Comparison of Survival, Tumor Incidence, and the Incidence of Chronic Progressive Nephropathy in Carcinogenicity Studies Conducted in CD®IGS Rats and CD-1®IGS Mice Fed 5002 or 5CR4 Certified Diets

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1 INTRODUCTION

LabDiet certified rodent 5002 and 5CR4 diets are two diets used in GLP carcinogenicity studies. One of the major differences between the two diets is the protein content (5002 contains ~20% protein; 5CR4 contains ~14% protein). To assess possible differences in the effects of these diets on carcinogenicity study endpoints, historical control parameters from carcinogenicity studies conducted within the last 5 years using 5CR4 diet and within the last 10 years using 5002 diets at our facility were compared in male and female CD®IGS rats (Crl: CD(SD)) and CD-1®IGS (Crl: CD1(ICR)) mice. Among the parameters evaluated were survival, tumor incidence, and the incidence of chronic progressive nephropathy (CPN) in rats and mice.

3 RESULTS: Chronic Progressive Nephropathy

CPN Severity	Incidence of Chronic Progressive Nephropathy							
	CD®IGS Rats				CD-1 Mice			
	5002 Diet		5CR4 Diet		5002 Diet		5CR4 Diet	
	Males		Males		Males		Males	
	Mean %	(Range)	Mean %	(Range)	Mean %	(Range)	Mean %	(Range)
All severity grades	83%	(70% - 92%)	66%	(61% - 72%)	67%	(32% - 97%)	43%	(8% - 69%)
Minimal	26%	(20% - 37%)	37%	(33% - 42%)	31%	(18% - 57%)	24%	(0% - 43%
Mild	28%	(22% - 33%)	19%	(18% - 19%)	23%	(3% - 47%)	14%	(7% - 19%)
Moderate	22%	(13% - 29%)	6%	(4% - 8%)	11%	(0% - 36%)	4%	(2% - 6%)
Marked/Severe	7%	(3% - 13%)	4%	(3% - 5%)	2%	(0% - 8%)	1%	(0% - 1%)
	Females		Females		Females		Females	
	Mean %	(Range)	Mean %	(Range)	Mean %	(Range)	Mean %	(Range)
All severity grades	44%	(23% - 65%)	20%	(17% - 23%)	56%	(29% - 97%)	38%	(27% - 46%)
Minimal	29%	(20% - 43%)	16%	(13% - 17%)	23%	(15% - 37%)	15%	(7% - 21%)
Mild	10%	(3% - 16%)	4%	(3% -5%)	21%	(5% - 55%)	9%	(7% - 10%)
Moderate	5%	(0% - 14%)	0%	(0% - 0%)	10%	(2% - 18%)	9%	(5% - 11%)
Marked/Severe	1%	(0% - 7%)	0%	(0% - 0%)	3%	(0% - 12%)	6%	(4% - 8%)

4 CONCLUSIONS

- Tumor profiles were generally comparable between animals fed 5CR4 or 5002 diets.
- The 5CR4 diet was associated with greater survival in male rats.
- The 5CR4 diet was associated with a lower incidence of chronic progressive nephropathy in male and female rats and mice.
- Further investigation is needed to determine the influence of the two diets on the severity of nephropathy and the role of nephropathy in survival.
- Based upon our initial evaluation, 5CR4 which has a lower protein content increases the survival in male rats and lowers the incidence of chronic progressive nephropathy in male and female rats and mice.

2 RESULTS: Survival and Tumor Incidence

Category	% Survival			
	CD®IGS Rats			
	Males		Females	
	5002	5CR4	5002	5CR4
Early Deaths	67%	56%	66%	70%
Scheduled Euthanasia	33%	44%	34%	30%
	CD-1 Mice			
	Males		Females	
	5002	5CR4	5002	5CR4
Early Deaths	60%	60%	65%	63%
Scheduled Euthanasia	40%	40%	35%	37%

Tissue	Diagnosis	Incidence of Selected Common Tumors in Male Rats by Diet			
		5002		5CR4	
		% with Neoplasms	Incidence Range (%)	% with Neoplasms	Incidence Range (%)
Adrenal	Pheochromocytoma, Benign	9.5%	1.3% - 20%	10.4%	10% - 11%
	Pheochromocytoma, Malignant	2.5%	0% - 8.3%	2.2%	0% - 5%
Hemolymphoreticular Neoplasms	Histiocytic Sarcoma	3.2%	0% - 5.3%	6.7%	6.7% - 6.7%
	Lymphoma	1.8%	0% - 4.6%	3.7%	1.7% - 5.3%
Liver	Hepatocellular Adenoma	0.5%	0% - 3.3%	3.7%	0% - 6.7%
	Hepatocellular Carcinoma	2.7%	0% - 6.2%	0%	0% - 0%
Pancreas	Acinar Cell Adenoma	1.3%	0% - 3.3%	2.2%	1.3% - 3.3%
	Islet Cell Adenoma	9.2%	3.3% - 16%	12.6%	5% - 19%
Pituitary	Adenoma	40.9%	35% - 48%	41.8%	39% - 44%
Skin	Basal Cell Tumor, Benign	0.9%	0% - 4%	2.2%	0% - 5%
	Fibroma	3.4%	0% - 6.7%	1.5%	1.3% - 1.7%
	Fibrosarcoma	0.9%	0% - 6.7%	1.5%	0% - 3.3%
	Keratoacanthoma	6.1%	1.7% - 11%	2.2%	0% - 5%
	Lipoma	1.1%	0% - 2.7%	3.0%	1.7% - 4%
	Squamous Cell Papilloma	4.1%	2.7% - 7.1%	3.0%	2.7% - 3.3%
Testes	Interstitial Cell Adenoma	1.8%	0% - 4%	0.7%	0% - 1.3%
Thyroid	C-Cell Adenoma	8.2%	2.9% - 15%	12.6%	9.3% - 17%
	C-Cell Carcinoma	0.6%	0% - 3.1%	0.7%	0% - 1.7%
	Follicular Cell Adenoma	2.1%	0% - 4.8%	4.4%	3.3% - 5.3%

Tissue	Diagnosis	Incidence of Selected Common Tumors in Female Rats by Diet			
		5002		5CR4	
		% with Neoplasms	Incidence Range (%)	% with Neoplasms	Incidence Range (%)
Adrenal	Adenoma	2.9%	1.2% - 6.7%	0.7%	0% - 1.7%
	Carcinoma	1.1%	0% - 1.7%	0.7%	0% -1.7%
	Pheochromocytoma, Benign	2.0%	0% - 6.8%	1.5%	1.3% - 1.7%
Cervix	Endometrial Stromal Polyp	0.2%	0% - 1.2%	0.7%	0% - 1.7%
	Endometrial Stromal Sarcoma	0.4%	0% - 1.7%	0.7%	0% - 1.7%
Hemolymphoreticular Neoplasms	Histiocytic Sarcoma	2.0%	0% - 4%	3.0%	0% - 5.3%
	Lymphoma	1.3%	0% - 3.5%	0.7%	0% - 1.3%
Mammary	Adenocarcinoma	26.5%	20% - 38%	15.6%	12% - 20%
	Adenoma	14.2%	9.3% - 20%	8.1%	5% - 11%
	Fibroadenoma	48.6%	42% - 59%	33.3%	28% - 37%
Pancreas	Islet Cell Adenoma	3.3%	0% - 6.8%	2.2%	0% - 4%
	Islet Cell Carcinoma	2.7%	0% - 6.7%	0%	0% - 0%
Pituitary	Adenocarcinoma	2.5%	0% - 12%	2.2%	0% - 4.1%
	Adenoma	71.9%	60% - 83%	79.1%	76% - 83%
Skin	Keratoacanthoma	0.7%	0% - 2.7%	1.5%	0% - 3.3%
Thyroid	C-Cell Adenoma	9.2%	2.7% - 17%	2.2%	1.7% - 2.7%
	C-Cell Carcinoma	0.5%	0% - 2.4%	0.7%	0% - 1.3%
	Follicular Cell Adenoma	1.1%	0% - 3.1%	0.7%	0% - 1.3%
Uterus	Endometrial Stromal Polyp	4.9%	1.7% - 7.7%	4.4%	1.7% - 6.7%

Tissue	Diagnosis	Incidence of Selected Common Tumors in Male Mice by Diet			
		5002		5CR4	
		% with Neoplasms	Incidence Range (%)	% with Neoplasms	Incidence Range (%)
Adrenal	Cortical Adenoma	1.1%	0% - 1.7%	1.4%	0% - 3.4%
	Subcapsular Cell Adenoma	0.5%	0% - 3.3%	2.9%	0% - 5%
Harderian Gland	Adenocarcinoma	1.0%	0% - 3.3%	3.6%	1.7% - 5%
	Adenoma	8.0%	1.7% - 18%	10.8%	10% - 11%
Hemolymphoreticular Neoplasms	Histiocytic Sarcoma	2.1%	0% - 5.3%	0.7%	0% - 1.7%
	Lymphoma	6.1%	3.1% - 12%	6.4%	5% - 8.3%
Liver	Hemangiosarcoma	5.4%	1.5% - 10%	3.6%	0% - 6.3%
	Hepatocellular Adenoma	10.2%	3.3% - 20%	20.0%	17% - 23%
	Hepatocellular Carcinoma	8.8%	1.5% - 17%	3.6%	0% - 6.3%
Lung/Bronchi	Bronchioloalveolar Adenoma	17.9%	12% - 25%	15.0%	14% - 17%
	Bronchioloalveolar Carcinoma	10.7%	6.7% -17%	6.4%	0% - 11%
Parathyroid	Adenoma	0.3%	0% - 2.6%	1.0%	0% - 1.6%
Testes	Interstitial Cell Adenoma	3.0%	0% - 8.3%	2.9%	1.7% - 3.8%
Thyroid	Follicular Cell Adenoma	0.6%	0% - 3.3%	0.7%	0% - 1.7%

Tissue`	Diagnosis	Incidence of Selected Common Tumors in Female Mice by Diet			
		5002		5CR4	
		% with Neoplasms	Incidence Range (%)	% with Neoplasms	Incidence Range (%)
Adrenal	Subcapsular Cell Adenoma	2.3%	0% - 5.1%	0.7%	0% - 1.7%
Cervix	Endometrial Stromal Polyp	1.0%	0% - 1.8%	2.2%	0% - 5%
	Leiomyoma	0.5%	0% - 3.4%	1.4%	1.3% - 1.7%
Harderian Gland	Adenoma	4.5%	0% - 8.3%	2.1%	1.7% - 2.5%
Hemolymphoreticular Neoplasms	Histiocytic Sarcoma	5.6%	0% - 12%	5.0%	3.3% - 6.3%
	Lymphoma	17.4%	10% - 25%	13.6%	10% - 18%
Liver	Hepatocellular Adenoma	2.7%	0% - 5%	0.7%	0% - 1.7%
Lung/Bronchi	Bronchioloalveolar Adenoma	12.3%	8.3% - 18%	8.6%	8.3% - 8.8%
	Bronchioloalveolar Carcinoma	5.6%	1.7% - 12%	6.4%	3.3% - 8.8%
Mammary Gland	Adenocarcinoma	1.6%	0% - 4.8%	5.2%	1.7% - 7.8%
Ovary	Cystadenoma	3.2%	0% - 8.3%	0.7%	0% - 1.3%
	Luteoma	1.0%	0% - 1.7%	1.4%	0% - 2.5%
Pituitary	Adenoma	3.1%	0% - 5.4%	1.4%	0% - 3.4%
Spleen	Hemangiosarcoma	1.4%	0% - 3.3%	2.9%	1.7% - 3.8%
Uterus	Adenocarcinoma	1.4%	0% - 4.7%	2.9%	2.5% - 3.3%
	Endometrial Stromal Polyp	11.7%	6.2% - 20%	6.4%	5% - 8.3%
	Endometrial Stromal Sarcoma	4.0%	0% - 8.0%	5.0%	1.7% - 7.5%