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

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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.

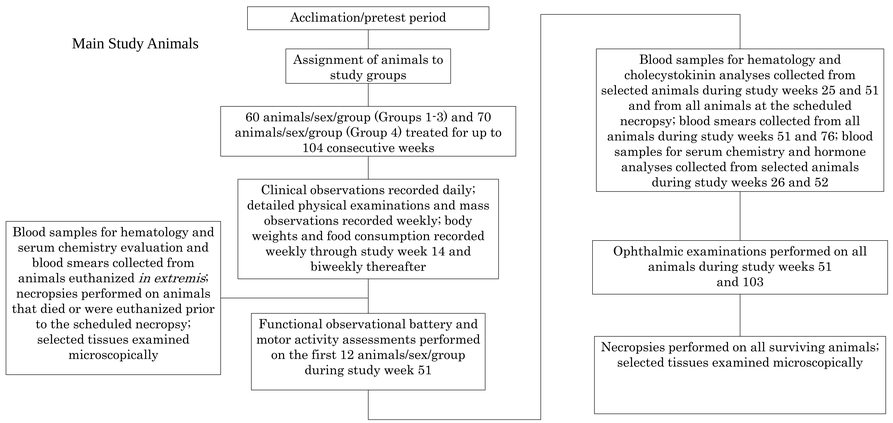
Methods

Chemical : Perfluorohexaoic acid (PFHxA) CAS no. 307-24-4

Animals: Crl:CD(SD) male and female rats

Dosages:

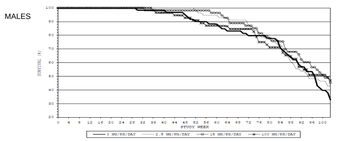
Group Number	Treatment	Dosage Level (mg/kg/day) Males	Females	Number of Animals Males	Females
1	Vechicle	0	0	60	60
2	PFHxA	2.5	5.0	60	60
3	PFHxA	15	30	60	60
4	PFHxA	100	200	70	70

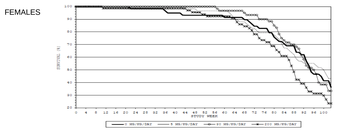


Results

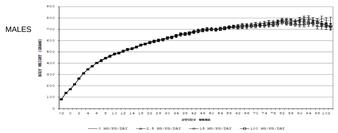
1. **Dosage levels of 2.5, 15, and 100 mg/kg/day (MTD) of PFHxA (males) and 5, 30, and 200 mg/kg/day(MTD) of PFHxA (females) were selected for the 2 year bioassay based on a 13-week range-finding study.**
2. **After two years of daily treatment, there was no evidence that PFHxA induced tumorigenesis in male or female rats at any of the 3 dosage levels examined.**
3. **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).**
4. **There were no PFHxA-related effects on body weights, food consumption, functional observational battery, clinical chemistry or motor activity assessments.**

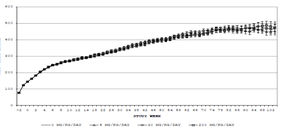
SUMMARY OF SURVIVAL [%]
EXCLUDING ACCIDENTAL DEATHS AND REFLUX INJURY-RELATED DEATHS



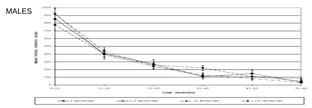


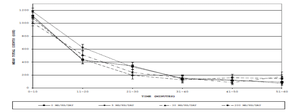
SUMMARY OF BODY WEIGHTS (G) (MEAN ± SE)



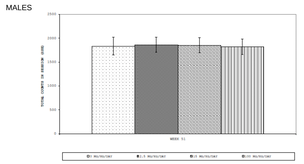


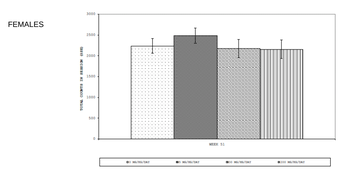
SUMMARY OF TOTAL MOTOR ACTIVITY COUNTS : WEEK 51





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





Tumor Incidence

Males

ORGAN	TUMOR		Control	Low	Mid	High	Dose Response
ADRENAL MEDULLA	TOTAL EXAMINED	(N)	60	60	60	70	
	#B PHEOCHROMOCYTOMA, BENIGN	(a)	4	4	2	1	
		(p)		0.3830	0.6890	0.7356	0.8450
BRAIN	TOTAL EXAMINED	(N)	60	60	59	70	
	#M ASTROCYTOMA, MALIGNANT	(a)	0	3	4	0	
		(p)		0.0961	0.0566	1.0000	0.5038
KIDNEYS	TOTAL EXAMINED	(N)	60	60	60	70	
	CARCINOMA/ADENOMA, RENAL TUBULE	(a)	1	2	0	0	
		(p)		0.5889	1.0000	1.0000	0.9582
	#B, ADENOMA, RENAL TUBULE	(a)	0	2	0	0	
		(p)		0.3056	1.0000	1.0000	0.8469
LIVER	TOTAL EXAMINED	(N)	60	60	60	70	
	CARCINOMA/ADENOMA, HEPATOCELLULAR	(a)	3	1	1	1	
		(p)		1.0000	0.6335	0.9148	0.7857
	#B ADENOMA, HEPATOCELLULAR	(a)	1	0	1	1	
		(p)		1.0000	0.8106	0.7017	0.4748
MULTIPLE ORGANS	TOTAL EXAMINED	(N)	60	60	60	70	
	FIBROSARCOMA/FIBROMA	(a)	1	4	2	1	
		(p)		0.1803	0.4508	0.6329	0.6173
	#M, SCHWANNOMA, MALIGNANT	(a)	1	2	0	0	
		(p)		0.5100	1.0000	1.0000	0.9444
	#B HIBERNOMA, BENIGN	(a)	1	1	0	0	
		(p)		0.1682	0.2341	0.2786	0.2311
PANCREAS	TOTAL EXAMINED	(N)	60	59	60	70	
	#M CARCINOMA, ISLET CELL	(a)	0	2	1	0	
		(p)		0.2305	0.4000	1.0000	0.5954
	#B ADENOMA, ISLET CELL	(a)	9	11	5	4	
		(p)		0.3433	0.9125	0.9241	0.9596
PARATHYROIDS	TOTAL EXAMINED	(N)	59	58	58	66	
	#B ADENOMA	(a)	2	0	2	1	
		(p)		1.0000	0.7290	0.9243	0.6697

ORGAN	TUMOR		Control	Low	Mid	High	Dose Response
PITUITARY	TOTAL EXAMINED	(N)	60	60	59	69	
	CARCINOMA/ADENOMA, PARS DISTALIS	(a)	32	38	35	29	
		(p)		0.0862	0.3955	0.5713	0.6348
	#M CARCINOMA, PARS DISTALIS	(a)	0	0	2	0	
		(p)		1.0000	0.1934	1.0000	0.2900
	#B ADENOMA, PARS DISTALIS	(a)	32	38	33	29	
		(p)		0.0862	0.5487	0.5713	0.6888
SKIN	TOTAL EXAMINED	(N)	60	59	60	70	
	#M FIBROSARCOMA	(a)	0	1	1	0	
		(p)		0.5098	0.5072	1.0000	0.6215
	#B PILOMATRICOMA	(a)	0	2	0	0	
		(p)		0.2460	1.0000	1.0000	0.8142
	#B PAPILLOMA, SQUAMOUS CELL	(a)	1	0	2	0	
		(p)		1.0000	1.0000	0.4624	0.2904
	#B KERATOACANTHOMA, BENIGN	(a)	2	1	0	0	
		(p)		0.6133	0.6330	0.3856	0.2801
	#B FIBROMA	(a)	1	0	1	1	
		(p)		0.4619	1.0000	1.0000	0.9316
SYSTEMIC TUMORS	TOTAL EXAMINED	(N)	60	60	60	70	
	#M SARCOMA, HISTIOCYTIC	(a)	1	4	3	2	
		(p)		0.2113	0.3545	0.3866	0.4171
	#M MESOTHELIOMA, MALIGNANT	(a)	0	1	1	1	
		(p)		0.5581	0.5581	0.5581	0.3539
	#M LYMPHOMA, MALIGNANT	(a)	0	1	0	1	
		(p)		0.5581	1.0000	0.5581	0.4161
	#M FIBROUS HISTIOCYTOMA, MALIGNANT	(a)	0	0	2	0	
		(p)		1.0000	0.3056	1.0000	0.4161
TESTES	TOTAL EXAMINED	(N)	60	60	60	70	
	#B INTERSTITIAL CELL TUMOR, BENIGN	(a)	1	1	1	0	
		(p)		0.7406	0.6455	1.0000	0.7820
THYROID GLANDS	TOTAL EXAMINED	(N)	60	60	60	70	
	CARCINOMA/ADENOMA, FOLLICULAR CELL	(a)	3	5	4	4	
		(p)		0.1865	0.6167	0.5747	0.3899
	#B ADENOMA, FOLLICULAR CELL	(a)	3	5	3	4	
		(p)		0.1865	0.8092	0.5747	0.4630
	#B ADENOMA, C-CELL	(a)	10	5	4	6	
		(p)		0.9104	0.9597	0.8545	0.8889

Females

ORGAN	TUMOR		Control	Low	Mid	High	Dose Response
ADRENAL CORTEX	TOTAL EXAMINED	(N)	60	60	60	70	
	#M CARCINOMA	(a)	0	0	2	0	
		(p)		1.0000	0.2959	1.0000	0.4090
	#B ADENOMA	(a)	2	1	0	2	
		(p)		0.8565	1.0000	0.8013	0.6959
ADRENAL MEDULLA	TOTAL EXAMINED	(N)	60	60	58	70	
	#B PHEOCHROMOCYTOMA, BENIGN	(a)	1	0	3	1	
		(p)		0.7558	0.3088	0.7420	0.5199
BRAIN	TOTAL EXAMINED	(N)	60	60	60	70	
	#M ASTROCYTOMA, MALIGNANT	(a)	1	0	1	1	
		(p)		1.0000	0.7497	0.7347	0.4699
	#B GRANULAR CELL TUMOR, BENIGN	(a)	0	1	0	1	
		(p)		0.5138	1.0000	0.5310	0.4012
CERVIX	TOTAL EXAMINED	(N)	60	60	60	70	
	#M SARCOMA, ENDOMETRIAL STROMAL	(a)	2	3	1	1	
		(p)		0.5239	0.8940	0.9079	0.8762
	#B GRANULAR CELL TUMOR, BENIGN	(a)	0	1	2	4	
		(p)		0.0705	0.2800	0.1063	0.0862
HEART	TOTAL EXAMINED	(N)	60	60	60	70	
	#M SCHWANNOMA, ENDOCARDIAL, MALIGNANT	(a)	0	1	1	0	
		(p)		0.5047	0.4878	1.0000	0.6032
LIVER	TOTAL EXAMINED	(N)	60	60	60	70	
	#B ADENOMA, HEPATOCELLULAR	(a)	0	0	2	0	
		(p)		1.0000	0.4878	1.0000	0.2449
MAMMARY GLAND	TOTAL EXAMINED	(N)	60	59	60	70	
	#M ADENOCARCINOMA	(a)	18	11	19	15	
		(p)		0.9555	0.583	0.7035	0.4707
	#B FIBROADENOMA	(a)	21	27	29	27	
		(p)		0.1878	0.1990	0.2271	0.2288
	#B ADENOMA	(a)	3	2	1	2	
		(p)		0.8461	0.4751	0.2602	0.1109
	ADENOCARCINOMA/ADENOMA	(a)	19	12	21	15	
		(p)		0.9704	0.4549	0.3476	0.1693
MULTIPLE ORGANS	TOTAL EXAMINED	(N)	60	60	60	70	
	FIBROSARCOMA/FIBROMA	(a)	3	0	3	1	
		(p)		1.0000	0.9435	0.9085	0.8707
	#M SCHWANNOMA, MALIGNANT	(a)	1	1	1	0	
		(p)		0.7675	0.7540	1.0000	0.8378

ORGAN	TUMOR		Control	Low	Mid	High	Dose Response
PANCREAS	TOTAL EXAMINED	(N)	60	60	60	70	
	#B ADENOMA, ISLET CELL	(a)	4	3	3	4	
		(p)		0.7170	0.6784	0.3878	0.3835
PITUITARY	TOTAL EXAMINED	(N)	60	60	60	70	
	CARCINOMA/ADENOMA, PARS DISTALIS	(a)	51	51	57	57	
		(p)		0.6506	0.6091	0.0766	0.0596
	#M CARCINOMA, PARS DISTALIS	(a)	1	0	0	1	
		(p)		1.0000	1.0000	0.4809	0.3069
	#B ADENOMA, PARS INTERMEDIA	(a)	0	1	0	1	
		(p)		0.5000	1.0000	0.6429	0.4242
	#B ADENOMA, PARS DISTALIS	(a)	50	51	54	55	
		(p)		0.5996	0.5201	0.6784	0.0668
SKIN	TOTAL EXAMINED	(N)	60	60	60	70	
	#B LIPOMA	(a)	0	4	1	0	
		(p)		0.0603	0.5122	1.0000	0.7530
SPLEEN	TOTAL EXAMINED	(N)	60	60	60	70	
	#M SARCOMA, UNDIFFERENTIATED	(a)	0	0	1	1	
		(p)		1.0000	0.5176	0.5577	0.2151
SYSTEMIC TUMORS	TOTAL EXAMINED	(N)	60	60	60	70	
	#M LYMPHOMA, MALIGNANT	(a)	0	0	0	2	
	(LARGE GRANULAR LYMPHOCYTE)	(p)		1.0000	1.0000	0.1667	0.0324
	#M LYMPHOMA, MALIGNANT	(a)	0	0	1	0	
		(p)		0.5435	1.0000	0.5143	0.3489
THYMUS	TOTAL EXAMINED	(N)	59	58	58	69	
	THYMOMA, MALIGNANT/BENIGN	(a)	0	2	0	0	
		(p)		0.3106	1.0000	1.0000	0.8244
THYROID GLANDS	TOTAL EXAMINED	(N)	60	60	60	70	
	CARCINOMA/ADENOMA, C-CELL	(a)	10	7	17	10	
		(p)		0.7906	0.1274	0.6109	0.3574
	#B ADENOMA, FOLLICULAR CELL	(a)	1	0	0	0	
		(p)		0.3779	0.4582	0.6703	0.4448
	#B ADENOMA, C-CELL	(a)	10	6	17	10	
		(p)		0.8673	0.1274	0.6109	0.3203
UTERUS	TOTAL EXAMINED	(N)	60	60	60	70	
	#B POLYP, ENDOMETRIAL STROMAL	(a)	2	2	3	2	
		(p)		0.7253	0.4993	0.7072	0.4768

(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

1. 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)
2. 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
3. ***Under the conditions of this study Perfluorohexanoic Acid is not carcinogenic in rats and its chronic toxicity was low***