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DUPONT HASKELL GLOBAL CENTERS FOR HEALTH & ENVIRONMENTAL SCIENCES
Discovery Toxicology Group

Repeated Dose Oral Toxicity 7-Day Gavage Study in Male Mice

WORK REQUEST:	17473
SERVICE CODE:	1655
HASKELL NUMBER:	28307
DUPONT REPORT NUMBER:	25281
TESTING SOP NUMBER:	DC007-T-001
STUDY START DATE:	26-October-07
STUDY END DATE:	14-December-07
NOTEBOOK(s):	E-111389-BG
STUDY DIRECTOR:	Diane L. Nabb, Staff Toxicologist
REPORT ISSUE DATE:	February 14, 2008

OBJECTIVE

To determine target organ toxicity in mice exposed to H-28307 orally for 7 days.

STUDY DESIGN

Test Substance:	HFPO Dimer Acid
Lot/Batch Number:	E112820-46MC
Purity:	99%
Species:	Mouse
Strain:	Crl:CD1(ICR)
Gender:	Male
Age at start:	~6 weeks
Group Size:	5 males
Dose Levels:	30 mg/kg
Route:	Oral gavage
Dosing Volume:	10 mL/kg
Dose Vehicle:	Water
Dosing Frequency:	Daily, Day 0-Day 6

PARAMETERS

Clinical signs, body weight, necropsy, organ weight, and histopathology.

RESULTS

The summary and individual pathology results are provided in Appendix A

Dose (mg/kg/day)	30
Deaths:	0/5
Comment:	No deaths.
Clinical Signs:	0/5
Comment:	No treatment-related clinical signs
Body Weights:	The mean body weight of the test animals on test day 7 was 106.2 ± 3.3% of control. Body weight effects compared to controls on test day 7 were significant in the 2 sample t-test ($p < 0.05$).

Dose (mg/kg/day)	0	30
Gross Path	No visible lesions	No visible lesions
Final Body Weight (g)	32.9 1.1(5)	35.0 1.1(5) 106%
Absolute Liver (g)	1.807 0.165 (5)	**4.022** **0.175(5)** **223%**
Liver/Brain %	386.305 71.174(5)	**860.549** **92.423(5)** **223%**
Liver/Body %	5.489 0.500	**11.498** **0.312(5)** **209%**
Comment:	Bold indicates statistically different from controls. Statistically significant and test substance-related organ weight changes were limited to the liver, which had approximately 2-fold elevations in all liver weight parameters.	

Dose (mg/kg/day)	0	30
Histopath		
Comment:	Test substance-related microscopic changes were limited to the liver and included the following: minimal single cell necrosis of hepatocytes, moderate hepatocellular hypertrophy, and moderate increases in mitotic figures. These changes occurred in mice administered the 30 mg/kg/day dose and were not seen in controls. Minimal vacuolation of hepatocytes was present in 2/5 treated mice. It is uncertain as to whether this change is test substance related.	

Appendix A
Summary and Individual Animal Pathology Data

Mean Final Body and Organ Weights from Male Mice

	Group 1 0 mg/kg/day	Group 2 30 mg/kg/day
MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)		
BRAIN	0.474 0.039(5)	0.471 0.041(5)
HEART	0.173 0.024(5)	0.165 0.016(5)
KIDNEYS	0.566 0.027(5)	0.610 0.069(5)
LIVER	1.807 0.165(5)	4.022* 0.175(5)
SPLEEN	0.190 0.249(5)	0.089 0.015(5)
TESTES	0.200 0.013(5)	0.205 0.025(5)
THYMUS	0.055 0.010(5)	0.053 0.012(5)
FINAL BODY WEIGHT (grams)		
	32.9 1.1(5)	35.0 1.1(5)
MEAN RELATIVE ORGAN WEIGHTS (% of body weight)		
BRAIN/ FINAL BODY * 100	1.440 0.139(5)	1.348 0.143(5)
HEART/ FINAL BODY * 100	0.524 0.070(5)	0.474 0.056(5)
KIDNEYS/ FINAL BODY * 100	1.719 0.104(5)	1.745 0.215(5)
LIVER/ FINAL BODY * 100	5.489 0.500(5)	11.498@ 0.312(5)
SPLEEN/ FINAL BODY * 100	0.575 0.745(5)	0.254 0.046(5)
TESTES/ FINAL BODY * 100	0.606 0.032(5)	0.586 0.058(5)
THYMUS/ FINAL BODY * 100	0.166 0.028(5)	0.152 0.033(5)

MEAN RELATIVE ORGAN WEIGHTS (% of brain weight)

HEART/	36.537	35.374
BRAIN * 100	4.772(5)	4.723(5)
KIDNEYS/	120.075	130.123
BRAIN * 100	11.333(5)	16.376(5)
LIVER/	386.305	860.549*
BRAIN * 100	71.174(5)	92.423(5)
SPLEEN/	39.472	18.899
BRAIN * 100	50.256(5)	3.134(5)
TESTES/	42.263	44.248
BRAIN * 100	2.855(5)	8.989(5)
THYMUS/	11.750	11.434
BRAIN * 100	3.007(5)	2.774(5)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at p < 0.05 by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at p < 0.05 by Dunn's test.

Incidences and Lesion Grades of Microscopic Findings in Male Mice
Neoplastic and Non-Neoplastic Lesions

	Group:	1	3
	Dosage (mg/kg):	0	30
	Number of Animals on Study :	5	5
BRAIN;			
Examined		(5)	(5)
Within Normal Limits		5	5
HEART;			
Examined		(5)	(5)
Within Normal Limits		4	5
Cardiomyopathy		(1)	(0)
minimal		1	0
KIDNEYS;			
Examined		(5)	(5)
Within Normal Limits		4	3
Hydronephrosis; unilateral		(1)	(1)
minimal		1	0
mild		0	1
Cyst; focal		(0)	(1)
minimal		0	1
LIVER;			
Examined		(5)	(5)
Within Normal Limits		5	0
Inflammation; subacute/chronic		(0)	(1)
minimal		0	1
Necrosis, single cell		(0)	(5)
minimal		0	5
Hypertrophy		(0)	(5)
moderate		0	5
Vacuolation		(0)	(2)
minimal		0	2
Mitotic figures; increased		(0)	(5)
moderate		0	5
NOSE;			
Examined		(5)	(5)
Within Normal Limits		5	5
SPLEEN;			
Examined		(5)	(5)
Within Normal Limits		5	5

TESTES;		
Examined	(5)	(5)
Within Normal Limits	5	5
THYMUS;		
Examined	(5)	(5)
Within Normal Limits	5	5

Individual Animal Final Body and Organ Weights

Group Sex	Animal Number	Bodywt g	Brain g	Heart g	Kidneys g	Liver g	Spleen g	Testes g	Thymus g
1m	101	33.3	0.491	0.215	0.535	1.777	0.635	0.209	0.043
	102	32.1	0.489	0.161	0.547	1.740	0.077	0.197	0.050
	103	32.6	0.411	0.158	0.564	2.071	0.081	0.179	0.065
	104	32.0	0.513	0.164	0.603	1.624	0.082	0.199	0.051
	105	34.7	0.464	0.165	0.579	1.825	0.077	0.214	0.065
	Mean	32.94	0.4736	0.1726	0.5656	1.8074	0.1904	0.1996	0.0548
	S.D.	1.11	0.0391	0.0239	0.0268	0.1650	0.2485	0.0135	0.0098
	N	5	5	5	5	5	5	5	5
3m	301	34.6	0.515	0.150	0.709	4.150	0.108	0.181	0.068
	302	36.9	0.424	0.147	0.576	4.266	0.077	0.242	0.060
	303	34.7	0.507	0.173	0.567	3.908	0.071	0.184	0.045
	304	34.5	0.434	0.183	0.653	3.867	0.096	0.207	0.056
	305	34.2	0.473	0.174	0.543	3.921	0.091	0.213	0.038
	Mean	34.98	0.4706	0.1654	0.6096	4.0224	0.0886	0.2054	0.0534
	S.D.	1.09	0.0413	0.0159	0.0692	0.1755	0.0148	0.0248	0.0119
	N	5	5	5	5	5	5	5	5

Nominal Dose: Group 1 - 0 mg/kg/day Group 3 - 30 mg/kg/day

Individual Animal Final Body and Organ Weights

Group Sex	Animal Number	Brain %FBW	Heart %FBW	Kidney %FBW	Liver %FBW	Spleen %FBW	Testes %FBW	Thymus %FBW
1m	101	1.4745	0.6456	1.6066	5.3363	1.9069	0.6276	0.1291
	102	1.5234	0.5016	1.7040	5.4206	0.2399	0.6137	0.1558
	103	1.2607	0.4847	1.7301	6.3528	0.2485	0.5491	0.1994
	104	1.6031	0.5125	1.8844	5.0750	0.2563	0.6219	0.1594
	105	1.3372	0.4755	1.6686	5.2594	0.2219	0.6167	0.1873
	Mean	1.43978	0.52398	1.71874	5.48882	0.57470	0.60580	0.16620
	S.D.	0.13916	0.06949	0.10354	0.49956	0.74483	0.03213	0.02774
	N	5	5	5	5	5	5	5
3m	301	1.4884	0.4335	2.0491	11.9942	0.3121	0.5231	0.1965
	302	1.1491	0.3984	1.5610	11.5610	0.2087	0.6558	0.1626
	303	1.4611	0.4986	1.6340	11.2622	0.2046	0.5303	0.1297
	304	1.2580	0.5304	1.8928	11.2087	0.2783	0.6000	0.1623
	305	1.3830	0.5088	1.5877	11.4649	0.2661	0.6228	0.1111
	Mean	1.34792	0.47394	1.74492	11.49820	0.25396	0.58640	0.15244
	S.D.	0.14264	0.05557	0.21520	0.31248	0.04638	0.05805	0.03304
	N	5	5	5	5	5	5	5

Nominal Dose: Group 1 - 0 mg/kg/day Group 3 - 30 mg/kg/day

Individual Animal Final Body and Organ Weights

Group Sex	Animal Number	Heart %Brain	Kidney %Brain	Liver %Brain	Spleen %Brain	Testes %Brain	Thymus %Brain
1m	101	43.7882	108.9613	361.9145	129.3279	42.5662	8.7576
	102	32.9243	111.8609	355.8282	15.7464	40.2863	10.2249
	103	38.4428	137.2263	503.8929	19.7080	43.5523	15.8151
	104	31.9688	117.5439	316.5692	15.9844	38.7914	9.9415
	105	35.5603	124.7845	393.3190	16.5948	46.1207	14.0086
	Mean	36.53688	120.07538	386.30476	39.47230	42.26338	11.74954
	S.D.	4.77195	11.33290	71.17395	50.25594	2.85462	3.00738
	N	5	5	5	5	5	5
3m	301	29.1262	137.6699	805.8252	20.9709	35.1456	13.2039
	302	34.6698	135.8491	1006.1321	18.1604	57.0755	14.1509
	303	34.1223	111.8343	770.8087	14.0039	36.2919	8.8757
	304	42.1659	150.4608	891.0138	22.1198	47.6959	12.9032
	305	36.7865	114.7992	828.9641	19.2389	45.0317	8.0338
	Mean	35.37414	130.12266	860.54878	18.89878	44.24812	11.43350
	S.D.	4.72289	16.37579	92.42316	3.13406	8.98888	2.77394
	N	5	5	5	5	5	5

Nominal Dose: Group 1 - 0 mg/kg/day Group 3 - 30 mg/kg/day