Cells exposed to ionizing radiation have genetic instability that is a relatively late-occurring event that appears several cell generations after irradiation and results in a reduced ability to replicate the genotype faithfully (Kadhim et al. 2013). The events indicating genomic instability include chromosome aberrations, gene mutations, microsatellite instability, and apoptosis. These events are observed after exposure to arsenic (Bhattacharjee et al. 2013) and cadmium (Filipic 2012).

Characteristic 4: Induces Epigenetic Alterations

The term "epigenetic" refers to stable changes in gene expression and chromatin organization that are not caused by changes in the DNA sequence itself and can be inherited over cell divisions (Herceg et al. 2013). Epigenetic phenomena, including changes to the DNA methylome and chromatin compaction states, along with histone modification can impact the carcinogenic process by affecting gene expression and DNA repair dynamics (Herceg et al. 2013). A wide range of carcinogens have been shown to deregulate the epigenome, and it has been suggested that their mechanism may involve disruption of epigenetic mechanisms (Pogribny and Rusyn 2013). However, evidence for a causal role of epigenetic changes in cancer caused by Group 1 agents was considered to be limited in Volume 100, and the impact of many agents on the epigenome was considered to be a secondary mechanism of carcinogenesis (Herceg et al. 2013). Herceg et al. (2013) have described a wealth of studies demonstrating the impact of carcinogens on epigenetic mechanisms. Most carcinogens (even those reviewed for Volume 100) were evaluated by IARC Working Groups before new data on their epigenetic effects became available (Chappell et al. 2016). This evolving area will generate new mechanistic data in the years to come.

Characteristic 5: Induces Oxidative Stress

Many carcinogens are capable of influencing redox balance within target cells. If an imbalance occurs, favoring formation of reactive oxygen and/or nitrogen species at the expense of their detoxification, this is referred to as oxidative stress. Reactive oxygen species and other free radicals arising from tissue inflammation, xenobiotic metabolism, interruption of mitochondrial oxidative phosphorylation (Figueira et al. 2013), or reduced turnover of oxidized cellular components may play key roles in many of the processes necessary for the conversion of normal cells to cancer cells. However, oxidative stress is not unique to cancer induction and is associated with a number of chronic diseases and pathological conditions—for example, cardiovascular disease (Kayama et al. 2015), neurodegenerative disease (Chen et al. 2016), and chronic inflammation (Suman et al. 2015). Oxidative stress is also a common occurrence in neoplastic tissue and can be part of the tumor environment (Suman et al. 2015).

Oxidative damage is considered a major factor in the generation of mutations in DNA, and > 100 different types of oxidative DNA damage have been identified (Klaunig et al. 2011). At least 24 base modifications are produced by reactive oxygen species, as well as DNA–protein crosslinks and other lesions (Berquist and Wilson 2012), all potentially leading to genomic instability. Oxidative damage to DNA can lead to point mutations, deletions, insertions, or

chromosomal translocations, which may cause oncogene activation and tumor suppressor gene inactivation, and potentially initiate or promote carcinogenesis (Berquist and Wilson 2012; Klaunig et al. 2011). Thus, the induction of oxygen radical–induced cellular injury is a characteristic of a set of diverse carcinogens, including radiation, asbestos, and carcinogenic infectious agents.

Characteristic 6: Induces Chronic Inflammation

Chronic inflammation from persistent infections, such as that caused by *Helicobacter pylori*, as well as that produced by chemical agents including silica or asbestos fibers, has been associated with several forms of cancer (Grivennikov et al. 2010). Indeed, inflammation has been hypothesized to contribute to multiple aspects of cancer development and progression (Trinchieri 2012) and is an enabling hallmark of cancer (Hanahan and Weinberg 2011). Inflammation acts by both intrinsic and extrinsic pathways. Persistent infection and chronic inflammation disrupt local tissue homeostasis and alter cell signaling, leading to the recruitment and activation of inflammatory cells. These constitute extrinsic pathways linking inflammation to cancer (Multhoff and Radons 2012). On the other hand, intrinsic pathways driven by activation of proto-oncogenes in pre-neoplastic and neoplastic cells recruit host-derived inflammatory cells that accelerate tumor promotion and progression (Grivennikov et al. 2010). Because strong links exist between inflammation and the induction of oxidative stress and genomic instability, it may be difficult to separate out the importance of each of these mechanisms.

Characteristic 7: Is Immunosuppressive

Immunosuppression is a reduction in the capacity of the immune system to respond effectively to foreign antigens, including antigens on tumor cells. Persistent immunosuppression presents a risk of cancer, especially excess risk for lymphoma. For example, immunosuppression poses a significant risk when it is accompanied by continuing exposure to foreign antigens, such as in people with organ transplants, or when it occurs in individuals who are latently infected with a carcinogenic virus (Hartge and Smith 2007; Smith et al. 2004). Immune suppression differs from other mechanisms of carcinogenesis in that agents that cause immunosuppression may not directly transform normal cells into potential tumor cells. Potentially neoplastic cells that arise naturally, or that have been transformed by other carcinogens acting by a mechanism such as genotoxicity or by the various mechanisms of action associated with carcinogenic viruses, escape immune surveillance in immunosuppressed individuals. As a result, survival of these cells and their replication to form tumors is greatly facilitated by immune suppression. Several carcinogens act entirely or largely by immunosuppression, often in concert with other Group 1 agents, especially oncogenic infectious agents. The Group 1 agents that act by immunosuppression include human immunodeficiency virus (HIV-1) and the immunosuppressive drug cyclosporin (Rafferty et al. 2012).

Characteristic 8: Modulates Receptor-Mediated Effects

Numerous carcinogens act as ligands to receptor proteins, including menopausal hormone therapy, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and PCBs (Wallace and Redinbo 2013). Receptor-mediated activation broadly falls into two categories: *a*) intracellular activation, mediated by nuclear receptors that translocate into the nucleus and act on DNA as transcription factors (Aranda and Pascual 2001); and *b*) activation of cell surface receptors that induce signal-transduction pathways resulting in biological responses that involve a variety of protein kinases (Griner and Kazanietz 2007). Most exogenous agents act as agonists by competing for binding with an endogenous ligand; however, there are also receptors for which few or no endogenous ligands have been identified, such as the aryl hydrocarbon (Ah) receptor (Baek and Kim 2014; Ma 2011). Receptor-mediated activation most often results in changes in gene transcription. Molecular pathways that are regulated through ligand-receptor interaction and are most relevant to carcinogenesis include cell proliferation (e.g., stimulation of the normal proliferative pathways, as is the case for estrogen-dependent tissues and hormone therapy), xenobiotic metabolism, apoptosis, as well as modulation of the bioavailability of endogenous ligands by affecting biosynthesis, bioactivation, and degradation (Rushmore and Kong 2002).

Characteristic 9: Causes Immortalization

Several human DNA and RNA viruses, including various human papillomaviruses, Epstein-Barr virus, Kaposi sarcoma–associated herpes virus, hepatitis B virus, hepatitis C virus, HIV, Merkel cell polyomavirus (MCPyV), and human T-lymphotropic virus type 1 (HTLV-1) are carcinogenic to humans (Bouvard et al. 2009). These viruses have evolved multiple molecular mechanisms to disrupt specific cellular pathways to facilitate aberrant replication. Although oncogenic viruses belong to different families, their strategies in human cancer development show many similarities and involve viral-encoded oncoproteins targeting the key cellular proteins that regulate cell growth (Saha et al. 2010). Recent studies show that virus and host interactions also occur at the epigenetic level (Allday 2013). The result of these viral effects is to immortalize the target tissue cells such that they are not subject to the Hayflick limit, the point at which cells can no longer divide due to DNA damage or shortened telomeres (Klingelhutz 1999). For example, the human papilloma virus type 16 (HPV-16) *E6* and *E7* oncogenes are selectively retained and expressed in cervical carcinomas, and expression of *E6* and *E7* is sufficient to immortalize human cervical epithelial cells (Yugawa and Kiyono 2009).

Characteristic 10: Alters Cell Proliferation, Cell Death, or Nutrient Supply

There are at least three scenarios related to carcinogenesis in which alterations in cellular replication and/or cell-cycle control have been described. One invokes the predisposition for unrepaired DNA damage leading to cancer-causing mutations in replicating cells; another has attempted to identify sustained replication as a key mechanistic event; and a third describes the ability of a transformed cell to escape normal cell-cycle control and to continue replication. A component common to all three scenarios is the evasion of apoptosis or other terminal programming, including autophagy, in at least a proportion of the cell population (Ryter et al. 2014).

Necrotic cell death releases pro-inflammatory signals into the surrounding tissue microenvironment, recruiting inflammatory immune cells to the site of trauma, which can enhance cancer-cell proliferation and promote cancer metastasis (Coussens and Pollard 2011; Coussens et al. 2013; Pollard 2008). In contrast, various forms of apoptosis and autophagy (Galluzzi et al. 2015) have the opposite effect by removing potentially cancerous cells from a population before they acquire the changes permitting malignancy. Many agents affect necrosis, apoptosis, and/or autophagy and can have profoundly divergent effects on cancer induction in different tissues.

In addition to cell death caused directly by agent toxicity, cells may die within a tumor as a result of an impaired nutrient supply. Neoplastic cell numbers can increase exponentially, quickly outstripping the supply capabilities of the existing tissue vasculature. Neoangiogenesis, in which new blood vessels grow into a tumor, is key to providing this supply of nutrients. Thus, agents that promote or inhibit angiogenesis will promote or delay tumor growth (Hu et al. 2015).

Cancer cells also usually show quite different cellular energetics, relying on glycolysis for energy even under aerobic conditions (Rajendran et al. 2004). Although a likely

consequence of mutation and altered gene expression rather than a cancer-inducing mechanism, any modification of cellular energetics may reflect an important cancer-relevant switch in the cell's or tissue's metabolic state.

Using the Key Characteristics to Systematically Identify, Organize, and Summarize Mechanistic Information

Step 1: Identifying the Relevant Information

The starting point for systematic evaluation is to conduct comprehensive searches of the peer-reviewed literature aimed at identifying mechanistic data (Kushman et al. 2013). The searches can be constructed to address a series of study questions in the PECO (population, exposure, comparator, and outcomes) framework (Higgins and Green 2011) wherein end points associated with the key characteristics are identified. Specifically, the question to be answered by the searches is "Does exposure to the agent induce end points associated with one or more specific key characteristic properties of carcinogens?" The population (humans and any relevant experimental systems), exposure (the agent and relevant metabolites), and comparator (the unexposed comparison group or condition) should be sufficiently broad to identify a range of available mechanistic data informative of the overall evaluation of carcinogenic hazard. This approach thus entails comprehensive, targeted literature searches using appropriate medical search heading (MeSH) terms and key words to identify evidence on the 10 key characteristics for the agent(s) or exposure(s) under evaluation.

Additional complementary literature searches may incorporate terms for the agent and its metabolites, alone or in combination with broad terms for carcinogenicity or related effects. For instance, because U.S. EPA IRIS toxicological reviews also encompass a range of non-cancer toxicities, "top-down" broad literature searches aimed at comprehensively identifying studies on all potential toxic effects of an agent are employed (NRC 2014; U.S. EPA 2014). These comprehensive searches of peer-reviewed literature are supplemented by examining past IARC Monographs or other authoritative reviews, databases (e.g., PubChem), and peer-reviewed government reports can also be systematically searched. The search terms used and literature retrieved

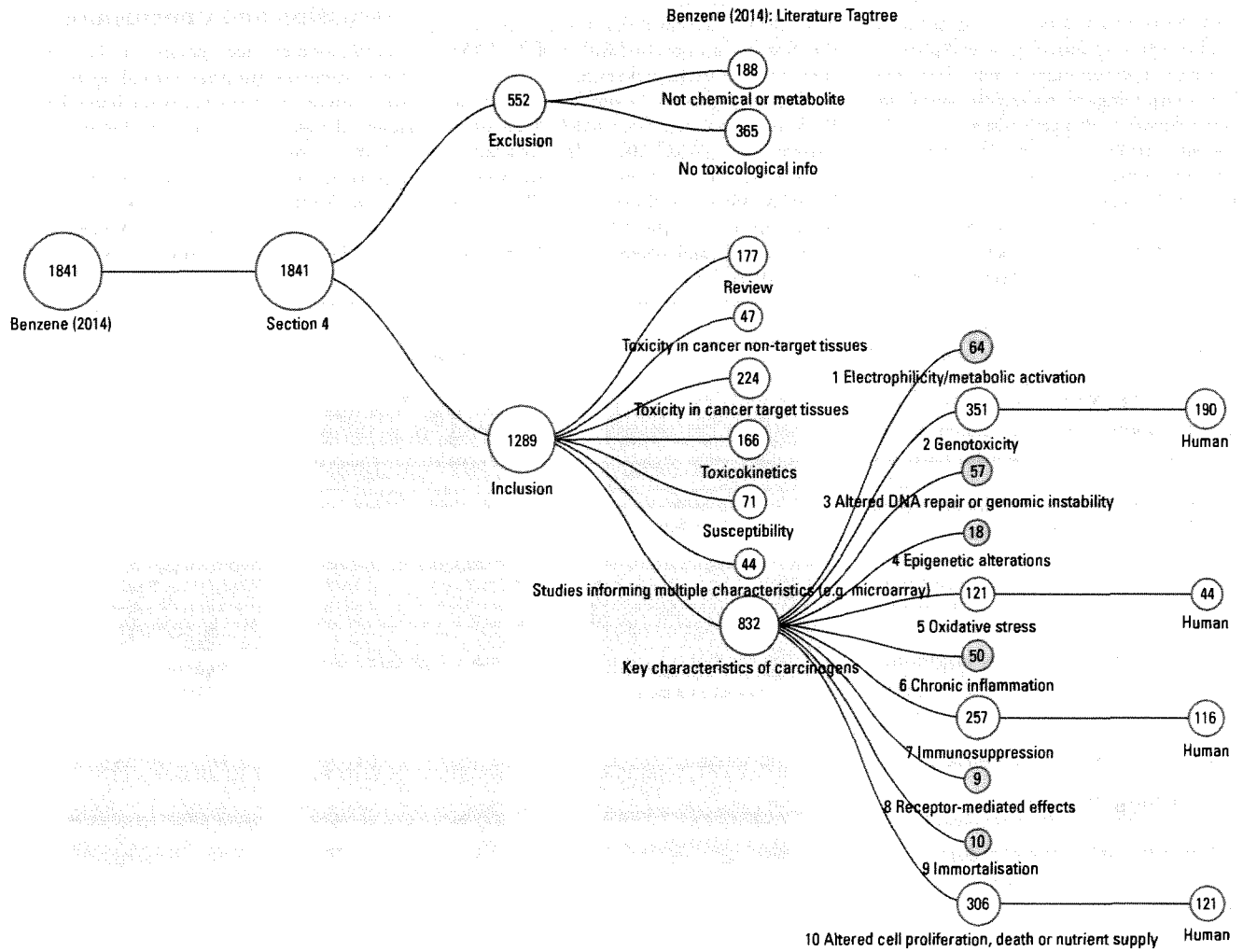

Figure 1. Literature flow diagram, illustrating the systematic identification and categorization process for benzene mechanistic studies. Using appropriate MeSH terms and key words, targeted literature searches were conducted for the 10 key characteristics using online tools available from the HAWC Project (https://hawcproject.org/). Section 4 refers to the location of the discussion of mechanistic data within the IARC Monograph structure (http://monographs.iarc.fr/ENG/Preamble/currentb4studiesother0706.php). All inclusion categories were expanded to document the number of studies attributed to each, down to the individual key characteristic level, which were expanded to illustrate human information when > 100 total studies were identified. Less frequently encountered key characteristic categories (blue-shaded circles) were left unexpanded for clarity. "Human" refers to both humans exposed *in vivo* and human cells exposed *in vitro*.

can be documented (e.g., using MyNCBI, which saves searches of the National Center for Biotechnology database, or https://hawcproject.org/).

Step 2: Screening and Organizing the Results

Based on title and abstract review, studies identified initially are excluded if no data on the chemical or a metabolite are reported, or if no data on toxicological or other cancer-related effects of the chemical are provided. For example, a study on levels of a chemical, but not effects of the chemical, would be excluded. Included studies are then organized by the population (human or experimental systems) and by the end points associated with the 10 key characteristics (Table 1). Studies relevant to toxicokinetics (covering absorption, distribution, metabolism, and excretion) are also identified. Additionally, authoritative, comprehensive review articles are identified, as are studies reporting toxicological end points in cancer target and non-target tissues. These may include morphological evaluations pertaining to the dysfunction of organs, tissues, and cells. Importantly, studies reporting end points that are relevant to multiple characteristics may fall under several categories.

To illustrate these two steps, targeted literature searches were conducted to identify end points for the effects of benzene pertinent to the 10 key characteristics, in populations comprising humans or experimental systems. The literature searches were conducted using the Health Assessment Workplace Collaborative (HAWC) Literature Search tool (https://hawcproject.org/), documenting the search terms, sources, and articles retrieved. Following title and abstract review, studies were excluded if they were not about benzene or its metabolites, or if they reported no data on toxicological end points. Included studies were further sorted into categories representing the 10 key characteristics based on the mechanistic end points and species evaluated (i.e., human *in vivo*, human *in vitro*, mammalian *in vivo*, mammalian *in vitro*, nonmammalian; Figure 1). The figure also identifies reviews, gene expression studies, and articles relevant to toxicokinetics, toxicity, or susceptibility.

Step 3: Using the Key Characteristics to Synthesize Mechanistic Information and to Develop Adverse-Outcome Networks

It is increasingly evident that multiple biological alterations or sets of different perturbations are necessary to convert a normal cell to a transformed cell and ultimately a tumor (Hanahan and Weinberg 2011). Carcinogens appear to affect this complex process in various ways and can act through multiple mechanisms to induce cancer and other adverse health outcomes (Goodson et al. 2015; Guyton et al. 2009). Using the 10 key characteristics as a basis, the collected information can be organized to form hypotheses and evaluate the evidentiary support for mechanistic events as a function of relevant aspects (e.g., dose, species, temporality) (Guyton et al. 2009). The diverse and complex mechanistic end points elicited by benzene can then be organized into an overview inclusive of multiple alterations and any linkages thereof (Figure 2). The resulting overview can provide guidance for further assessments of the literature, including dose relevance, species relevance, and temporality of events. This additional detailed information can then be used to produce proposed mechanisms or adverse outcome pathway networks as described by McHale et al. (2012) and the EPA's NexGen Risk Assessment Report (U.S. EPA 2014). We note that there is evidence that benzene is associated with 8 of the 10 key characteristics we have described.

Figure 3 presents a similar overview for PCBs based on data from IARC Monograph Volume 107 (IARC 2015). In summarizing the mechanistic evidence, this Monograph Working Group indicated that PCBs may induce up to 7 of the 10 key characteristics in producing carcinogenicity (Lauby-Secretan et al. 2013). The less chlorinated PCBs are associated with key characteristics similar to benzene (metabolic activation, DNA damage, cellular proliferation), whereas the dioxin-like PCBs are associated primarily with receptor-mediated activities.

Recently, using this same approach, the Working Groups of IARC Monograph Volume 112 and Volume 113 (in progress) concluded that strong mechanistic evidence exists for five key characteristics being involved in malathion carcinogenicity (i.e., genotoxicity, oxidative stress, inflammation, receptor-mediated effects, and cell proliferation or death), three in DDT carcinogenicity (i.e., immunosuppression, receptor-mediated effects and oxidative stress), and two each for diazinon and glyphosate (i.e., genotoxicity and oxidative stress), providing evidence to support their classification as probable human carcinogens in Group 2A (Guyton et al. 2015; Loomis et al. 2015).

Discussion and Conclusions

Identification and incorporation of important, novel scientific findings providing insights into cancer mechanisms is an increasingly essential aspect of carcinogen hazard identification and risk assessment. Systematic approaches are needed to organize the available mechanistic data relevant to the overall evaluation of the carcinogenic hazard of an agent. Information to support the identification of 10 key characteristics of human carcinogens was obtained during the Volume

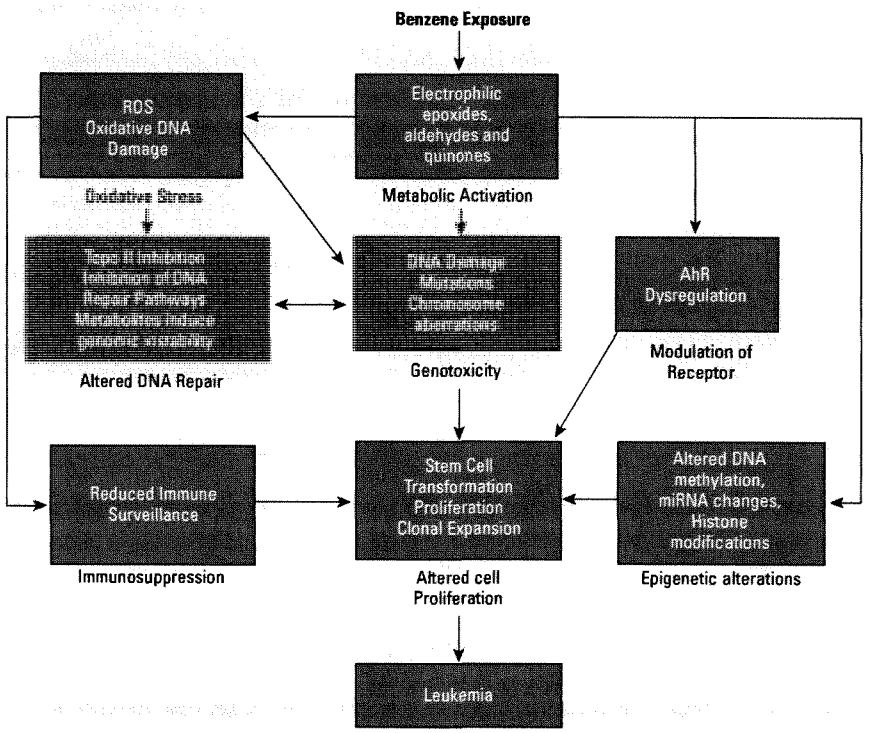

Figure 2. An overview of how benzene induces eight of the key characteristics in a probable mechanism of carcinogenicity. A full review of these mechanistic data is given by McHale et al. (2012), from which this figure was adapted.

100 Monographs and two subsequent expert workshops. These characteristics, although not necessarily representing mechanisms themselves, provide the rationale for an objective approach to identifying and organizing relevant mechanistic data. Using literature collected previously by others as well as by us, we have categorized the literature data according to the 10 characteristics for benzene and PCBs. This approach identified pertinent positive literature for 8 of the 10 key characteristics on benzene and 7 for PCBs, thereby providing a practical, objective method for organizing the large mechanistic literature associated with these chemicals.

This approach also lays the groundwork for a structured evaluation of the strength of the mechanistic evidence base, and therefore its utility in supporting hazard classifications. In the IARC Monographs the strength of the evidence that any carcinogenic effect observed is attributable to a particular mechanism is evaluated using the terms "weak," "moderate," or "strong" (http://monographs.iarc.fr/ENG/Preamble/index.php). In general, the strongest indications that a particular mechanism operates in humans derive from data obtained in exposed humans or in human cells *in vitro*. Data from experimental animals can support a mechanism by findings of consistent results and from studies that challenge the hypothesized mechanism experimentally. Other considerations include whether multiple mechanisms might contribute to tumor development, whether different mechanisms might operate in different dose ranges, whether separate mechanisms might operate in humans and experimental animals, and whether a unique mechanism might operate in a susceptible group. The possible contribution of alternative mechanisms must be considered before concluding that tumors observed in experimental animals are not relevant to humans. An uneven level of experimental support for different mechanisms may reflect that disproportionate resources have been focused on investigating a favored mechanism. All of these factors make assignment of descriptors such as "strong" to the mechanistic evidence challenging; but recent experience with two IARC Monograph meetings suggest that the weighing of the evidence on the basis of the 10 key characteristics focuses the group discussion on the available science and allows rapid consensus to be reached regardless of the strength of the evidence base (Guyton et al. 2015; Loomis et al. 2015).

Because the literature search and categorization approach described herein is comprehensive, it may aid consideration of the overall strength of the mechanistic database according to these principles. In particular, it is inclusive of diverse mechanistic evidence, enabling support for divergent or related mechanisms from human and experimental systems to be identified. Moreover, the literature support for end points relevant to specific mechanisms can be evaluated in an integrated manner when the mechanism is complex. Additionally, comparisons across agents will be facilitated, including evaluation of any similarities or differences in the pattern of key characteristics with agents that are currently classified.

As this approach is carried forward, we hope it will facilitate the objective identification of mechanistic data for consideration in the context of epidemiology, animal bioassay, or other types of evidence (e.g., studies in model organisms or *in vitro* assays) when classifying agents with regard to carcinogenic hazard. Equally important is to consider whether key characteristics of carcinogens are apparent upon exposures that are relevant to human health (Thomas et al. 2013). Overall, these developments will aid advancement of future evaluations of newly introduced agents, including those for which mechanistic data provide the primary evidence of carcinogenicity.

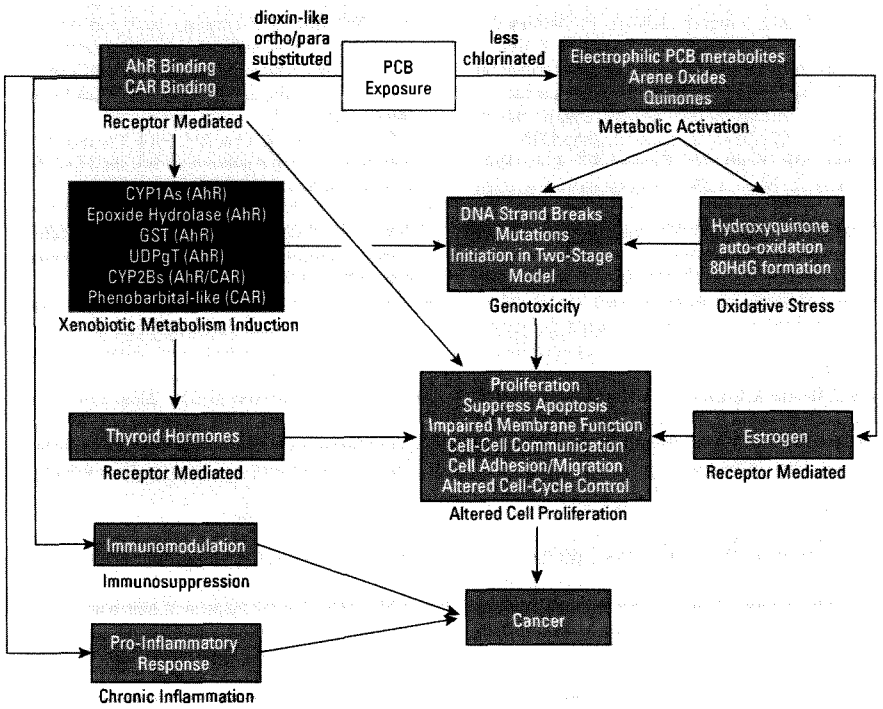

Figure 3. An overview of how polychlorinated biphenyls (PCBs) may induce seven key characteristics in their carcinogenicity (Lauby-Secretan et al. 2013). Highly chlorinated PCBs act as ligands for the aryl hydrocarbon receptor (AhR) and other receptors activating a large number of genes in a tissue- and cell-specific manner that can lead to cell proliferation, apoptosis, and other effects that influence cancer risk. Less chlorinated PCBs can be activated to electrophilic metabolites, such as arene oxides and quinones, which can cause genotoxic effects and induce oxidative stress. Receptor binding to CAR (constitutive androstane receptor) and AhR (a key characteristic) leads to xenobiotic metabolism induction (not a key characteristic; brown box) that in turn leads to genotoxicity and other key characteristics.

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Biomonitoring of Genotoxic Risk in Agricultural Workers from Five Colombian Regions: Association to Occupational Exposure to Glyphosate

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In order to assess possible human effects associated with glyphosate formulations used in the Colombian aerial spray program for control of illicit crops, a cytogenetic biomonitoring study was carried out in subjects from five Colombian regions, characterized by different exposure to glyphosate and other pesticides. Women of reproductive age (137 persons 15–49 yr old) and their spouses (137 persons) were interviewed to obtain data on current health status, history, lifestyle, including past and current occupational exposure to pesticides, and factors including those known to be associated with increased frequency of micronuclei (MN). In regions where glyphosate was being sprayed, blood samples were taken prior to spraying (indicative of baseline exposure), 5 d after spraying, and 4 mo after spraying. Lymphocytes were cultured and a cytokinesis-block micronucleus cytome assay was applied to evaluate chromosomal damage and cytotoxicity. Compared with Santa Marta, where organic coffee is grown without pesticides, the baseline frequency of binucleated cells with micronuclei (BNMN) was significantly greater in subjects from the other four regions. The highest frequency of BNMN was in Boyacá, where no aerial eradication spraying of glyphosate was conducted, and in Valle del Cauca, where glyphosate was used for maturation of sugar cane. Region, gender, and older age (≥35 yr) were the only variables associated with the frequency of BNMN measured before spraying. A significant increase in frequency of BNMN between first and second sampling was observed in Nariño, Putumayo, and Valle immediately (<5 d) after spraying. In the post-spray sample, those who reported direct contact with the eradication spray showed a higher quantitative frequency of BNMN compared to those without glyphosate exposure. The increase in frequency of BNMN observed immediately after the glyphosate spraying was not consistent with the rates of application used in the regions and there was no association between self-reported direct contact with eradication sprays and frequency of BNMN. Four months after spraying, a statistically significant decrease in the mean frequency of BNMN compared with the second sampling was observed in Nariño, but not in Putumayo and Valle del Cauca. Overall, data suggest that genotoxic damage associated with glyphosate spraying for control of illicit crops as evidenced by MN test is small and appears to be transient. Evidence indicates that the genotoxic risk potentially associated with exposure to glyphosate in the areas where the herbicide is applied for coca and poppy eradication is low.

Glyphosate (*N*-phosphonomethyl glycine), a nonselective herbicide, is the active ingredient of a number of herbicide formulations and one of the most widely used pesticides on a global basis (Baylis, 2000; Woodburn, 2000; Duke & Powles, 2008). It is a postemergence herbicide, effective for the control of annual, biennial, and perennial species of grasses, sedges, and broadleaf weeds. The relatively high water solubility and the ionic nature of glyphosate retard penetration through plant hydrophobic cuticular waxes. For this reason, glyphosate is commonly formulated with surfactants that decrease the surface tension of the solution and increase penetration into the tissues of plants (World Health Organization International Program on Chemical Safety, 1994; Giesy et al., 2000).

A large number of glyphosate-based formulations are registered in more than 100 countries and are available under different brand names. One of the most commonly applied glyphosate-based products is Roundup, containing glyphosate as the active ingredient (AI) and polyethoxylated tallowamine

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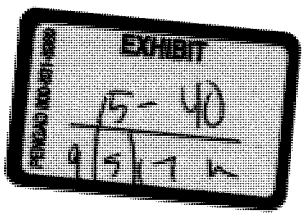

(POEA) as a surfactant. Glyphosate and its formulations have been extensively investigated for potential adverse effects in humans (Williams et al., 2000). This pesticide was reported to exert a low acute toxicity to different animal species. Experimental evidence showed that glyphosate did not bioaccumulate in any animal tissues (Williams et al., 2000). Chronic feeding studies in rodents did not find evidence of carcinogenic activity or any other relevant chronic effects (U.S. EPA, 1993; World Health Organization International Program on Chemical Safety, 1994).

With in vitro studies with tissue cultures or aquatic organisms, several of the formulated products are more toxic than glyphosate AI (Giesy et al., 2000; Williams et al., 2000). Differences in the response of test organisms to the AI and the commercial formulation, e.g., Roundup, are likely due to the toxicity of different formulants and surfactants contained in commercial products. There is a general agreement that adjuvants may be more toxic for animals than glyphosate itself (Giesy et al., 2000; Williams et al., 2000; Richard et al., 2005). Cytotoxicity of the commercial formulation Roundup to human peripheral mononuclear cells was 30-fold higher (LC_{50} = 56 mg/L) than for the AI (LC_{50} = 1640 mg/L) (Martinez et al., 2007). Several in vitro and in vivo studies with parallel testing of glyphosate AI and Roundup showed that only the commercial formulation was genotoxic (Rank et al., 1993; Bolognesi et al., 1997b; Gebel et al., 1997; Grisolia 2002). Cytotoxic and genotoxic effects were observed with Roundup and other formulations of glyphosate, but not with glyphosate AI alone in comparative studies involving different experimental systems (Peluso et al., 1998; Richard et al., 2005; Dimitrov et al., 2006). The observed differences were attributed to some ingredients of Roundup, mainly surfactants, and/or to a synergic effect of glyphosate and components of the formulation (Sirisattha et al., 2004; Peixoto 2005).

Epidemiological studies generally showed no consistent or strong relationships between human exposure to glyphosate or glyphosate-containing products and health outcomes in human populations. No statistically significant association in humans was found with spontaneous abortion, fetal deaths, preterm birth, neural tube defects (Rull et al., 2006), and cancer incidence overall, although a suggested association between cumulative exposure to glyphosate and the risk of multiple myeloma was reported (De Roos et al., 2005).The epidemiologic evidence is insufficient to verify a cause–effect relationship for childhood cancer (Wigle et al., 2008). Four case-control studies suggested an association between reported glyphosate use and the risk of non-Hodgkin's lymphoma (NHL) in age groups from 20 to 70 yr (Hardell & Eriksson, 1999; McDuffie et al., 2001; Hardell et al., 2002; De Roos et al., 2003; Eriksson et al., 2008).

Glyphosate AI and Roundup were extensively tested for genotoxicity in a wide range of in vitro and in vivo systems evaluating different genetic endpoints (gene mutation, chromosome mutation, DNA damage and repair) using bacteria and mammalian somatic cells (Williams et al., 2000). The active ingredient did not induce any relevant genotoxic effects such as gene mutations in a variety of in vitro bacterial assays including the *Salmonella typhimurium* reversion assay, with and without metabolic activation (Wildeman & Nazar 1982; Moriya et al., 1983; Li & Long, 1988) and *Escherichia coli* WP-2 (Moriya et al., 1983; Li & Long, 1988). The active ingredient was also negative in the Chinese hamster ovary cell HGPRT gene mutation assay and in primary hepatocyte DNA repair assay (Li & Long, 1988). The genotoxic potential of the formulation Roundup was investigated in a number of studies evaluating various genetic endpoints in different biological systems and was (1) negative in the *S. typhimurium* reversion assay (Kier et al., 1997), (2) negative in the sex-linked recessive lethal assay with *Drosophila melanogaster* (Gopalan & Njagi, 1981), and (3) negative for in vivo micronucleus (MN) induction in mouse bone marrow (Rank et al., 1993; Kier et al., 1997; Dimitrov et al., 2006). The Roundup formulation was reported in a number of studies to exert weak genotoxic effects in short-term assays.

Differences in the response of test organisms to the active ingredient glyphosate and the commercial formulation Roundup might be due to the toxicity of different co-formulants and surfactants contained in commercial products. Several studies with parallel testing of glyphosate and Roundup showed that only the commercial formulation was genotoxic (Rank et al., 1993; Bolognesi et al., 1997b; Gebel et al., 1997; Grisolia 2002). A recent study on the genotoxic potential of glyphosate formulations found that in some cases the genotoxic effects were obtained under exposure conditions that are not relevant for humans (Heydens et al., 2008).

An in vitro study described a concentration-dependent increase of DNA single-strand breaks (SSB), evaluated by comet assay, in two different human cell lines treated with glyphosate at sublethal concentrations (Monroy et al., 2005). Roundup formulations were shown to affect the cell cycle by inhibiting the G2/M transition and DNA synthesis leading to a genomic instability (Marc et al., 2004a, 2004b). Evidence of DNA damage in peripheral lymphocytes from a small group of subjects potentially exposed to glyphosate was reported in a recent paper (Paz-y-Miño et al., 2007). The number of subjects (21 control and 24 exposed) was small and there were 23 females and only 1 male in the exposed group, making interpretation of the results difficult.

Frequency of MN in human lymphocytes has been widely used for biomonitoring exposure to pesticides (Bolognesi, 2003; Costa et al., 2006; Montero et al., 2006). The MN test, an index of chromosomal damage, is one of the most appropriate biomarkers for monitoring a cumulative exposure to genotoxic agents. Chromosomal damage, as a result of inefficient or incorrect DNA repair, is expressed during the cell

division and represents an index of accumulated genotoxic effects. The cytokinesis-block micronucleus (CBMN) methodology (Fenech & Morley, 1985) allows a distinction to be made between a mononucleated cell that did not divide and a binucleated cell that has divided once, expressing any genomic damage associated to recent exposure. The test in its comprehensive application, as was proposed by Fenech (2007) including a set of markers of gene amplification, cellular necrosis, and apoptosis, allows evaluation of genotoxic and cytotoxic effects induced by exposure to a genotoxic agent.

Colombia's anti-drugs strategy includes a number of measures ranging from aerial spraying of a mixture of a commercial formulation of glyphosate (Glyphos) and an adjuvant, Cosmo-Flux (Solomon et al., 2007b), to manual eradication, including alternative development and crop substitution programs (UNODC, 2007). In order to assess the potential genotoxic risk associated with the aerial spraying program with the glyphosate mixture, a cytogenetic biomonitoring study was carried out in subjects from five Colombian regions, characterized by different exposure to glyphosate formulations and other pesticides.

MATERIALS AND METHODS

The study was carried out in five regions of Colombia, with different potential exposure to glyphosate as reported by Sanin et al. (2009). Briefly, the characteristics of the study areas are described here:

Sierra Nevada de Santa Marta—where organic coffee is grown without use of pesticides.

Boyacá—an area of illicit crops, where manual eradication is performed and the use of pesticides and other chemical agents is common.

Putumayo and Nariño—where aerial spraying of glyphosate is performed for coca and poppy eradication. The aerial application rate for eradication of coca is 3.69 kg glyphosate a.e. (acid equivalents)/ha (Solomon et al., 2007b). In order to maximize penetration and effectiveness of the spray formulation, Glyphos is tank-mixed with an adjuvant (Cosmo-Flux® 411F; Cosmoagro, Bogotá).

Valle del Cauca—where glyphosate is applied through aerial spraying for sugar cane maturation. Roundup 747 is the most commonly used product and is applied at a rate of 1 kg a.e./ha, and has no additional adjuvant (personal communication, ASOCAÑA, the Colombian Association for Sugar Growers, December 2008).

Study Population

Two hundred and seventy-four individuals were included in the study. The objective was to sample 30 couples of reproductive age in each area and, where possible, the same couples in the study conducted by Sanin et al. (2009) were sampled. In Putumayo, Nariño, and Valle del Cauca, the population was selected based on the scheduled aerial spraying of glyphosate. This schedule was confidential and provided exclusively for the purpose of the study by the Antinarcotics Police (Putumayo and Nariño) or ASOCAÑA (Valle del Cauca). In Valle del Cauca, a sample size of 30 couples could not be achieved because spraying was not carried out in populated areas of the study region. Most spraying during the study period was carried out on sugar cane crops where no inhabitants were found. All reported areas to be sprayed in Valle del Cauca were visited to search for couples; however, only 14 could be included.

In Sierra Nevada de Santa Marta and Boyacá, the same areas investigated in a previous study (Sanin et al., 2009) were identified, although, due to the instability of the population and high migration, most couples from the previous study were not located. In all regions, the same strategy as described before (Sanin et al., 2009) was followed, visiting household by household until completing 30 couples who fulfilled the inclusion criteria, women of reproductive age (15–49 yr of age) and their spouses, who voluntarily accepted to participate in the study.

Field Data Collection

Field data collection was carried out between October 2006 and December 2007. Epidemiologists and interviewers in the five regions who participated in the Sanin et al. (2009) study were informed about the objectives of the study and trained for data collection. The Ethical Committee of Fundacion Santa Fe de Bogotá approved the study protocol and the informed consent forms used for the study. All the subjects were informed about the aims of the study. All of them gave their informed consent and volunteered to donate blood for sampling. They did not self-report illness at the time of blood sampling and interviews. Every volunteer was interviewed with a standardized questionnaire, designed to obtain relevant details about the current health status, history, and lifestyle. This included information about possible confounding factors for chromosomal damage: smoking, use of medicinal products, severe infections or viral diseases during the last 6 mo, recent vaccinations, presence of known indoor/outdoor pollutants, exposure to diagnostic x-rays, and previous radio- or chemotherapy. A simplified food frequency questionnaire that had already been used in other regions of Colombia was also applied, in order to evaluate dietary folic acid intake. Folic acid intake was characterized because of the role of folic acid deficiency in baseline genetic damage in human lymphocytes (Fenech & Rinaldi, 1994). Specific information about exposure at the time of aerial spraying in Putumayo, Nariño, and Valle del Cauca was addressed in the questionnaire.

Blood Sampling and Cell Culture

Blood samples were collected twice in Boyacá, at the beginning of the study and 1 mo after the first survey, and at 3 different times in Nariño, Putumayo, and Valle del Cauca: immediately before spraying, within 5 d after spraying, and 4 mo later. A sample of 10 ml whole blood was collected from each subject, by venipuncture, using heparinized Vacutainer tubes kept at room temperature and sent within 24 h for the establishment of the lymphocyte cultures. The samples were coded before culturing. The modified cytokinesis-blocked method of Fenech and Morley (1985) was used to determine frequency of MN in lymphocytes. Whole blood cultures were set up for cytogenetic analysis in Bogotá (Colombia) by personnel specifically trained by cytogeneticists from Environmental Carcinogenesis Unit of the National Cancer Research Institute (Genoa, Italy).

Three sterile cultures of lymphocytes were prepared. A 0.4-ml aliquot of whole blood was incubated at 37°C in duplicate in 4.6 ml RPMI 1640 (Life Technologies, Milano, Italy) supplemented with 10% fetal bovine serum (Gibco BRL, Life Technologies SrL, Milano, Italy), 1.5% phytohemoagglutinin (Murex Biotech, Dartford, UK), 100 units/ml penicillin, and 100 µg/ml streptomycin. After 44 h, cytochalasin B (Sigma, Milano, Italy) was added at a concentration of 6 µg/ml. At the end of incubation at 37°C for 72 h, cells were centrifuged (800 × g, 10 min), then treated with 5 ml of 0.075 m*M* KCl for 3 min at room temperature to lyse erythrocytes. The samples were then treated with pre-fixative (methanol:acetic acid 3:1) and centrifuged . The cellular pellets were resuspended in 1 ml methanol. At this step the samples were sent to the Environmental Carcinogenesis Unit (National Cancer Research Institute, Genoa, Italy). All the samples were centrifuged in methanol. Treatment with fixative (methanol:acetic acid, 5:1) followed by centrifugation was repeated twice for 20 min. Lymphocytes in fresh fixative were dropped onto clean iced slides, air-dried, and stained in 2% Giemsa (Sigma, Milano, Italy). MN analysis was performed blind only on lymphocytes with preserved cytoplasm. On average, 2000 cells were analyzed for each subject. Cells were scored cytologically using the cytome approach to evaluate viability status (necrosis, apoptosis), mitotic status (mononucleated, binucleated, multinucleated) and chromosomal damage or instability status (presence of micronuclei, nucleoplasmic bridges, nucleoplasmic buds) (Fenech 2007). The proliferation index (PI) was calculated as follows:

$$\begin{aligned} PI = &(\text{number of mononucleated cells} + 2 \\ &\times \text{number of binucleated cells} + 3 \\ &\times \text{number of polynucleated cells})/ \text{total number of cells.} \end{aligned}$$

Statistical Analysis

Continuous variables were characterized using mean and standard deviation, while categorical variables were expressed as proportions. Dependent variables, micronuclei per binucleated cell (BNMN), and differences in MN between sampling were square-root transformed where required to comply with the required assumptions of normal distribution and equal variances. Comparison of MN between areas was made by one-way analysis of variance (ANOVA). A significance level at 5% was used to assess differences among areas. For multiple comparisons, the Bonferroni test was applied ($\alpha = .05$). Significance of differences in frequency of BNMN between first and second, and second and third sampling were tested by the unpaired *t*-test with equal variances. Difference and 95% confidence interval were used to compare between samplings.

Bivariate analysis between dependent variables and putative risk factors was performed by one-way ANOVA, comparing exposed and nonexposed subjects. In cases where risk factor was continuous, such as age, folic acid intake, alcohol consumption, and coffee consumption, the correlation coefficient was used.

A multiple linear regression was conducted to assess association with BNMN at the first sampling with different variables: region, age (as continuous variable as well as categorical age), ethnicity as a dichotomous variable, exposure to genotoxic products as defined earlier, gender (female vs. male), and intake of folic acid (categorized in quartiles). Regression analysis was conducted with transformed variables, with square root transformation of BNMN and natural logarithm of age, to obtain a normal distribution.

RESULTS

Demographic characteristics and habits of the study groups are described in Table 1. The study population comprised 274 subjects (137 female and 137 male; average age 30.4 ± 7.8 yr). The mean age of the subjects was similar in the different regions. A large part of the studied population was mestizo, with the exception of the Nariño area consisting of individuals of African origin. In the total population, 38% of interviewees had not completed primary education. Putumayo had the largest proportion with education and Valle del Cauca the lowest as shown in Table 1. Only 10% of all subjects were smokers, (20% in Putumayo); a large majority of subjects were drinkers of beer or liquor with a consistent consumption of guarapo (traditional alcoholic beverage prepared by fermentation of maize) in Santa Marta and Boyacá. No statistically significant differences of folic acid intake were observed between different regions (the mean values ranged from 750 and 1189 µg/wk).

One hundred and nine (39.8%) of 274 participants reported current use of pesticides in their occupation or other activities. Nariño (76.6%) and Putumayo (61.7%) were the two regions where prevalence of use of genotoxic pesticides was higher; Boyacá (24.2%) and Valle del Cauca (28.6%) reported lower use. None of the study subjects in Santa Marta reported use of pesticides. No data regarding quantity of pesticide used were available. Fifty (18.3%) out of 273 who gave information

TABLE 1
Demographic Characteristics and Possible Confounding Exposures in the Study Populations

Area	Santa Marta	Boyacá	Putumayo	Nariño	Valle del Cauca
Number of subjects	60	62	60	64	28
Age (mean (SD))	27.0 (5.6)	29.1 (8.8)	31.4 (7.2)	32.5 (7.4)	33.4 (8.7)
Ethnicity (%)					
Mestizo	100	100	88.3	3.1	60.7
African			6.7	96.9	39.3
Indian			5.0		
Education (%)					
None		4.8	1.7		
Primary incomplete	26.7	38.7	53.3	42.2	21.4
Primary complete	21.7	29.0	20.0	23.4	32.1
High school incomplete	25.0	8.1	20.0	25.0	28.6
High school complete	26.7	19.4	3.3	9.4	17.9
Technical			1.7		
Occupation (%)					
Agriculture	10.0	41.9	60.0	62.5	7.1
Housewife	40.0	50.0	38.3	34.4	50.0
Other	50.0	8.1	1.7	3.1	42.9
Health insurance (%)					
Uninsured	50.0	9.7	36.7	71.9	7.1
Subsidized	38.3	83.9	60.0	18.7	50.0
Insured	11.7	6.4	3.3	9.4	42.9
Coffee consumption (cups/day)					
Mean (SD)	1.8 (2.3)	1.7 (0.8)	2.3 (4.1)	1.3 (0.4)	1.7 (1.2)
Percent of population	80.0	67.7	88.3	76.6	82.1
Smoking (%)					
Nonsmokers	91.7	95.2	80.0	87.5	92.9
Alcohol (%)					
Liquor	28.3	25.8	53.3	78.1	78.6
Beer	51.6	67.7	63.1	82.8	64.3
Guarapo	6.7	59.7	1.7	3.2	10.7
Users of illicit drugs (%)	6.7	0	5.0	7.8	0
Diet					
Folic acid intake (μg/wk)	1189	873	750	1160	812

about x-ray examination reported to having been exposed at some time; however, only 21 out of 46 who gave information on dates of x-ray reported exposure in the last 6 mo before the interview and first blood sample. Sixty-one percent of population reported viral infections, the highest prevalence in Nariño (89.5%) and the lowest in Putumayo (49.2%). However, 89.3% of viral infections were the common cold and 6.1% dengue fever. Hepatitis was reported by six interviewees without any specification of the type of the infection.

The means and standard deviations of frequency of MN and related parameters according to regions are shown in Table 2 and presented graphically in Figure 1. Compared with Santa Marta, where people grow organic coffee without the use of pesticides and which is considered as a reference area, the baseline frequency of BNMN was significantly greater in subjects from the other four regions. The highest frequency of BNMN was in Boyacá, where no aerial eradication spraying of glyphosate was carried out, and Valle del Cauca, where aerial spraying was for maturation of sugar cane. There was no significant difference between mean frequency of BNMN in Boyacá and Valle del Cauca. There was no significant difference in frequency of BNMN between Putumayo and Nariño,

TABLE 2

Mean (SD) Frequency of Binucleated Cells with Micronuclei (BNMN), Total Micronuclei (MNL) per 1000 Binucleated Peripheral Lymphocytes, Frequency of Mononucleated Cells per 1000 Lymphocytes (MNMO), and Proliferation Index (PI) by Region before the Exposure (Phase 1), 5 d after Spraying (Phase 2) and 4 mo Later (Phase 3)

Region	Santa Marta	Boyacá	Putumayo	Nariño	Valle del Cauca
Phase 1					
Number of subjects	60	62	58	63	28
BNMN	1.83 (0.97)	5.64 (1.72)	3.61 (1.51)	4.12 (1.65)	5.75 (2.48)
MNL	1.97 (1.05)	6.16 (1.91)	3.90 (1.66)	4.36 (1.85)	6.02 (2.50)
MNMO	0.41 (0.44)	0.99 (0.64)	0.47 (0.51)	0.51 (0.39)	1.12 (0.88)
PI	1.54 (0.14)	1.45 (0.14)	1.68 (0.15)	1.47 (0.12)	1.51 (0.15)
Phase 2					
Number of subjects	ND	55	53	55	27
BNMN		4.96 (2.00)	4.64 (2.45)	5.98 (2.03)	8.64 (2.81)
MNL		5.41 (2.25)	5.02 (2.95)	6.35 (2.18)	8.98 (2.93)
MNMO		0.87 (0.65)	0.44 (0.46)	0.70 (0.45)	1.65 (0.62)
PI		1.72 (0.14)	1.66 (0.20)	1.40 (0.18)	1.51 (0.14)
Phase 3					
Number of subjects	ND	ND	50	56	26
BNMN			5.61(3.08)	3.91 (1.99)	7.38 (2.41)
MNL			5.96 (3.23)	4.13 (2.20)	8.17 (2.72)
MNMO			0.82 (0.54)	0.55 (0.42)	0.98 (0.60)
PI			1.43 (0.17)	1.41 (0.14)	1.45 (0.20)

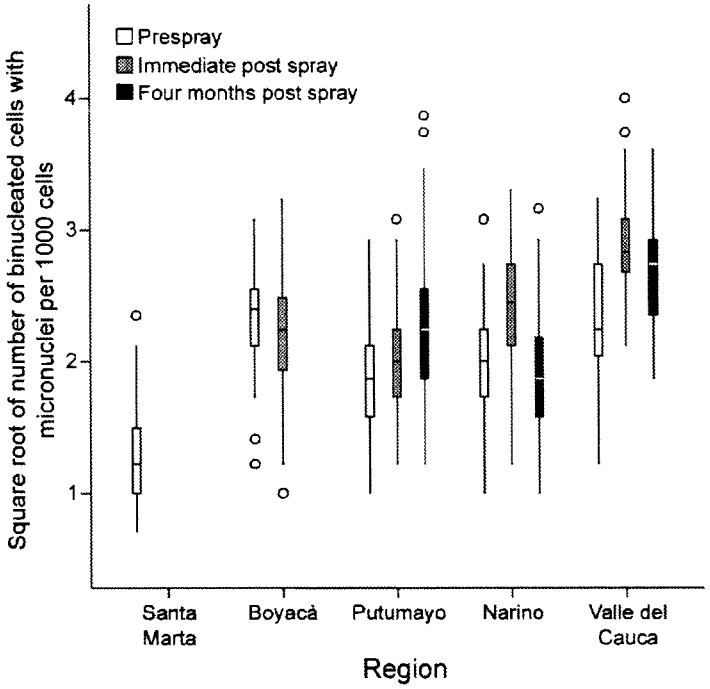

FIG. 1. Box plot of frequency of BNMN in the five study regions with samples taken prespray, 4–5 d post-spray, and 4 mo post-spray. Box plots: The center horizontal line marks the median of the sample. The length of each box shows the range within which the central 50% of the values fall, with the top and bottom of the box at the first and third quartiles. The vertical T-lines represent intervals in which 90% of the values fall. The O symbols show outliers. See text for description of statistically significant differences.

although Boyacá and Valle del Cauca showed a significantly higher frequency than Nariño and Putumayo. A higher frequency of BNMN in Boyacá was also observed in a second sampling 1 mo later.

There were differences in frequency of BNMN between sampling periods. A statistically significant difference in frequency of BNMN between first and second sampling was observed in Valle, Putumayo, and Nariño immediately (<5 d) after spraying. Four months after spraying in Nariño, there was a statistically significant decrease in the mean frequency of BNMN compared with the second sampling, but in Valle del Cauca the decrease was not significant nor was the increase observed in Putumayo significant (Figure 1 and Table 2).

The frequency of mononucleated cells with micronuclei (MOMN) was used as an index of background level of chromosomal damage accumulated in vivo (Table 2). The lowest frequency of MOMN for the first sampling was observed in Santa Marta; however, there was no marked difference in frequency of MOMN in Santa Marta, Putumayo, and Nariño and no statistically significant difference between Valle and Boyacá. However, Valle and Boyacá had a significantly higher frequency of MOMN than Putumayo, Nariño, and Santa Marta at first sampling. Immediately after spraying, Valle showed a significantly higher frequency of MOMN compared to Putumayo and Nariño, and Nariño was also higher than Putumayo. Between first and second sampling, the increase in frequency of MOMN in Nariño and Valle was statistically significant, but there was no difference in Putumayo nor in Boyacá 4 mo after the first sampling. Data suggest greater exposure to genotoxic agents in these populations is independent of the exposure to glyphosate products.

The proliferation index (PI) in all the studied groups was in the range of normal values described in the literature. No significant reduction of PI was observed in association with environmental exposures in groups of subjects from the different regions. A statistically significant correlation coefficient (0.288) between PI values from the first and the second samplings was observed, confirming the association with individual characteristics and not with any toxicity related to the exposure or to the culture techniques. Due to the low frequency observed, data with respect to other nuclear alterations, including in cytome analysis (Fenech, 2007), are not described in Table 2: the mean frequency of nucleoplasmic bridges (NPB) for all subjects was 0.010 per 1000 cells, that of nuclear buds was 0.022 per 1000 cells, and only rare necrotic and apoptotic cells were found in some samples.

Gender was the most important demographic variable affecting the BNMN index. Frequencies of BNMN in females were greater than those in males (mean 4.43 ± 2.36 vs. 3.61 ± 1.82, respectively, in total population) (Table 3). The groups of subjects were evenly matched for gender by including only couples in the study. No association was found between frequency of MN and age as a categorical variable, nor was there an association with smoking, but prevalence of smoking was low (~10% in the total population). A higher baseline frequency of MN was observed in subjects of African origin, suggesting greater susceptibility. Other lifestyle factors such as alcohol, coffee consumption, or illicit drug intake were not associated with initial measures of BNMN and MOMN.

One hundred and thirty-four of the 152 subjects in Nariño, Putumayo, and Valle reported information on contact with Glyphos and Cosmo-Flux after eradication spraying. The other 18 did not provide information in the second survey or blood samples were inadequate for testing micronuclei. Sixty-six (49.2.0%) reported no contact with the spray and 68 (50.8%) reported coming into contact with the spray because they entered sprayed fields or reported contact with the spray droplets. The mean BNMN in Nariño and Putumayo was greater in respondents who self-reported exposure, but differences were not statistically significant (Table 4). In Valle, only one respondent reported contact with glyphosate.

Region, gender, and older age (≥35 yr) were the only variables associated with the frequency of BNMN before spraying (Table 5). In fact, using Santa Martha, where no use of pesticides was reported, as reference, Boyacá, Valle del Cauca, Putumayo, and Nariño showed a statistically significant higher mean frequency of BNMN. There were also significant differences between Boyacá and Valle and Putumayo and Nariño. Females had a statistically higher mean frequency of BNMN than males after adjusting for all other variables. Greater age was also associated with greater frequency of BNMN. Neither exposure to genotoxic products, nor ethnicity, nor intake of folic acid was associated with frequency of BMMN at the first sampling. The multiple linear regression analysis of difference between second and first sampling only demonstrated statistically significant association with region after adjusting for all other variables, indicating that Putumayo, Nariño, and Valle had significantly greater differences between second and first sampling than Boyacá.

DISCUSSION

The main objective of this study was to test whether there was an association between aerial spraying of glyphosate and cytogenetic alterations, evaluated as frequency of MN in peripheral leukocytes. Biomonitoring was carried out in three regions of Colombia in populations exposed to aerial spraying of glyphosate: Putumayo and Nariño, where the application was performed for eradication of coca and poppy, and Valle del Cauca where the herbicide was used for maturation of sugar cane. Two control populations not exposed to aerial spraying of glyphosate were also selected: the first one from Sierra Nevada de Santa Marta, where organic coffee is grown without the use of any pesticides, and the other from Boyacá, with a region of illicit crops, where manual eradication is performed and subjects were potentially exposed to several pesticides but not glyphosate for aerial eradication. The ex vivo analysis of leukocytes in the presence of cytochalasin B, added 44 h after the

TABLE 3
Association of Mean (SD) Frequency of Binucleated Cells (First Sampling) with Micronuclei (BNMN/1000 Binucleated Lymphocytes) and Demographic Variables

Variable	Santa Marta	Boyacá	Putumayo	Nariño	Valle del Cauca	Total
Sex						
Females	1.98 (1.03)	6.22 (1.79)	3.91 (1.71)	4.57(1.77)	6.45 (2.82)	4.43 (2.36)
Males	1.68 (0.90)	5.06 (1.46)	3.31 (1.25)	3.66 (1.39)	5.05 (1.94)	3.61 (1.82)
p	.236	.007	.131	.028	.138	.002
Age						
18–24 yr	2.00 (1.14)	5.50 (1.96)	3.32 (1.25)	3.64 (1.72)	6.19 (2.15)	3.67 (2.16)
25–34 yr	1.66 (0.87)	5.70 (1.66)	3.53 (1.17)	4.20 (1.77)	4.20 (0.76)	3.97 (2.08)
35 yr and older	1.93 (0.67)	5.62 (1.73)	3.84 (1.86)	4.25 (1.52)	6.04 (2.84)	4.41 (2.19)
p	.438	.929	.574	.564	.313	.093
Ethnicity						
Mestizo	1.83 (0.97)	5.64 (1.72)	3.72 (1.52)	4.75 (1.06)	5.82 (2.44)	3.94(2.24)
Africa and Indian	0	0	2.86 (1.31)	4.10 (1.66)	5.64 (2.65)	4.20(1.90)
p			.162	.588	.850	.368
Smoking						
Yes	2.00 (1.06)	5.33 (0.76)	3.31 (1.00)	4.77 (1.51)	4.50 (1.41)	3.83 (1.60)
No	1.82 (0.97)	5.65 (1.76)	3.80 (1.56)	4.03 (1.66)	5.90 (2.57)	4.07 (2.20)
p	.693	.756	.395	.233	.459	.592
Folic acid intake (quartiles)						
1	1.92 (0.99)	6.11 (1.95)	3.23 (1.12)	4.50 (1.75)	5.86 (2.34)	3.89 (2.23)
2	1.64 (0.66)	5.70 (1.75)	3.47 (1.49)	3.80 (1.47)	5.86 (2.74)	3.97 (2.21)
3	1.69 (0.92)	5.69 (1.82)	4.00 (1.37)	3.85 (2.04)	6.58 (2.84)	4.47 (2.22)
4	1.94 (1.20)	4.94 (1.13)	3.69 (2.429)	4.28 (1.51)	4.63 (2.05)	3.75 (1.89)
p	.779	.399	.515	.645	.612	.220

TABLE 4
Mean Frequency of Binucleated Cells with Micronuclei (BNMN) at the Second Sampling per 1000 Binucleated Lymphocytes and Self-Reported Exposures to the Glyphosate Spray in Three Areas Where Aerial Application Had Occurred

	Nariño (*n* = 55)		Putumayo (*n* = 53)		Valle del Cauca (*n* = 26)	
Route of exposure	*n*	Mean BNMN (SD)	*n*	Mean BNMN (SD)	*n*	Mean BNMN (SD)
No exposure	28	5.81 (1.85)	13	3.84 (1.30)	25	8.56 (2.90)
Spray in air	5	7.30 (0.57)	1	5.50 (0)		
Spray on skin	8	5.62 (1.60)	15	4.90 (1.87)	1	9.50 (0)
Entered sprayed field	14	6.06 (2.77)	24	4.87 (3.18)		
p Value (ANOVA)		0.472		0.612		0.760
Any exposure	27	6.16 (2.22)	40	4.90 (2.69)	1	9.50 (0)
p Value (no exposure vs. any exposure)		0.525		0.181		0.760

Note. The data comprise respondents in the second survey from which blood samples were obtained.

TABLE 5
Multiple Linear Regression Analysis Adjusted for Region, Age, Gender, Ethnicity, and Folic Acid Intake

Variable	Coefficient	*p*	95% CI
Region			
Boyacá	3.75	≤.0001	3.19, 4.31
Putumayo	1.58	≤.0001	1.00, 2.16
Nariño	2.06	≤.0001	1.49, 2.64
Valle del Cauca	3.65	≤.0001	2.92, 4.39
Age (yr)			
25–34	0.28	.250	–0.20, 0.76
35 and older	0.75	.008	0.20, 1.31
Gender			
Females	1.00	≤.0001	0.60, 1.40

start of cultivation, made it possible to distinguish between non-dividing mononucleated cells—as an index of accumulated chromosomal damage—and binucleated cells, which had completed one nuclear division during in vitro culture and expressed MN associated with recent exposure to genotoxic agents.

The baseline level of chromosomal damage, evaluated as frequency of BNMN, was associated with the different regions considered in our study. The frequency of BNMN before spraying was also associated with region, gender, and age. Gender difference in the background incidence of MN in peripheral leukocytes, with the frequency being consistently higher in females, and a strong correlation between MN frequency and increasing age are well documented (Bonassi et al., 1995, 2001; Bolognesi et al., 1997a).

Data demonstrated no significant effect of smoking, confirming findings from the literature (Bonassi et al., 2003) although prevalence of smoking in our study population was small (7–20%, Table 1). No association with alcohol consumption was observed. A higher susceptibility of people of African origin compared to the mestizo group was suggested by a greater baseline frequency of BNMN and increased frequency at the second sampling period.

There was some indication of an association between BNMN and exposure to pesticides in general. The lowest frequency of BNMN was observed in Sierra Nevada de Santa Marta, where people self-reported that they did not use pesticides. The mean frequency of BNMN in this group of subjects (1.83 ± 0.97) was similar to that observed in healthy unexposed subjects for the same range of age (Bolognesi et al., personal communication). The higher mean frequency of BNMN observed in Boyacá and Valle del Cauca (5.64 ± 1.72 and 5.75 ± 2.48, respectively) and that in Nariño and Putumayo (4.12 ± 1.65 and 3.65 ± 1.51, respectively), compared to Santa Marta, are in agreement with similar biomonitoring studies carried out in subjects exposed to pesticides using the MN test or other genetic endpoints (Bolognesi, 2003; Bull et al., 2006).

There was no clear relationship between BNMN and the reported use of pesticides classified as genotoxic. Participants in Boyacá and Valle del Cauca showed higher frequency of BNMN than those in Putumayo and Nariño. However, a greater proportion of participants in the latter regions self-reported the use genotoxic pesticides (76.6% in Nariño and 61.7% in Putumayo). There is no information available on other relevant factors such as frequency of use, rate applied, time of exposure, and protective measures used, and we could therefore not characterize exposures to explain the differences. There were further inconsistencies; for example, in Boyacá, where more frequent use of pesticides was expected, only 24.2% of participants self-reported use, compared with the greater values in Nariño and Putumayo. However, it is possible that in areas such as Boyacá, individuals might be potentially exposed to persistent pesticides applied in the past and still present in the environment.

There was no evidence of an association between BNMN and folic acid deficiency. An assessment of folic acid intake from the semiquantitative food frequency questionnaire showed that, according to accepted recommendations (Herbert, 1987), the diet of the study populations was not deficient in folic acid and there were only small differences between regions. Consistent with these data, no association was found between MN and folic acid intake, either as a continuous variable or by quartiles.

The frequency of BNMN increased after spraying with glyphosate but not consistently. The results obtained with a second sampling, carried out immediately after the glyphosate spraying, showed a statistically significant increase in frequency of BNMN in the three regions where glyphosate was sprayed. However, this was not consistent with the rates of application use in the regions. The increase in frequency of BNMN in Valle (application rate = 1 kg a.e. glyphosate/ha) was greater than that in Nariño and Putumayo (3.69 kg a.e. glyphosate/ha).

There was no significant association between self-reported direct contact with eradication sprays and frequency of BNMN. The frequency of BNMN in participants who self-reported that they were exposed to glyphosate because they entered the field immediately after spraying (to pick the coca leaves), felt spray drops in their skin, or they thought they were exposed because they had contact with the chemical in the air, was not significantly greater than in subjects living in the same areas but who were not present during spraying. Decreases in frequency of BNMN in the recovery period after glyphosate spraying were not consistent. The third sampling, 4 mo after spraying, demonstrated a statistically significant decrease in frequency of BNMN only in Nariño.

Overall, these results suggest that genotoxic damage associated with glyphosate spraying, as evidenced by the MN test, is small and appears to be transient. The frequencies of BNMN in Nariño and Putumayo during the second and the third sampling fell within the range of values observed in Boyacá, an area

where people were exposed to a complex mixture of different pesticides (including glyphosate). A greater increase in frequency of BNMN was observed in Valle del Cauca, but it cannot be attributed only to the glyphosate exposure, because the application rate of the herbicide in this area was one-third compared with that in Nariño and Putumayo. This conclusion is further supported by the frequency of MN in mononucleated cells (MOMN), which provides an indication of the background level of chromosome/genome mutations accumulated in vivo (Manteuca et al., 2006). A statistically significant increase of MOMN was observed in Boyacá and Valle del Cauca before and after the aerial spraying, suggesting exposure to other genotoxic compounds in these populations was independent of the exposure to glyphosate. Evidence indicates that the genotoxic risk potentially associated with exposure to glyphosate in the areas where the herbicide is applied for eradication of coca and poppy is of low biological relevance. One of the strengths of our study was the detection of a transient chromosomal damage, evaluated as MN frequency in peripheral blood of the exposed subjects, since it was possible to compare the baseline before spraying with the effects detected immediately after spraying. Glyphosate persists in the environment for only a short time (half-life for biological availability in soil and sediments is hours, and 1-3 d in water; Giesy et al., 2000), is rapidly excreted by mammals and other vertebrates (Williams et al., 2000; Acquavella et al., 2004) and chronic effects, if any, would not be expected.

One of the major drawbacks of environmental epidemiology studies is the characterization of exposures to the agents being investigated. In this study two approaches were used to characterize exposures to glyphosate: ecological and self-reported. In the ecological study design, frequency of BNMN in participants was compared from regions with different patterns of pesticide use. As previously discussed (Sanin et al., 2009), this ecological design may result in misclassification of exposures (Arbuckle et al., 2004), but as an exploratory assessment of exposure it is useful (Ritter et al., 2006).

Others have attempted to improve assessment of exposure to pesticides in epidemiological studies. One study used a self-administered questionnaire for the assessment of exposure to glyphosate, which was defined as (a) ever personally mixed or applied products containing glyphosate; (b) cumulative lifetime days of use, or "cumulative exposure days" (years of use times days/year); and (c) intensity-weighted cumulative exposure days (years of use times days/year times estimated intensity level) (De Roos et al., 2005). A pesticide exposure score based on self-reported work practices was recently developed to estimate annual exposure level (Firth et al., 2007). Based on an algorithm to estimate lifetime exposure to glyphosate from questionnaire information, a moderate correlation was found with concentrations of glyphosate in urine and no significant correlation with self-reported exposure (Acquavella et al., 2004).

In our study, questions related to whether there was direct contact with the spray were used but this did not consider area of skin exposed, region of skin exposed, differences in rates of penetration, or personal hygiene.

Given the situation, the best approach possible, a prospective cohort, was used but the need to use better procedures to estimate the exposure is acknowledged. Based on the applicable Bradford–Hill guidelines (Hill, 1965), it is not possible to assign causality to the increases in frequency of BNMN observed in our study. There was a smaller frequency of BNMN and MOMN in the region of no pesticide use compared with the regions where pesticides (including glyphosate) were used, which is consistent with other reports in the literature. Although temporality was satisfied in the increase in frequency of BNMN after spraying, this response did not show strength as it was not consistently correlated with the rate of application. Recovery was also inconsistent with decreases in frequency of BNMN in the areas of eradication spraying but not in the area where lower rates were applied on sugar cane.

Further studies are needed to better characterize the potential genotoxic risk associated with the application of glyphosate for sugar cane maturation. The smaller number of subjects recruited in this study and small amount of information about the exposure precluded any conclusions. Many pesticides are used in conventional agriculture in Colombia and many pesticides are used in the production of coca (Solomon et al., 2007a, 2007b); however, there is not sufficient information to correlate the frequency of MN to the pesticide exposure.

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UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

IN RE: ROUNDUP PRODUCTS LIABILITY LITIGATION	MDL No. 2741 Case No. 16-md-02741-VC
This document relates to: ALL ACTIONS	**MONSANTO COMPANY'S NOTICE TO TAKE ORAL AND VIDEOTAPED DEPOSITION OF DR. CHRISTOPHER PORTIER**

To: All MDL plaintiffs, by and through, the Court's appointed co-lead counsel, Robin Greenwald of Weitz & Luxenberg, PC, Michael Miller of The Miller Firm, LLC, and Aimee Wagstaff of Andrus Wagstaff, PC

Please take notice that, pursuant to Rule 30 and Rule 45 of the Federal Rules of Civil Procedure, defendant Monsanto Company shall take the videotaped deposition upon oral examination of **Dr. Christopher Portier on September 5, 2017** before a person duly authorized to administer oaths. The deposition shall commence at **9:00 a.m. ET at Weitz & Luxenberg PC, 700 Broadway, New York, NY 10003**. The conduct of the deposition, including its continuation if necessary, shall be governed by Pretrial Order No. 7: Deposition Protocol (ECF No. 103) and Rule 30 of the Federal Rules of Civil Procedure. Dr. Portier shall produce any documents identified in Schedule A attached to his Document Subpoena, at least 10 days prior to the deposition.

DATED: August 16, 2017

Respectfully submitted,

/s/ Heather A. Pigman

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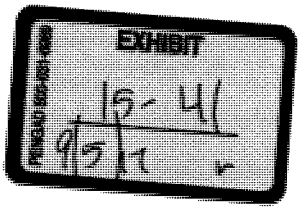

AO 88B (Rev. 02/14) Subpoena to Produce Documents, Information, or Objects or to Permit Inspection of Premises in a Civil Action

UNITED STATES DISTRICT COURT

for the

Northern District of California

IN RE: ROUNDUP PRODS. LIABILITY LITIG.
Plaintiff
v.
Defendant

Civil Action No. 16-md-2741-VC

SUBPOENA TO PRODUCE DOCUMENTS, INFORMATION, OR OBJECTS OR TO PERMIT INSPECTION OF PREMISES IN A CIVIL ACTION

To: Dr. Christopher Portier

(Name of person to whom this subpoena is directed)

☑ *Production:* **YOU ARE COMMANDED** to produce at the time, date, and place set forth below the following documents, electronically stored information, or objects, and to permit inspection, copying, testing, or sampling of the material: SEE ATTACHED SCHEDULE A

Place:	Date and Time:
Hollingsworth LLP, 1350 I St., NW Washington, D.C. 20005	08/26/2017 5:00 pm

☐ *Inspection of Premises:* **YOU ARE COMMANDED** to permit entry onto the designated premises, land, or other property possessed or controlled by you at the time, date, and location set forth below, so that the requesting party may inspect, measure, survey, photograph, test, or sample the property or any designated object or operation on it.

Place:	Date and Time:

The following provisions of Fed. R. Civ. P. 45 are attached – Rule 45(c), relating to the place of compliance; Rule 45(d), relating to your protection as a person subject to a subpoena; and Rule 45(e) and (g), relating to your duty to respond to this subpoena and the potential consequences of not doing so.

Date: 08/16/2017

CLERK OF COURT

OR

Signature of Clerk or Deputy Clerk

/s/ Heather Pigman
Attorney's signature

The name, address, e-mail address, and telephone number of the attorney representing *(name of party)* Monsanto, who issues or requests this subpoena, are:

Heather Pigman, 1350 I Street, NW Washington, D.C. 20005, hpigman@hollingsworthllp.com, 202-898-5800

Notice to the person who issues or requests this subpoena

If this subpoena commands the production of documents, electronically stored information, or tangible things or the inspection of premises before trial, a notice and a copy of the subpoena must be served on each party in this case before it is served on the person to whom it is directed. Fed. R. Civ. P. 45(a)(4).

Civil Action No. 16-md-2741-VC

PROOF OF SERVICE

(This section should not be filed with the court unless required by Fed. R. Civ. P. 45.)

I received this subpoena for *(name of individual and title, if any)* _____

on *(date)* _____ .

❒ I served the subpoena by delivering a copy to the named person as follows: _____

_____

_____ on *(date)* _____ ; or

❒ I returned the subpoena unexecuted because: _____

_____ .

Unless the subpoena was issued on behalf of the United States, or one of its officers or agents, I have also tendered to the witness the fees for one day's attendance, and the mileage allowed by law, in the amount of

$ _____ .

My fees are $ _____ for travel and $ _____ for services, for a total of $ 0.00 .

I declare under penalty of perjury that this information is true.

Date: _____

_____
Server's signature

_____
Printed name and title

_____
Server's address

Additional information regarding attempted service, etc.:

Federal Rule of Civil Procedure 45 (c), (d), (e), and (g) (Effective 12/1/13)

(c) Place of Compliance.

(1) ***For a Trial, Hearing, or Deposition.*** A subpoena may command a person to attend a trial, hearing, or deposition only as follows:

(A) within 100 miles of where the person resides, is employed, or regularly transacts business in person; or

(B) within the state where the person resides, is employed, or regularly transacts business in person, if the person

(i) is a party or a party's officer; or

(ii) is commanded to attend a trial and would not incur substantial expense.

(2) ***For Other Discovery.*** A subpoena may command:

(A) production of documents, electronically stored information, or tangible things at a place within 100 miles of where the person resides, is employed, or regularly transacts business in person; and

(B) inspection of premises at the premises to be inspected.

(d) Protecting a Person Subject to a Subpoena; Enforcement.

(1) ***Avoiding Undue Burden or Expense; Sanctions.*** A party or attorney responsible for issuing and serving a subpoena must take reasonable steps to avoid imposing undue burden or expense on a person subject to the subpoena. The court for the district where compliance is required must enforce this duty and impose an appropriate sanction—which may include lost earnings and reasonable attorney's fees—on a party or attorney who fails to comply.

(2) ***Command to Produce Materials or Permit Inspection.***

(A) *Appearance Not Required.* A person commanded to produce documents, electronically stored information, or tangible things, or to permit the inspection of premises, need not appear in person at the place of production or inspection unless also commanded to appear for a deposition, hearing, or trial.

(B) *Objections.* A person commanded to produce documents or tangible things or to permit inspection may serve on the party or attorney designated in the subpoena a written objection to inspecting, copying, testing, or sampling any or all of the materials or to inspecting the premises—or to producing electronically stored information in the form or forms requested. The objection must be served before the earlier of the time specified for compliance or 14 days after the subpoena is served. If an objection is made, the following rules apply:

(i) At any time, on notice to the commanded person, the serving party may move the court for the district where compliance is required for an order compelling production or inspection.

(ii) These acts may be required only as directed in the order, and the order must protect a person who is neither a party nor a party's officer from significant expense resulting from compliance.

(3) ***Quashing or Modifying a Subpoena.***

(A) *When Required.* On timely motion, the court for the district where compliance is required must quash or modify a subpoena that:

(i) fails to allow a reasonable time to comply;

(ii) requires a person to comply beyond the geographical limits specified in Rule 45(c);

(iii) requires disclosure of privileged or other protected matter, if no exception or waiver applies; or

(iv) subjects a person to undue burden.

(B) *When Permitted.* To protect a person subject to or affected by a subpoena, the court for the district where compliance is required may, on motion, quash or modify the subpoena if it requires:

(i) disclosing a trade secret or other confidential research, development, or commercial information; or

(ii) disclosing an unretained expert's opinion or information that does not describe specific occurrences in dispute and results from the expert's study that was not requested by a party.

(C) *Specifying Conditions as an Alternative.* In the circumstances described in Rule 45(d)(3)(B), the court may, instead of quashing or modifying a subpoena, order appearance or production under specified conditions if the serving party:

(i) shows a substantial need for the testimony or material that cannot be otherwise met without undue hardship; and

(ii) ensures that the subpoenaed person will be reasonably compensated.

(e) Duties in Responding to a Subpoena.

(1) ***Producing Documents or Electronically Stored Information.*** These procedures apply to producing documents or electronically stored information:

(A) *Documents.* A person responding to a subpoena to produce documents must produce them as they are kept in the ordinary course of business or must organize and label them to correspond to the categories in the demand.

(B) *Form for Producing Electronically Stored Information Not Specified.* If a subpoena does not specify a form for producing electronically stored information, the person responding must produce it in a form or forms in which it is ordinarily maintained or in a reasonably usable form or forms.

(C) *Electronically Stored Information Produced in Only One Form.* The person responding need not produce the same electronically stored information in more than one form.

(D) *Inaccessible Electronically Stored Information.* The person responding need not provide discovery of electronically stored information from sources that the person identifies as not reasonably accessible because of undue burden or cost. On motion to compel discovery or for a protective order, the person responding must show that the information is not reasonably accessible because of undue burden or cost. If that showing is made, the court may nonetheless order discovery from such sources if the requesting party shows good cause, considering the limitations of Rule 26(b)(2)(C). The court may specify conditions for the discovery.

(2) ***Claiming Privilege or Protection.***

(A) *Information Withheld.* A person withholding subpoenaed information under a claim that it is privileged or subject to protection as trial-preparation material must:

(i) expressly make the claim; and

(ii) describe the nature of the withheld documents, communications, or tangible things in a manner that, without revealing information itself privileged or protected, will enable the parties to assess the claim.

(B) *Information Produced.* If information produced in response to a subpoena is subject to a claim of privilege or of protection as trial-preparation material, the person making the claim may notify any party that received the information of the claim and the basis for it. After being notified, a party must promptly return, sequester, or destroy the specified information and any copies it has; must not use or disclose the information until the claim is resolved; must take reasonable steps to retrieve the information if the party disclosed it before being notified; and may promptly present the information under seal to the court for the district where compliance is required for a determination of the claim. The person who produced the information must preserve the information until the claim is resolved.

(g) Contempt.

The court for the district where compliance is required—and also, after a motion is transferred, the issuing court—may hold in contempt a person who, having been served, fails without adequate excuse to obey the subpoena or an order related to it.

For access to subpoena materials, see Fed. R. Civ. P. 45(a) Committee Note (2013).

SCHEDULE A

DEFINITIONS

1. The term "Communication," as used in these Requests, is intended to have the broadest possible meaning and shall include any contact or act by which information or knowledge is transmitted or conveyed between two or more persons and includes, without limitation: (1) written contact, including but not limited to letters, memoranda, PowerPoint presentations, email, text message, telegram, telex, internet-based meetings, or other written or electronic documents or files; (2) oral contact, whether by face-to-face meetings, internet-based meetings, video conferences, telephonic conversations, or otherwise; and (3) nonverbal acts intended to communicate or convey any meaning, understanding or other message.

2. "Concerns," "concerning," "relates," or "relating" shall mean and include contain or containing, constitute or constituting, describe or describing, discuss or discussing, refer or referring, state or stating, assess or assessing, and record or recording.

3. "Documents" shall be construed in the broadest sense and includes, but is not limited to, the original and any non-conforming copies of any and all written, printed, typed, graphic, photographic, visual or otherwise recorded matter of any kind or nature, and all microfilm, or electronic sound recording or transcripts thereof however produced or reproduced, including non-identical copies, whether different from the original by reason of any notation made on such copies or otherwise, writings, drawings, records and recordings of every kind and description, whether inscribed by hand or by mechanical, electronic, microfilm, photographic or other means, as well as audio or visual reproduction of all statements, conversations or events including, but not limited to, agreements, bids, bonds, bulletins, calendars and appointment books, checks, circulars, communications, contracts, correspondence, statements, telegrams, receipts, returns, summaries, data books, accounting records, including ledgers, vouchers and books of account, computer printouts, information storage, media diaries and diary entries, drawings and charts, including additions and revisions, estimates, evaluations, financial statements and records, instructions, inter- and intra-office communications, invoices, job site reports, investigative reports, audits, logs, memoranda of any type, minutes of all meetings, notes

of all types, orders, including change, proceed and purchase orders, questionnaires and surveys, photographs, price sheets, records, results of investigations, schedules including additions and revisions, statistical records, reports, analyses and studies of any kind, tape recordings, including any form of any recording of any telephone or other conversation, interview, conference, or meeting, and all contract and working papers as well as drawings, papers and files. A reference herein to any one or more of these types of documents shall be construed to include all other types of documents without limitations.

4. Words used in the singular shall, where the context permits, include the plural, and words used in the plural shall, where the context permits, include the singular.

5. "You" and "your" refers to the person served with and responding to these Requests.

6. "Roundup®/glyphosate litigation" refers to any lawsuit, litigation, or other matter, including, but is not limited to, the multidistrict litigation captioned, *In re Roundup Products Liability Litigation*, Case No. 3:16-md-02741-CV (N.D. Cal.), in which an individual has asserted or will assert, a claim against Monsanto Company ("Monsanto") asserting that the use of Monsanto's Roundup®-branded products has caused their non-Hodgkin's lymphoma ("NHL") or other cancers that have been or will be alleged.

REQUESTS FOR PRODUCTION

As stated in the foregoing Notice, you are required to produce the following documents:

1. All documents provided to you, or that you have, related to the Roundup®/glyphosate litigation that are not publicly or otherwise available.

2. All studies, literature, materials, research files, publications, treatises or any other documents that are not publicly or otherwise available that you have reviewed and upon which you rely and/or intend to rely upon as a basis for the opinions that you intend to offer in the Roundup®/glyphosate litigation or that were reviewed by you in working on, or rendering opinions in, the Roundup®/glyphosate litigation. This request includes all documents not cited in

your expert reports that contain data or other information considered by you in the course of formulating your opinions.

3. Your most recent curriculum vitae.

4. All billing records, invoices, or other documents reflecting time spent and/or fees charged by you (either directly or through your employer or other entity) in connection with the Roundup®/glyphosate litigation and/or consulting work regarding glyphosate, IARC, Roundup®, or Monsanto at C. Portier Consultations.

5. Any retainer letter, contract, agreement, or other document setting forth the retention of you to work in the Roundup®/glyphosate litigation.

6. A copy of all abstracts, articles, draft articles, books or book excerpts of which you are an author, co-author or editor which has as all or part of its subject matter NHL, glyphosate, and/ or Roundup®, that are not publicly or otherwise available.

7. A copy of all handouts, power points or other documents used by you at any lecture you have given on NHL, glyphosate, IARC, and/ or Roundup®, that are not publicly or otherwise available.

8. All documents and communications regarding glyphosate, NHL, Roundup®, or IARC sent to or received on or after January 1, 2013 from any current or former employee or current or former member of the International Agency for Research on Cancer (IARC) or IARC Working Group 112, Collegium Ramazzini or the Ramazzini Institute, December 2016 EPA Scientific Advisory Panel on glyphosate, media organizations such as U.S. Right to Know (USRTK) and Russia Today (RT), non-governmental organizations such as the Organic Consumers Association (OCA) or Natural Resources Defense Council (NRDC), regulatory bodies such as the California Office of Environmental Health Hazard Assessment (OEHHA), the United States Environmental Protection Agency (EPA) or the European Food Safety Authority (EFSA), governmental agencies such as the U.S. National Institute of Environmental Health Sciences (NIEHS) or the U.S. National Toxicology Program (NTP), or any other national or state regulatory body.

9. All documents, communications, or computer programs setting forth underlying mathematical formulations used to compute trend analyses and/or "P Hist" statistics discussed in animal toxicology section of original and revised report.

DATED: August 16, 2017

Respectfully submitted,

/s/ Heather A. Pigman