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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:	17474
SERVICE CODE:	1655
HASKELL NUMBER:	28308
DUPONT REPORT NUMBER:	24010
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-28308 orally for 7 days.

STUDY DESIGN

Test Substance:	HFPO Dimer Acid Ammonium Salt
Lot/Batch Number:	E1131181-6
Purity:	86.6% (dose corrected for purity)
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 105.4 ± 3.0% of control. Body weight effects compared to controls on test day 7 were significant in the 2-sample t-test ($p \leq 0.05$).

Dose (mg/kg/day)	0	30
Gross Path	No visible lesions	No visible lesions
Final Body Weight (g)	32.9 1.1(5)	**34.7** **1.0(5)** **105%**
Absolute Liver (g)	1.807 0.165 (5)	**3.920** **0.161(5)** **217%**
Liver/Brain %	386.305 71.174(5)	**881.997** **77.505(5)** **228%**
Liver/Body %	5.489 0.500	**11.298** **0.579(5)** **206%**
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 1/5 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)	0.447 0.036(5)
HEART	0.173 0.024(5)	0.173 0.018(5)
KIDNEYS	0.566 0.027(5)	0.601 0.041(5)
LIVER	1.807 0.165(5)	3.920* 0.161(5)
SPLEEN	0.190 0.249(5)	0.083 0.009(5)
TESTES	0.200 0.013(5)	0.212 0.025(4)
THYMUS	0.055 0.010(5)	0.043 0.018(5)
FINAL BODY WEIGHT (grams)		
	32.9 1.1(5)	34.7* 1.0(5)
MEAN RELATIVE ORGAN WEIGHTS (% of body weight)		
BRAIN/ FINAL BODY * 100	1.440 0.139(5)	1.289 0.130(5)
HEART/ FINAL BODY * 100	0.524 0.070(5)	0.497 0.046(5)
KIDNEYS/ FINAL BODY * 100	1.719 0.104(5)	1.732 0.140(5)
LIVER/ FINAL BODY * 100	5.489 0.500(5)	11.298* 0.579(5)
SPLEEN/ FINAL BODY * 100	0.575 0.745(5)	0.240 0.029(5)
TESTES/ FINAL BODY * 100	0.606 0.032(5)	0.611 0.065(4)
THYMUS/ FINAL BODY * 100	0.166 0.028(5)	0.124 0.051(5)

MEAN RELATIVE ORGAN WEIGHTS (% of brain weight)

HEART/	36.537	38.896
BRAIN * 100	4.772(5)	5.547(5)
KIDNEYS/	120.075	134.875
BRAIN * 100	11.333(5)	8.832(5)
LIVER/	386.305	881.997@
BRAIN * 100	71.174(5)	77.505(5)
SPLEEN/	39.472	18.624
BRAIN * 100	50.256(5)	1.454(5)
TESTES/	42.263	46.195
BRAIN * 100	2.855(5)	5.575(4)
THYMUS/	11.750	9.698
BRAIN * 100	3.007(5)	4.103(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	2
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	4
Hydronephrosis; unilateral	(1)	(1)
minimal	1	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)	(1)
minimal	0	1
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
2m	201	35.2	0.399	0.159	0.560	4.039	0.067	NW	0.045
	202	34.0	0.489	0.165	0.587	4.001	0.088	0.225	0.033
	203	33.4	0.469	0.165	0.645	3.903	0.087	0.185	0.047
	204	35.3	0.424	0.203	0.569	3.647	0.088	0.196	0.021
	205	35.7	0.452	0.171	0.643	4.010	0.086	0.240	0.070
	Mean	34.72	0.4466	0.1726	0.6008	3.9200	0.0832	0.2115	0.0432
	S.D.	0.97	0.0357	0.0175	0.0406	0.1610	0.0091	0.0254	0.0183
	N	5	5	5	5	5	5	4	5

NW = Not Weighed

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 - 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
2m	201	1.1335	0.4517	1.5909	11.4744	0.1903	NW	0.1278
	202	1.4382	0.4853	1.7265	11.7676	0.2588	0.6618	0.0971
	203	1.4042	0.4940	1.9311	11.6856	0.2605	0.5539	0.1407
	204	1.2011	0.5751	1.6119	10.3314	0.2493	0.5552	0.0595
	205	1.2661	0.4790	1.8011	11.2325	0.2409	0.6723	0.1961
	Mean	1.28862	0.49702	1.73230	11.29830	0.23996	0.61080	0.12424
	S.D.	0.13035	0.04643	0.14034	0.57890	0.02886	0.06510	0.05093
	N	5	5	5	5	5	4	5

NW = Not Weighed

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 - 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
2m	201	39.8496	140.3509	1012.2807	16.7920	NW	11.2782
	202	33.7423	120.0409	818.2004	17.9959	46.0123	6.7485
	203	35.1812	137.5267	832.1962	18.5501	39.4456	10.0213
	204	47.8774	134.1981	860.1415	20.7547	46.2264	4.9528
	205	37.8319	142.2566	887.1681	19.0265	53.0973	15.4867
	Mean	38.89648	134.87464	881.99738	18.62384	46.19540	9.69750
	S.D.	5.54679	8.83196	77.50544	1.45414	5.57466	4.10265
	N	5	5	5	5	4	5

NW = Not Weighed

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 - 30 mg/kg/day