

A 24-Month Oral Combined Chronic Toxicity/Carcinogenicity Study of Perfluorohexanoic Acid (PFHxA) in Rats

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STP 2011 June 19-23

Abstract

The dosage levels of 2.5, 15, and 100 mg/kg/day of PFHxA (males) and 5, 30, and 200 mg/kg/day of PFHxA (females) were selected for the 2-year bioassay based on a previous 13-week study (Kirkpatrick, 2006, WIL-534003). The results of this 13-week study determined that the maximum tolerated dose (MTD) for PFHxA was 100 mg/kg/day of PFHxA for males and 200 mg/kg/day of PFHxA for female rats. In the present 2 year bioassay, some systemic toxicity was evidenced at the high dosage level in both males and females based on survival and renal effects (urinalysis parameter changes in males and papillary necrosis and/or tubular degeneration in females). The no-observed-effect level (NOEL) in the two year chronically administered bioassay for non-neoplastic systemic toxicity of PFHxA was observed to be 15 mg/kg/day for males and 30 mg/kg/day for females. As there was no evidence of carcinogenicity in either male or female rats, the NOEL for neoplastic findings of PFHxA was 100 mg/kg/day for males and 200 mg/kg/day for females, the highest dosages examined.

Methods

Chemical : Perfluorohexanoic acid (PFHxA) CAS no. 307-24-4
Animals: CrI:CD(SD) male and female rats

Dosages:

Group	Number	Treatment	Dosage Level (mg/kg/day)		Number of Animals	
			Males	Females	Males	Females
1		Vehicle	0	0	60	60
2		PFHxA	2.5	5.0	60	60
3		PFHxA	15	30	60	60
4		PFHxA	100	200	70	70

Results

- Dosage levels of 2.5, 15, and 100 mg/kg/day (MTD) of PFHxA (males) and 5, 30, and 200 mg/kg/day (MTD) of PFHxA (females) were selected for the 2 year bioassay based on a 13-week range-finding study.
- After two years of daily treatment, there was no evidence that PFHxA induced tumorigenesis in male or female rats at any of the 3 dosage levels examined.
- Some systemic toxicity was evidenced in the high dose groups in both males and female rats based on survival and renal effects (urinalysis parameter changes in males and papillary necrosis and/or tubular degeneration in females).
- There were no PFHxA-related effects on body weights, food consumption, functional observational battery, clinical chemistry or motor activity assessments.

Tumor Incidence

Males

ORGAN	TUMOR	(N)	Control	Low	Mid	High	Dose Response
ADRENAL MEDULLA	TOTAL EXAMINED	(N)	60	60	60	70	
	# PHEOCHROMOCYTOMA, BENIGN	(a)	4	2	2,6890	7,356	0.8450
BRAIN	TOTAL EXAMINED	(N)	60	60	60	70	
	# ASTROCYTOMA, MALIGNANT	(a)	0	2	4	0	
KIDNEYS	TOTAL EXAMINED	(N)	60	60	60	70	
	# ADENOMA, RENAL TUBULE	(a)	0	0	0	0	
LIVER	TOTAL EXAMINED	(N)	60	60	60	70	
	# ADENOMA, HEPATOCELLULAR	(a)	3	0	0	0	
MULTIPLE ORGANS	TOTAL EXAMINED	(N)	60	60	60	70	
	# FIBROSARCOMA/FIBROMA	(a)	1	4	1,803	2,4508	0.6173
PANCREAS	TOTAL EXAMINED	(N)	60	60	60	70	
	# ADENOMA, ISLET CELL	(a)	0	0	0	0	
PARATHYROID	TOTAL EXAMINED	(N)	59	58	58	66	
	# ADENOMA	(a)	2	1,000	0,7290	0,9243	0,6697

ORGAN	TUMOR	(N)	Control	Low	Mid	High	Dose Response
PITUITARY	TOTAL EXAMINED	(N)	60	60	60	70	
	# ADENOMA, PARS DISTALIS	(a)	32	38	35	29	
SKIN	TOTAL EXAMINED	(N)	60	59	60	70	
	# PILOMATRICOMA	(a)	0	1	1	0	
SYSTEMIC TUMORS	TOTAL EXAMINED	(N)	60	60	60	70	
	# SARCOMA, HISTIOCYTIC	(a)	1	0	0	2	
TESTES	TOTAL EXAMINED	(N)	60	60	60	70	
	# INTERSTITIAL CELL TUMOR, BENIGN	(a)	1	1	0	0	
THYROID GLANDS	TOTAL EXAMINED	(N)	60	60	60	70	
	# ADENOMA, FOLLICULAR CELL	(a)	3	4	4	4	

Females

ORGAN	TUMOR	(N)	Control	Low	Mid	High	Dose Response
ADRENAL CORTEX	TOTAL EXAMINED	(N)	60	60	60	70	
	# ADENOMA, ISLET CELL	(a)	4	3	4	4	
ADRENAL MEDULLA	TOTAL EXAMINED	(N)	60	60	60	70	
	# PHEOCHROMOCYTOMA, BENIGN	(a)	1	2	1	0	
BRAIN	TOTAL EXAMINED	(N)	60	60	60	70	
	# ASTROCYTOMA, MALIGNANT	(a)	1	1	2	1	
CERVIX	TOTAL EXAMINED	(N)	60	60	60	70	
	# SARCOMA, ENDOMETRIAL STROMAL	(a)	2	3	0	1	
HEART	TOTAL EXAMINED	(N)	60	60	60	70	
	# SCHWANNOMA, MALIGNANT	(a)	0	1	1	0	
LIVER	TOTAL EXAMINED	(N)	60	60	60	70	
	# ADENOMA, HEPATOCELLULAR	(a)	0	0	1	2	
MAMMARY GLAND	TOTAL EXAMINED	(N)	60	59	60	70	
	# ADENOCARCINOMA	(a)	18	11	19	15	
MULTIPLE ORGANS	TOTAL EXAMINED	(N)	60	60	60	70	
	# SCHWANNOMA, MALIGNANT	(a)	1	1	0	0	

ORGAN	TUMOR	(N)	Control	Low	Mid	High	Dose Response
PITUITARY	TOTAL EXAMINED	(N)	60	60	60	70	
	# ADENOMA, PARS DISTALIS	(a)	51	51	54	57	
SKIN	TOTAL EXAMINED	(N)	60	60	60	70	
	# LIPOMA	(a)	0	4	1	0	
SPLEEN	TOTAL EXAMINED	(N)	60	60	60	70	
	# SARCOMA, UNDIFFERENTIATED	(a)	0	0	0	0	
SYSTEMIC TUMORS	TOTAL EXAMINED	(N)	60	60	60	70	
	# LYMPHOMA, MALIGNANT	(a)	0	0	0	2	
THYROID GLANDS	TOTAL EXAMINED	(N)	60	60	60	70	
	# ADENOMA, FOLLICULAR C-CELL	(a)	10	7	17	10	
UTERUS	TOTAL EXAMINED	(N)	60	60	60	70	
	# POLYP, ENDOMETRIAL STROMAL	(a)	2	2	2	2	

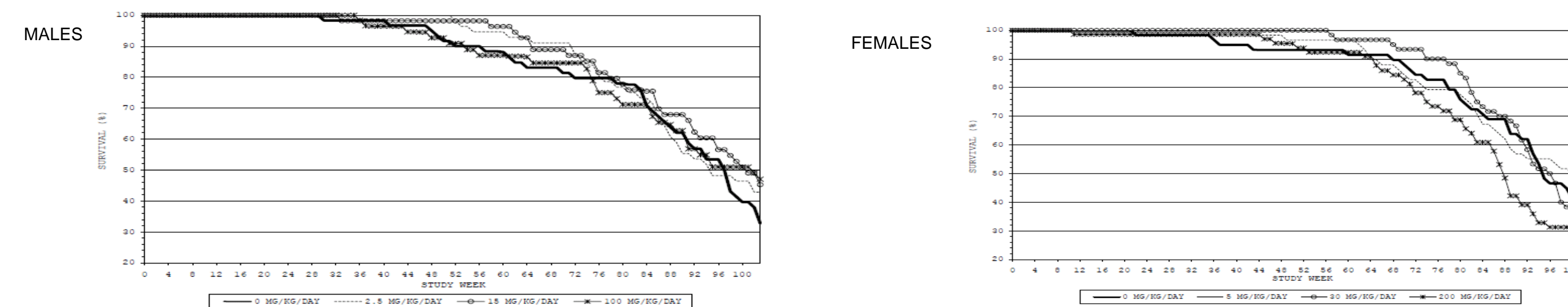
(N) NUMBER OF ANIMALS EXAMINED
(a) NUMBER OF ANIMALS WITH TUMOR
(p) P-VALUES FOR PETO ANALYSES INCLUDING CONTROL:
LISTED UNDER INDIVIDUAL TREATMENT GROUP: 1-SIDED PAIRWISE COMPARISON OF CONTROL WITH TREATMENT GROUP
LISTED UNDER 'DOSE RESPONSE': 1-SIDED TREND TEST INCLUDING CONTROL AND ACTIVE TREATMENT GROUPS

Conclusion

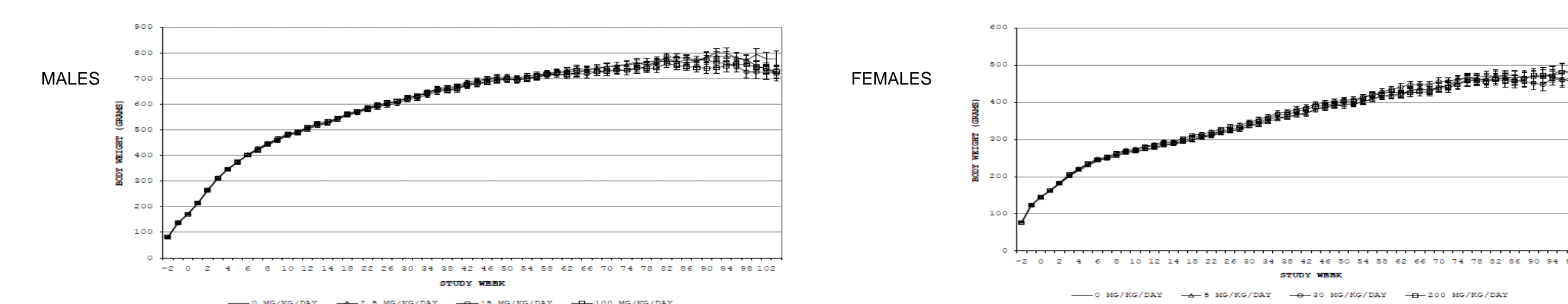
- The NOEL for neoplastic findings was determined to be 100 mg/kg/day (males), 200 mg/kg/day (females) (the highest dosages examined and the previously determined MTD)
- The NOEL for non-neoplastic systemic toxicity (Based on some survival and renal effects (urinalysis parameter changes in males and papillary necrosis and/or tubular degeneration in females) was observed to be 15 mg/kg/day for male rats and 30 mg/kg/day for female rats
- Under the conditions of this study Perfluorohexanoic Acid is not carcinogenic in rats and its chronic toxicity was low

SUMMARY OF SURVIVAL [%]

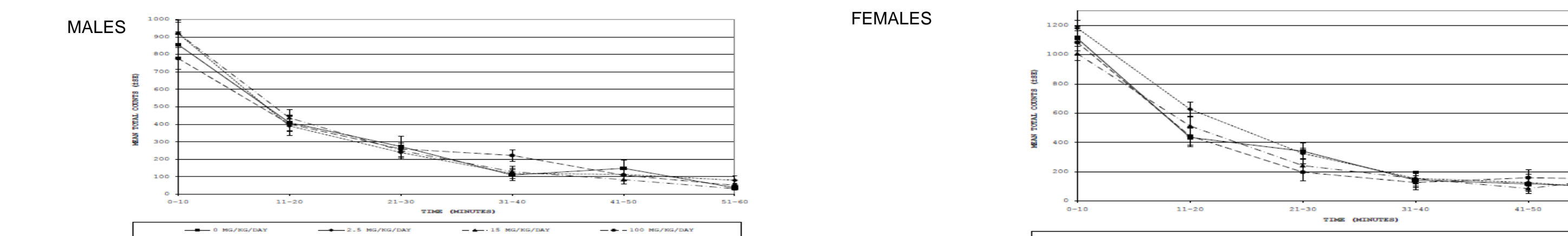
EXCLUDING ACCIDENTAL DEATHS AND REFLUX INJURY-RELATED DEATHS



SUMMARY OF BODY WEIGHTS (G)



SUMMARY OF TOTAL MOTOR ACTIVITY COUNTS : WEEK 51



SUMMARY OF TOTAL MOTOR ACTIVITY COUNTS - TOTAL COUNTS IN SESSION : WEEK 51

