GenX Toxicity Study Summary Tables for Benchmark Dose Modeling

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Foreword

The following are summary tables of data presented in toxicity studies provided by Chemours for GenX. These tables have been put together by staff for potential use in benchmark dose modeling. Only endpoints with significant differences between treatment groups and controls are presented. Additionally, endpoints were only included where significant findings showed a dose-response and where data was available for all dose groups tested. Staff relied on the statistical analysis conducted by the report authors/registrant in presenting data. Where statistical analysis was not performed by the report authors (i.e. macroscopic and microscopic findings), staff has presented data that showed an apparent dose-response trend. Some of these endpoints were deemed by the report authors/registrant to be either non-adverse or not considered related to the test substance because responses were within range of historical controls for laboratory animal strains. This information is not presented in the following summary tables. Endpoints are presented under the categories used in the original reports (i.e. hematology, clinical chemistry, etc.) and in the order presented in the original report tables the data was pulled from.

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Summary Tables

A 28-day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery

Continuous Data (Body Weight)

Cumulative Body Weight Change - Week 0-4 (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	20	3.2	1.47	
	0.1	10	2.9	1.64	
	3	10	3.4	1.32	
	30	20	5.4	1.83	significant at p=0.01
Females	0	19	1.7	1.51	
	0.1	10	2.6	0.74	
	3	10	2.6	0.85	
	30	19	3.6	1.45	significant at p=0.01

Erythrocyte Count (mil/µL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	9	8.8	0.519	
	0.1	8	8.44	0.421	
	3	8	8.28	0.401	
	30	9	8.13	0.447	significant at p=0.05
Females	No significant differences				

Hemoglobin (g/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	9	14.1	0.53	
	0.1	8	13.8	0.45	
	3	8	13.4	0.46	significant at p=0.05
	30	9	13.1	0.53	significant at p=0.01
Females	No significant differences				

Hematocrit (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	9	40.1	1.72	
	0.1	8	38.8	1.06	
	3	8	38.1	1.36	significant at p=0.05
	30	9	37.5	1.54	significant at p=0.01
Females	No significant differences				

Differential Leukocyte Count - Monocyte Percent (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	9	2.4	1.12	
	0.1	8	2.2	0.96	
	3	8	2.6	1.2	
	30	9	4.7	1.63	significant at p=0.01
Females	No significant differences				

Differential Leukocyte Count - Large Unstained Cell Percent (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	9	0.5	0.27	
	0.1	8	0.4	0.22	
	3	8	0.6	0.3	
	30	9	1.3	0.59	significant at p=0.01
Females	No significant differences				

Differential Leukocyte Count - Monocyte Absolute (thous/µL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	9	0.1	0.048	
	0.1	8	0.07	0.029	
	3	8	0.12	0.062	
	30	9	0.27	0.146	significant at p=0.01
Females	No significant differences				

Differential Leukocyte Count - Large Unstained Cell Absolute (thous/µL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	9	0.02	0.013	
	0.1	8	0.01	0.008	
	3	8	0.04	0.031	
	30	9	0.07	0.055	significant at p=0.01
Females	No significant differences				

A 28-day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery

Continuous Data (Serum Chemistry)

Albumin (g/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	3.2	0.17	
	0.1	10	3.2	0.22	
	3	10	3.3	0.18	
	30	10	4.2	0.36	significant at p=0.01
Females	0	10	3.6	0.16	
	0.1	10	3.4	0.11	
	3	10	3.5	0.21	
	30	10	3.8	0.25	significant at p=0.05

Total Protein (g/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	5.3	0.24	
	0.1	10	5.2	0.35	
	3	10	5	0.22	
	30	10	6	0.51	significant at p=0.01
Females	No significant differences				

Globulin (g/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	2.1	0.14	
	0.1	10	2.1	0.18	
	3	10	1.7	0.16	significant at p=0.01
	30	10	1.8	0.22	significant at p=0.01
Females	0	10	1.9	0.14	
	0.1	10	1.8	0.13	
	3	10	1.6	0.11	significant at p=0.01
	30	10	1.5	0.13	significant at p=0.01

A 28-day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery

Continuous Data (Serum Chemistry)

Albumin/Globulin Ratio					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	1.54	0.134	
	0.1	10	1.56	0.128	
	3	10	1.92	0.222	significant at p=0.01
	30	10	2.32	0.241	significant at p=0.01
Females	0	10	1.93	0.159	
	0.1	10	1.98	0.134	
	3	10	2.2	0.087	significant at p=0.01
	30	10	2.46	0.19	significant at p=0.01

Urea Nitrogen (mg/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	9	20.1	1.84	
	0.1	10	19.3	2.82	
	3	10	22.3	4.89	
	30	10	24.5	3.49	significant at p=0.05
Females	No significant differences				

Alkaline Phosphatase (U/L)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	88	29.5	
	0.1	10	73	18.2	
	3	10	144	51.2	
	30	10	1163	682.4	significant at p=0.01
Females	0	10	90	21.9	
	0.1	10	97	22.1	
	3	10	96	19.7	
	30	10	216	51.3	significant at p=0.01

Alanine Aminotransferase (U/L)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	52	37.2	
	0.1	10	38	11	
	3	10	82	30.8	
	30	10	704	311.9	significant at p=0.01
Females	No significant differences				

Aspartate Aminotransferase (U/L)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	72	18.5	
	0.1	10	72	13.3	
	3	10	90	38	
	30	10	416	218.3	significant at p=0.01
Females	No significant differences				

Chloride (mEq/L)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	113	2	
	0.1	10	112	1.3	
	3	9	114	1.1	
	30	9	112	1.1	significant at p=0.05
Females	No significant differences				

A 28-day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery

Continuous Data (Serum Chemistry)

Sorbitol Dehydrogenase (U/L)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	24	5.4	
	0.1	10	22	3.4	
	3	10	46	20.4	
	30	9	456	225.2	significant at p=0.01
Females	0	10	14	5.1	
	0.1	10	16	4.8	
	3	10	16	5.5	
	30	10	40	20.2	significant at p=0.01

A 28-day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery

Dichotomous Data (Macroscopic)

Enlarged Liver				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	0	10	0	
	0.1	10	0	
	3	10	0	
	30	10	7	
Females	No apparent trend			

Adrenal Gland Weight (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	0.0046	0.00101	
	0.1	10	0.0045	0.00176	
	3	10	0.0059	0.00092	
	30	10	0.0075	0.00177	significant at p=0.01
Females	No significant differences				

Adrenal Gland Weight to Final Body Weight (g/100g final body weight)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	0.013	0.003	
	0.1	10	0.013	0.0058	
	3	10	0.017	0.0032	
	30	10	0.022	0.0065	significant at p=0.01
Females	No significant differences				

Adrenal Gland Weight to Brain Weight (g/100g brain)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	0.95	0.1895	
	0.1	10	0.915	0.3706	
	3	10	1.215	0.1869	
	30	10	1.561	0.3172	significant at p=0.01
Females	No significant differences				

Liver Weight (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	1.6907	0.24208	
	0.1	10	1.8046	0.19656	
	3	10	2.9609	0.5503	significant at p=0.01
	30	10	4.5021	0.87032	significant at p=0.01
Females	0	10	1.2765	0.17847	
	0.1	10	1.41	0.13589	
	3	10	1.7115	0.23249	significant at p=0.01
	30	10	2.657	0.43326	significant at p=0.01

Liver Weight to Final Body Weight (g/100g final body weight)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	4.816	0.4493	
	0.1	10	5.282	0.3908	
	3	10	8.555	1.0672	significant at p=0.01
	30	10	12.669	1.8178	significant at p=0.01
Females	0	10	4.785	0.4267	
	0.1	10	5.156	0.3002	
	3	10	6.321	0.6333	significant at p=0.01
	30	10	9.699	1.2157	significant at p=0.01

Liver Weight to Brain Weight (g/100g brain)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	347.314	35.9339	
	0.1	10	365.446	37.5748	
	3	10	611.951	119.6603	significant at p=0.01
	30	10	948.956	204.0532	significant at p=0.01
Females	0	10	270.582	31.8333	
	0.1	10	285.47	29.77	
	3	10	347.618	38.6819	significant at p=0.01
	30	10	554.315	65.5015	significant at p=0.01

Kidney Weight (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	0.3348	0.0357	
	0.1	10	0.3717	0.01943	significant at p=0.05
	3	10	0.3521	0.02851	
	30	10	0.4038	0.03444	significant at p=0.01

Kidney Weight to Final Body Weight (g/100g final body weight)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	1.259	0.0989	
	0.1	10	1.364	0.093	significant at p=0.05
	3	10	1.303	0.0808	
	30	10	1.478	0.0746	significant at p=0.01

Kidney Weight to Brain Weight (g/100g brain)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	70.988	5.5906	
	0.1	10	75.148	2.9615	
	3	10	71.59	4.2751	
	30	10	84.553	4.0094	significant at p=0.01

Uterus Weight (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	10	0.1807	0.05967	
	0.1	10	0.1548	0.06753	
	3	10	0.1579	0.05248	
	30	10	0.1101	0.0258	significant at p=0.05

Uterus Weight to Final Body Weight (g/100g final body weight)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	10	0.681	0.2206	
	0.1	10	0.562	0.2247	
	3	10	0.588	0.2006	
	30	10	0.405	0.0985	significant at p=0.01

Uterus Weight to Brain Weight (g/100g brain)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	10	38.595	13.4197	
	0.1	10	31.328	13.6494	
	3	10	32.515	11.703	
	30	10	23.042	5.2689	significant at p=0.05

Adrenal Cortical Hypertrophy				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	0	10	0	
	0.1	10	0	
	3	10	0	
	30	10	8	8 minimal
Females	No apparent trend			

Hepatocellular Hypertrophy				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	0	10	0	
	0.1	10	0	
	3	10	10	8 mild, 2 moderate
	30	10	10	10 moderate
Females	0	10	0	
	0.1	10	0	
	3	10	10	8 minimal, 2 mild
	30	10	10	10 moderate

Liver, Increased Mitoses				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	0	10	0	
	0.1	10	0	
	3	10	0	
	30	10	9	6 minimal, 1 mild, 2 moderate
Females	0	10	0	
	0.1	10	0	
	3	10	0	
	30	10	5	2 minimal, 3 mild

Liver Necrosis, Single Cell				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	0	10	0	
	0.1	10	0	
	3	10	4	4 minimal
	30	10	10	10 minimal
Females	0	10	0	
	0.1	10	0	
	3	10	0	
	30	10	4	4 minimal

Diestrus Stage of the Estrous Cycle at Necropsy				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Females	0	10	3	
	0.1	10	6	
	3	10	5	
	30	10	10	Registrant notes that significance of these results are unclear due to similarities between treated and control groups in other estrous cycle indicators (i.e. copora lutea)

A 28-day Oral (Gavage) Toxicity Study of H-28397 in Mice with a 28-day Recovery

Notes on Data Presented

1) **Clinical Observations and Mortality not included:** Per the registrant: "All clinical findings in the test substance-treated groups were noted with similar incidence in the control group, were limited to single animals, were not noted in a dose-related manner and/or were common findings for laboratory [mice] of this age and strain."
2) Only final body weight and final cumulative body weight change data included here. Some statistical differences were observed at variable timepoints, however these were not consistent and are not presented here. See report for additional information.

A 28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-Day Recovery

Summary Tables

A 28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-Day Recovery

Continuous Data (Hematology)

Erythrocyte Count (mil/µL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	8.44	0.298	
	0.3	10	8.27	0.335	
	3	10	8.12	0.205	significant at p=0.05
	30	10	7.97	0.253	significant at p=0.01
Females	No significant differences				

Hemoglobin (g/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	16.3	0.36	
	0.3	10	16.3	0.47	
	3	10	15.8	0.42	significant at p=0.05
	30	10	15.2	0.61	significant at p=0.01
Females	No significant differences				

Hematocrit (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	45.6	1.66	
	0.3	10	44.9	1.37	
	3	10	43.4	1.4	significant at p=0.01
	30	10	42	1.6	significant at p=0.01
Females	No significant differences				

Reticulocyte (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	2.2	0.41	
	0.3	10	2.3	0.37	
	3	10	2.4	0.42	
	30	10	2.8	0.36	significant at p=0.01
Females	No significant differences				

A 28-Day Oral (Gavage) Toxicity Study of H-28397 in Rats with a 28-Day Recovery

Continuous Data (Serum Chemistry)

Albumin (g/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	4.1	0.14	
	0.3	10	4.1	0.12	
	3	10	4.3	0.19	
	30	10	4.7	0.18	significant at p=0.01
Females	No significant differences				

Globulin (g/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	2.3	0.23	
	0.3	10	2.1	0.18	
	3	10	2	0.22	significant at p=0.05
	30	10	1.8	0.14	significant at p=0.01
Females	0	10	2.3	0.17	
	3	10	2.4	0.24	
	30	10	2.4	0.2	
	300	10	2.1	0.18	significant at p=0.05

Albumin/Globulin Ratio					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	1.84	0.196	
	0.3	10	1.93	0.17	
	3	10	2.13	0.224	significant at p=0.01
	30	10	2.59	0.232	significant at p=0.01
Females	0	10	1.93	0.17	
	3	10	1.97	0.208	
	30	10	1.97	0.156	
	300	10	2.32	0.157	significant at p=0.01

Urea Nitrogen (mg/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	14.9	2.18	
	0.3	10	15	1.11	
	3	10	15.1	1.85	
	30	10	18.4	1.3	significant at p=0.01
Females	No significant differences				

Glucose (mg/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	105	14.2	
	0.3	10	95	8.9	
	3	10	105	8.2	
	30	10	121	11.3	significant at p=0.01
Females	No significant differences				

Cholesterol (mg/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	51	9.8	
	0.3	10	40	6.1	significant at p=0.05
	3	10	41	10.5	significant at p=0.05
	30	10	37	9	significant at p=0.01
Females	No significant differences				

Sorbitol Dehydrogenase (U/L)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	14	3.6	
	0.3	10	9	2.8	significant at p=0.01
	3	10	13	3.3	
	30	10	11	2.2	significant at p=0.05
Females	No significant differences				

Kidney Weight (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	3.06	0.227	
	0.3	10	3.2	0.3	
	3	10	3.36	0.237	significant at p=0.05
	30	10	3.59	0.218	significant at p=0.01
Females	No significant differences				

Kidney Weight to Final Body Weight (g/100g final body weight)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	0.888	0.0339	
	0.3	10	0.927	0.0614	
	3	10	0.93	0.0532	
	30	10	1.021	0.0662	significant at p=0.01
Females	No significant differences				

Kidney Weight to Brain Weight (g/100g brain weight)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	151.293	12.5222	
	0.3	10	159.886	15.3836	
	3	10	166.051	10.6711	
	30	10	177.201	15.0766	significant at p=0.01
Females	No significant differences				

Liver Weight (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	11.05	1.269	
	0.3	10	11.21	1	
	3	10	13.75	1.512	significant at p=0.01
	30	10	17.54	1.802	significant at p=0.01
Females	No significant differences				

Liver Weight to Final Body Weight (g/100g final body weight)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	3.199	0.1782	
	0.3	10	3.251	0.2536	
	3	10	3.794	0.2937	significant at p=0.01
	30	10	4.975	0.4315	significant at p=0.01
Females	0	10	3.409	0.1199	
	3	10	3.393	0.1681	
	30	10	3.391	0.2883	
	300	10	3.822	0.1864	significant at p=0.01

Liver Weight to Brain Weight (g/100g brain weight)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	546.486	62.2678	
	0.3	10	560.332	49.3673	
	3	10	679.305	74.8864	significant at p=0.01
	30	10	867.076	121.2461	significant at p=0.01
Females	No significant differences				

Hepatocellular Hypertrophy, Centrilobular				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence #**	**Notes**
Males	0	10	0	
	0.3	10	0	
	3	10	4	4 minimal
	30	10	7	6 minimal, 1 mild
Females	0	10	0	
	3	10	0	
	30	10	0	
	300	10	4	4 minimal

Hepatocellular Necrosis				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence #**	**Notes**
Males	0	10	0	
	0.3	10	0	
	3	10	0	
	30	10	3	3 minimal
Females	No apparent trend			

H-28548: Subchronic Toxicity 90-Day Gavage Study in Mice

Summary Tables

H-28548: Subchronic Toxicity 90-day Gavage Study in Mice

Continuous Data (Body Weight)

Overall Body Weight Gain (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	15	8	2.6	
	0.1	15	8.8	2	
	0.5	14	8.4	2.3	
	5	15	10.9	1.5	significant at p=0.05
Females	No significant differences				

Final Body Weight (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	38.7	3.4	
	0.1	10	40.3	3.2	
	0.5	10	38.9	2.4	
	5	10	44.3	2	significant at p=0.05
Females	No significant differences				

H-28548: Subchronic Toxicity 90-day Gavage Study in Mice

Continuous Data (Food Consumption)

Overall Daily Food Consumption (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	15	5.6	0.6	
	0.1	15	5.8	0.6	
	0.5	14	5.9	0.8	
	5	15	6.2	0.5	significant at p=0.05
Females	No significant differences				

Overall Daily Food Efficiency (g weight gain/g food consumed)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	15	0.015	0.004	
	0.1	15	0.017	0.004	
	0.5	14	0.016	0.003	
	5	15	0.019	0.002	significant at p=0.05
Females	No significant differences				

Mean Corpuscular (Cell) Hemoglobin Concentration (g/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	32.4	0.6	
	0.1	9	32	0.7	
	0.5	10	31.9	0.6	
	5	9	31.5	0.4	significant at p=0.05
Females	No significant differences				

Platelet Count ($x10^3/\mu L$)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	5	998	124	
	0.1	5	1124	80	
	0.5	7	1263	160	significant at p=0.05
	5	6	1257	240	significant at p=0.05
Females	No significant differences				

Aspartate Aminotransferase (U/L)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	62	11	
	0.1	10	67	21	
	0.5	10	84	21	
	5	10	128	80	significant at p=0.05
Females	No significant differences				

Alanine Aminotransferase (U/L)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	49	16	
	0.1	10	62	22	
	0.5	10	66	48	
	5	10	255	114	significant at p=0.05
Females	0	10	36	12	
	0.1	10	36	8	
	0.5	9	32	6	
	5	9	51	20	significant at p=0.05

Sorbitol Dehydrogenase (U/L)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	26.6	2.5	
	0.1	10	26	2.4	
	0.5	10	25.8	5.4	
	5	10	108.5	47.2	significant at p=0.05
Females	0	10	25.3	11.7	
	0.1	9	22.9	2	
	0.5	9	23.6	3.6	
	5	9	33.5	9.3	significant at p=0.05

Alkaline Phosphatase (U/L)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	50	12	
	0.1	10	55	22	
	0.5	10	70	30	
	5	10	617	339	significant at p=0.05
Females	0	10	65	19	
	0.1	10	77	25	
	0.5	9	72	18	
	5	9	158	38	significant at p=0.05

Bilirubin (mg/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	9	0.14	0.01	
	0.1	9	0.14	0.01	
	0.5	9	0.14	0.02	
	5	9	0.12	0.02	significant at p=0.05

Cholesterol (mg/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	133	25	
	0.1	10	125	22	
	0.5	10	134	26	
	5	10	98	30	significant at p=0.05
Females	No significant differences				

Total Protein (g/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	4.9	0.2	
	0.1	10	5	0.3	
	0.5	10	5	0.3	
	5	10	5.4	0.3	significant at p=0.05
Females	No significant differences				

Albumin (g/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	2.8	0.2	
	0.1	10	2.8	0.2	
	0.5	10	2.9	0.2	
	5	10	3.2	0.2	significant at p=0.05
Females	0	10	2.8	0.1	
	0.1	10	2.8	0.2	
	0.5	9	2.9	0.1	
	5	9	2.9	0.2	significant at p=0.05

Potassium (mmol/L)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	9	5.17	0.56	
	0.1	10	4.84	0.5	
	0.5	9	4.99	0.49	
	5	10	4.5	0.37	significant at p=0.05
Females	0	9	4.39	0.4	
	0.1	9	4.46	0.18	
	0.5	9	4.68	0.35	
	5	9	3.98	0.21	significant at p=0.05

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Continuous Data (Clinical Chemistry)

Chloride (mmol/L)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	9	109.6	2	
	0.1	10	109.3	1	
	0.5	9	109.9	1.7	
	5	10	111.5	1.3	significant at p=0.05
Females	No significant differences				

Total Bile Acids (µmol/L)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	1.2	0.3	
	0.1	10	1.2	0.3	
	0.5	10	1.4	0.5	
	5	10	11.1	6	significant at p=0.05
Females	No significant differences				

Liver Weight (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	1.955	0.265	
	0.1	10	2.024	0.169	
	0.5	10	2.186	0.267	
	5	10	5.144	1.806	significant at p=0.05
Females	0	10	1.693	0.385	
	0.1	10	1.697	0.139	
	0.5	9	1.745	0.288	
	5	9	2.867	0.993	significant at p=0.05

Brain Weight to Final Body Weight (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	1.312	0.092	
	0.1	10	1.242	0.111	
	0.5	10	1.298	0.12	
	5	9	1.125	0.073	significant at p=0.05
Females	No significant differences				

Epididymides Weight to Final Body Weight (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	0.338	0.031	
	0.1	10	0.424	0.395	
	0.5	10	0.315	0.039	
	5	10	0.268	0.06	significant at p=0.05

Liver Weight to Final Body Weight (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	5.06	0.583	
	0.1	10	5.028	0.272	
	0.5	10	5.618	0.616	
	5	10	11.637	4.113	significant at p=0.05
Females	0	10	5.225	0.542	
	0.1	10	5.309	0.602	
	0.5	9	5.337	0.44	
	5	9	8.811	2.837	significant at p=0.05

Spleen Weight to Final Body Weight (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	0.369	0.035	
	0.1	10	0.332	0.059	
	0.5	9	0.292	0.055	significant at p=0.05
	5	7	0.301	0.05	significant at p=0.05

Heart Weight to Brain Weight (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	38.416	2.275	
	0.1	10	40.694	6.963	
	0.5	10	39.552	3.998	
	5	9	43.988	4.361	significant at p=0.05
Females	No significant differences				

Kidney Weight to Brain Weight (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	122.786	14.395	
	0.1	10	119.221	12.956	
	0.5	10	122.402	13.474	
	5	9	139.565	17.752	significant at p=0.05
Females	No significant differences				

Liver Weight to Brain Weight (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	386.366	45.011	
	0.1	10	407.101	36.407	
	0.5	10	437.1	69.385	
	5	9	935.966	193.179	significant at p=0.05
Females	0	10	332.826	66.34	
	0.1	10	334.248	30.441	
	0.5	9	350.216	59.323	
	5	9	555.33	193.239	significant at p=0.05

Spleen Weight to Brain Weight (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	23.395	3.76	
	0.1	10	20.898	3.522	
	0.5	9	19.004	3.721	significant at p=0.05
	5	7	18.672	4.223	significant at p=0.05

Liver Discoloration				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	0	10	0	
	0.1	10	0	
	0.5	10	4	
	5	10	5	
Females	0	9	1	
	0.1	10	0	
	0.5	10	0	
	5	7	3	

Enlarged Liver				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	0	10	0	
	0.1	10	0	
	0.5	10	1	
	5	10	9	
Females	0	9	0	
	0.1	10	0	
	0.5	10	0	
	5	7	3	

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Dichotomous Data (Microscopic)

Kidney Hypertrophy Tubular Epithelium				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	0	10	0	
	0.1	10	0	
	0.5	10	0	
	5	10	9	9 minimal
Females	No apparent trend			

Hepatocellular Hypertrophy				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	0	10	0	
	0.1	10	0	
	0.5	10	8	8 minimal
	5	10	10	1 minimal, 9 mild
Females	0	10	0	
	0.1	10	0	
	0.5	10	0	
	5	10	10	6 minimal, 4 mild

Liver, Mitotic Figures				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	0	10	0	
	0.1	10	0	
	0.5	10	0	
	5	10	9	6 minimal, 3 mild
Females	No apparent trend			

Liver Pigment Increased, Kupffer Cells				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	0	10	0	
	0.1	10	0	
	0.5	10	0	
	5	10	10	10 minimal
Females	No apparent trend			

Single Cell Necrosis, Hepatocellular				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	0	10	0	
	0.1	10	0	
	0.5	10	0	
	5	10	10	10 minimal
Females	No apparent trend			

H-28548: Subchronic Toxicity 90-day Gavage Study in Mice

Notes on Data Presented

1) Only final body weight and overall body weight change data presented here. Some statistical differences were observed at variable timepoints, however these were not consistent and are not presented here. See report for additional information.

A 90-Day Oral (Gavage) Toxicity Study of H-28548 in Rats with a 28-Day Recovery

Summary Tables

A 90-Day Oral (Gavage) Toxicity Study of H-28548 in Rats with a 28-Day Recovery Period

Continuous Data (Food Consumption)

Overall Food Consumption (g/animal/day)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	20	27	0.8	
	0.1	10	27	1.3	
	10	10	25	0.9	significant at p=0.01
	100	16	27	1.2	
Females	0	20	18	1.1	
	10	10	18	1.3	
	100	10	17	1.5	
	1000	16	20	1.4	significant at p=0.01

Erythrocyte Count (mil/µL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	9.16	0.323	
	0.1	10	9.02	0.41	
	10	10	8.52	0.396	significant at p=0.01
	100	10	8.15	0.356	significant at p=0.01
Females	0	10	8.41	0.318	
	10	10	8.34	0.414	
	100	9	8.15	0.521	
	1000	10	6.02	1.193	significant at p=0.01

Hemoglobin (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	16.4	0.59	
	0.1	10	16.3	0.81	
	10	10	15.3	0.94	significant at p=0.01
	100	10	14.3	0.56	significant at p=0.01
Females	0	10	15.8	0.4	
	10	10	16	0.76	
	100	9	15.6	0.63	
	1000	10	12.5	2.07	significant at p=0.01

Hematocrit (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	46.8	1.5	
	0.1	10	46.3	2.53	
	10	10	43.5	2.64	significant at p=0.01
	100	10	41.2	1.36	significant at p=0.01
Females	0	10	44.4	1.4	
	10	10	44.8	2.67	
	100	9	43.2	1.99	
	1000	10	36.3	5.99	significant at p=0.01

Mean Corpuscular Volume (fL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	52.8	1.74	
	10	10	53.7	2.07	
	100	9	53.1	1.52	
	1000	10	60.9	4.36	significant at p=0.01

Mean Corpuscular Hemoglobin (pg)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	18.8	0.57	
	10	10	19.2	0.54	
	100	9	19.2	0.75	
	1000	10	20.9	1.24	significant at p=0.01

Mean Corpuscular Hemoglobin Concentration (g/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	35.7	0.76	
	10	10	35.8	0.78	
	100	9	36.1	0.78	
	1000	10	34.3	1.33	significant at p=0.01

Platelets (thous/µL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	1302	120.5	
	0.1	10	1183	95.5	
	10	10	1289	297.5	
	100	10	1521	208.2	significant at p=0.05
Females	0	10	1085	133.6	
	10	10	1168	90	
	100	9	1105	161	
	1000	10	1405	108.8	significant at p=0.01

Reticulocyte (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	1.2	0.23	
	0.1	10	1.2	0.32	
	10	10	1.5	0.35	
	100	10	2	0.62	significant at p=0.01
Females	0	10	1.3	0.28	
	10	10	1.5	0.45	
	100	9	1.1	0.35	
	1000	10	6.4	5.89	significant at p=0.01

Reticulocyte Absolute (thous/µL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	108.6	17.71	
	0.1	10	112.7	27.17	
	10	10	125.8	28.55	
	100	10	165.5	46.69	significant at p=0.01
Females	0	10	104.8	23.41	
	10	10	120.1	37.09	
	100	9	87.9	27.61	
	1000	10	326.7	167.59	significant at p=0.01

Basophil (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	0.4	0.08	
	0.1	10	0.3	0.07	
	10	10	0.3	0.14	significant at p=0.05
	100	10	0.2	0.14	significant at p=0.01
Females	0	10	0.3	0.07	
	10	10	0.3	0.15	
	100	9	0.2	0.1	
	1000	10	0.2	0.08	significant at p=0.01

Basophil Absolute (thous/µL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	0.04	0.013	
	0.1	10	0.03	0.007	
	10	10	0.03	0.012	
	100	10	0.02	0.014	significant at p=0.05
Females	No significant differences				

Albumin (g/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	4.2	0.26	
	0.1	10	4.3	0.23	
	10	10	4.6	0.23	significant at p=0.05
	100	10	4.7	0.33	significant at p=0.01
Females	No significant differences				

Total Protein (g/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	7.4	0.45	
	10	10	7.6	0.29	
	100	10	7.4	0.46	
	1000	10	6.7	0.52	significant at p=0.01

Globulin (g/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	2.6	0.17	
	0.1	10	2.5	0.22	
	10	10	2.3	0.28	significant at p=0.05
	100	10	2.2	0.25	significant at p=0.01
Females	0	10	2.4	0.27	
	10	10	2.4	0.16	
	100	10	2.3	0.23	
	1000	10	1.6	0.34	significant at p=0.01

Albumin/Globulin Ratio					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	1.64	0.179	
	0.1	10	1.73	0.195	
	10	10	2.06	0.289	significant at p=0.01
	100	10	2.22	0.357	significant at p=0.01
Females	0	10	2.13	0.233	
	10	10	2.2	0.152	
	100	10	2.19	0.24	
	1000	10	3.37	0.636	significant at p=0.01

Total Bilirubin (mg/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	0.12	0.025	
	10	10	0.12	0.025	
	100	10	0.09	0.017	significant at p=0.01
	1000	10	0.06	0.019	significant at p=0.01

Urea Nitrogen (mg/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	14.6	1.79	
	0.1	10	15.1	2.03	
	10	10	15.2	1.47	
	100	10	20.1	3.93	significant at p=0.01
Females	No significant differences				

Alkaline Phosphatase (U/L)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	80	12.9	
	0.1	10	79	15.4	
	10	10	118	30.9	
	100	10	165	41.5	significant at p=0.01
Females	0	10	58	23.4	
	10	10	53	13.8	
	100	10	46	10.2	
	1000	10	96	19.9	significant at p=0.01

Gamma Glutamyltransferase (U/L)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	1.6	0.66	
	10	10	0.9	0.53	
	100	10	0.9	0.45	
	1000	10	0.5	0.49	significant at p=0.01

Cholesterol (mg/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	68	17.7	
	0.1	10	63	7.6	
	10	10	59	14.8	
	100	10	47	8.9	significant at p=0.01
Females	0	10	81	12.8	
	10	10	81	13	
	100	10	65	14.7	significant at p=0.05
	1000	10	56	9.2	significant at p=0.01

Phosphorus (mg/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	6.3	0.26	
	0.1	10	6.7	0.35	
	10	10	6.9	0.43	significant at p=0.01
	100	10	7	0.48	significant at p=0.01
Females	0	10	6.1	1	
	10	10	6.1	1.06	
	100	10	6.4	0.39	
	1000	10	7.2	1.19	significant at p=0.05

pH					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	6.5	0.28	
	10	10	6.2	0.54	
	100	10	6.3	0.26	
	1000	10	6	0	significant at p=0.05

Total Volume (mL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	3.4	1.43	
	10	10	3.4	2.17	
	100	10	3.9	2.02	
	1000	10	12.1	4.48	significant at p=0.01

Kidney Weight (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	3.78	0.285	
	0.1	10	3.75	0.38	
	10	10	3.98	0.404	
	100	10	4.18	0.36	significant at p=0.05
Females	0	10	2.02	0.244	
	10	10	2.1	0.233	
	100	10	2.11	0.213	
	1000	10	2.39	0.155	significant at p=0.01

Kidney Weight to Final Body Weight (g/100g final body weight)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	0.721	0.063	
	0.1	10	0.693	0.0626	
	10	10	0.814	0.0764	significant at p=0.05
	100	10	0.838	0.1053	significant at p=0.01
Females	0	10	0.708	0.0638	
	10	10	0.774	0.0573	significant at p=0.05
	100	10	0.775	0.0529	significant at p=0.05
	1000	10	0.871	0.0373	significant at p=0.01

Kidney Weight to Brain Weight (g/100g brain weight)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	174.447	15.7769	
	0.1	10	173.001	14.5426	
	10	10	187.176	15.9831	
	100	10	194.72	14.8618	significant at p=0.05
Females	0	10	104.886	12.7364	
	10	10	108.258	11.4453	
	100	10	105.925	7.9978	
	1000	10	123.624	12.1872	significant at p=0.01

Liver Weight (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	14.28	1.203	
	0.1	10	14.8	1.576	
	10	10	17.53	3.443	significant at p=0.05
	100	10	22.76	3.274	significant at p=0.01
Females	0	10	7.63	0.993	
	10	10	7.65	0.625	
	100	10	7.86	1.032	
	1000	10	13.53	2.051	significant at p=0.01

Liver Weight to Final Body Weight (g/100g final body weight)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	2.716	0.1319	
	0.1	10	2.727	0.2125	
	10	10	3.556	0.4752	significant at p=0.01
	100	10	4.535	0.5144	significant at p=0.01
Females	0	10	2.667	0.1829	
	10	10	2.823	0.2161	
	100	10	2.882	0.2323	
	1000	10	4.922	0.5771	significant at p=0.01

Liver Weight to Brain Weight (g/100g brain weight)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	657.943	47.9593	
	0.1	10	682.492	66.4246	
	10	10	825.582	161.3767	significant at p=0.01
	100	10	1060.36	136.53	significant at p=0.01
Females	0	10	395.868	50.387	
	10	10	394.124	30.7584	
	100	10	394.704	42.1305	
	1000	10	699.436	106.8156	significant at p=0.01

A 90-Day Oral (Gavage) Toxicity Study of H-28548 in Rats with a 28-Day Recovery Period

Dichotomous Data (Microscopic)

Hepatocellular Hypertrophy				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence #**	**Notes**
Males	0	10	0	
	0.1	10	0	
	10	10	3	3 minimal
	100	10	10	10 minimal
Females	0	10	0	
	10	10	0	
	100	10	0	
	1000	10	10	10 minimal

1) Clinical findings were observed in the 1000 mg/kg/day females. However, statistical analysis was not performed on this data and it is not presented here.

H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary Tables

Erythrocytes - 3 months (10^6/µL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	9.251	0.4152	
	0.1	10	8.897	0.3945	
	1	10	9.127	0.262	
	50	10	8.454	0.5994	significant at p=0.01
Females	0	9	8.359	0.2972	
	1	10	8.208	0.2342	
	50	8	8.35	0.1949	
	500	10	7.295	0.9092	significant at p=0.05

Erythrocytes - 6 months (10^6/µL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	9	8.256	0.6244	
	1	10	8.28	0.5425	
	50	10	8.087	0.3277	
	500	10	6.819	1.2705	significant at p=0.05

Erythrocytes - 12 months (10^6/µL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	7.703	0.3181	
	1	10	7.483	0.5247	
	50	10	7.221	0.4492	significant at p=0.05
	500	10	5.549	0.8304	significant at p=0.01

Hemoglobin - 3 months (g/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	16.07	0.464	
	0.1	10	15.51	0.586	
	1	10	15.69	0.418	
	50	10	14.65	0.861	significant at p=0.01
Females	0	9	15.92	0.449	
	1	10	15.32	0.522	significant at p=0.05
	50	8	15.85	0.548	
	500	10	13.9	1.768	significant at p=0.05

Hemoglobin - 6 months (g/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	15.99	0.645	
	0.1	10	15.76	1.082	
	1	10	16.22	0.587	
	50	10	14.86	1.064	significant at p=0.05
Females	0	9	15.77	0.925	
	1	10	15.54	0.778	
	50	10	15.5	0.874	
	500	10	13.3	1.83	significant at p=0.01

Hemoglobin - 12 months (g/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	14.38	0.689	
	1	10	13.7	0.579	
	50	10	13.64	0.819	
	500	10	10.94	1.232	significant at p=0.01

Hematocrit - 3 months (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	48.2	1.892	
	0.1	10	46.44	1.553	
	1	10	47.47	1.477	
	50	10	44.26	2.508	significant at p=0.01
Females	0	9	45.6	1.112	
	1	10	44.33	1.81	
	50	8	45.3	1.677	
	500	10	40.27	5.601	significant at p=0.05

Hematocrit - 6 months (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	48.15	1.706	
	0.1	10	47.61	2.762	
	1	10	48.98	2.836	
	50	10	44.85	2.974	significant at p=0.05
Females	0	9	46.89	3.858	
	1	10	45.99	2.34	
	50	10	45.48	3.23	
	500	10	40.62	4.536	significant at p=0.05

Hematocrit - 12 months (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	46.46	2.082	
	1	10	44.47	2.107	
	50	10	44.05	2.935	
	500	10	37.24	4.655	significant at p=0.01

Mean Corpuscular Volume - 12 months (fL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	60.33	2.036	
	1	10	59.53	2.223	
	50	10	61.02	2.056	
	500	10	67.54	6.256	significant at p=0.05

Mean Corpuscular Hemoglobin Concentration - 12 months (g/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	30.94	0.378	
	1	10	30.87	0.683	
	50	10	30.99	0.428	
	500	10	29.46	0.662	significant at p=0.01

Activated Partial Thromboplastin Time - 12 months (sec)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	21.95	1.691	
	1	10	21.18	2.866	
	50	10	18.21	3.886	
	500	10	15.8	4.886	significant at p=0.01

Potassium - 12 months (mEq/L)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	6.18	0.938	
	1	10	6.33	0.946	
	50	10	6.08	0.947	
	500	10	7.88	2.084	significant at p=0.05

Chloride - 6 months (mEq/L)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	100.1	0.88	
	1	10	101.7	1.25	significant at p=0.05
	50	10	101.6	1.65	
	500	10	102.4	1.84	significant at p=0.01

Phosphorus - 3 months (mg/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	6.97	0.455	
	0.1	10	7.6	0.414	significant at p=0.01
	1	10	7.17	0.397	
	50	10	7.71	0.335	significant at p=0.01
Females	No significant differences				

Phosphorus - 6 months (mg/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	6.34	0.31	
	0.1	10	6.57	0.419	
	1	10	6.55	0.217	
	50	10	7.06	0.871	significant at p=0.05
Females	No significant differences				

Phosphorus - 12 months (mg/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	5.97	0.792	
	1	10	6.33	1.004	
	50	10	6.35	0.674	
	500	10	7.38	0.932	significant at p=0.01

Alkaline Phosphatase - 3 months (U/L)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	137.4	29.38	
	0.1	10	150.8	35.95	
	1	10	143.5	34.63	
	50	10	209.5	47.18	significant at p=0.01
Females	No significant differences				

Alkaline Phosphatase - 6 months (U/L)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	88.3	17.47	
	0.1	10	114.1	44.23	
	1	10	99.7	29.54	
	50	10	186.2	50.43	significant at p=0.01
Females	No significant differences				

Alkaline Phosphatase - 12 months (U/L)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	73	15.06	
	0.1	10	93.5	26.22	
	1	10	107	31.7	
	50	10	204.7	67.12	significant at p=0.01
Females	No significant differences				

Total Bilirubin - 3 months (mg/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	0.18	0.042	
	1	10	0.17	0.048	
	50	10	0.13	0.048	significant at p=0.05
	500	10	0.12	0.042	significant at p=0.05

Total Bilirubin - 6 months (mg/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	0.19	0.032	
	1	10	0.17	0.048	
	50	10	0.15	0.053	
	500	10	0.1	0	significant at p=0.01

Total Bilirubin - 12 months (mg/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	0.16	0.052	
	1	10	0.14	0.052	
	50	10	0.11	0.032	significant at p=0.05
	500	10	0.1	0	significant at p=0.01

Gamma Glutamyltransferase - 6 months (U/L)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	3	1.49	
	1	10	2.3	0.67	
	50	10	2.4	0.52	
	500	10	1.8	0.63	significant at p=0.05

Alanine Aminotransferase - 6 months (U/L)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	115.9	124.12	
	1	10	75	43.12	
	50	10	59.7	28.05	
	500	10	40	9.79	significant at p=0.05

Alanine Aminotransferase - 12 months (U/L)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	39.7	12.97	
	0.1	10	34.8	5.2	
	1	10	37.4	8.51	
	50	10	130.3	85.73	significant at p=0.05
Females	No significant differences				

Sorbitol Dehydrogenase - 12 months (U/L)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	13.32	6.006	
	0.1	10	14.47	3.873	
	1	10	15.7	4.848	
	50	10	32.08	26.424	significant at p=0.05
Females	No significant differences				

Urea Nitrogen - 3 months (mg/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	15.9	2.23	
	0.1	10	16.3	1.49	
	1	10	16.5	2.8	
	50	10	18.5	2.42	significant at p=0.05
Females	No significant differences				

Urea Nitrogen - 6 months (mg/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	12	1.15	
	0.1	10	13.3	1.25	
	1	10	12.7	1.89	
	50	10	14	1.89	significant at p=0.05
Females	No significant differences				

Urea Nitrogen - 12 months (mg/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	11.9	1.97	
	1	10	11.6	1.71	
	50	10	12.3	1.64	
	500	10	16.1	3.07	significant at p=0.01

Total Protein - 6 months (g/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	8.29	0.335	
	1	10	8.07	0.51	
	50	10	8.1	0.309	
	500	10	7.54	0.513	significant at p=0.01

Albumin - 3 months (g/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	3.5	0.115	
	0.1	10	3.61	0.145	
	1	10	3.56	0.158	
	50	10	3.87	0.2	significant at p=0.01
Females	0	10	3.95	0.196	
	1	10	4.08	0.424	
	50	10	4.17	0.287	
	500	10	4.36	0.344	significant at p=0.05

Albumin - 6 months (g/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	3.52	0.162	
	0.1	10	3.61	0.088	
	1	10	3.61	0.129	
	50	10	3.84	0.255	significant at p=0.01
Females	No significant differences				

Albumin - 12 months (g/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	3.12	0.22	
	0.1	10	3.33	0.164	
	1	10	3.38	0.169	significant at p=0.05
	50	10	3.63	0.236	significant at p=0.01
Females	No significant differences				

Globulin - 3 months (g/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	3.78	0.358	
	0.1	10	3.65	0.264	
	1	10	3.48	0.204	
	50	10	3.44	0.246	significant at p=0.05
Females	0	10	3.63	0.149	
	1	10	3.82	0.326	
	50	10	3.56	0.232	
	500	10	3.37	0.189	significant at p=0.05

Globulin - 6 months (g/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	3.85	0.172	
	1	10	3.85	0.264	
	50	10	3.6	0.189	significant at p=0.05
	500	10	3.18	0.266	significant at p=0.01

Globulin - 12 months (g/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	3.69	0.251	
	1	10	3.63	0.365	
	50	10	3.57	0.327	
	500	10	3.14	0.212	significant at p=0.01

Albumin/Globulin Ratio - 3 months					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	0.92	0.063	
	0.1	10	0.99	0.088	
	1	10	1.02	0.079	significant at p=0.05
	50	10	1.14	0.084	significant at p=0.01
Females	0	10	1.09	0.057	
	1	10	1.08	0.079	
	50	10	1.17	0.048	significant at p=0.05
	500	10	1.31	0.074	significant at p=0.01

Albumin/Globulin Ratio - 6 months					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	0.95	0.053	
	0.1	10	1.03	0.134	
	1	10	1.04	0.07	
	50	10	1.12	0.079	significant at p=0.01
Females	0	10	1.15	0.053	
	1	10	1.09	0.099	
	50	10	1.25	0.085	significant at p=0.05
	500	10	1.38	0.114	significant at p=0.01

Albumin/Globulin Ratio - 12 months					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	0.88	0.063	
	0.1	10	0.94	0.135	
	1	10	1.02	0.092	significant at p=0.05
	50	10	1.13	0.125	significant at p=0.01
Females	0	10	1.12	0.092	
	1	10	1.12	0.092	
	50	10	1.16	0.201	
	500	10	1.38	0.103	significant at p=0.01

Cholesterol - 6 months (mg/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	116.5	25.36	
	1	10	95.6	19.11	
	50	10	95.8	28.13	
	500	10	88.6	9.4	significant at p=0.05

Cholesterol - 12 months (mg/dL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	124.8	33.84	
	1	10	101.8	22.77	
	50	10	102.9	30.08	
	500	10	94.7	18.58	significant at p=0.05

Urine Volume - 6 months (mL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	5.35	2.636	
	1	10	6.55	3.059	
	50	10	6.9	5.28	
	500	10	14.9	10.503	significant at p=0.01

Urine Volume - 12 months (mL)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	10.95	5.885	
	0.1	10	5.85	3.93	significant at p=0.05
	1	10	6.7	3.787	significant at p=0.05
	50	10	6.35	3.118	significant at p=0.05
Females	0	10	10.35	3.659	
	1	10	6.33	4.477	
	50	10	8.55	4.01	
	500	10	19.6	8.096	significant at p=0.05

Urine Specific Gravity - 6 months					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	1.0541	0.01554	
	1	10	1.0452	0.01351	
	50	10	1.051	0.01787	
	500	10	1.0305	0.01137	significant at p=0.01

Urine Specific Gravity - 12 months					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	1.0406	0.01385	
	1	9	1.048	0.01254	
	50	9	1.0452	0.01853	
	500	10	1.0231	0.00438	significant at p=0.01

Urine pH - 6 months					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	7.25	0.486	
	0.1	10	7.7	0.258	
	1	10	8.05	0.497	significant at p=0.01
	50	10	8	0.527	significant at p=0.01
Females	0	10	6.8	0.422	
	1	10	7.3	0.35	significant at p=0.05
	50	10	7.1	0.394	
	500	10	7.75	0.425	significant at p=0.01

Urine pH - 12 months					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	7.55	0.438	
	0.1	9	8.17	0.5	significant at p=0.05
	1	10	8.2	0.35	significant at p=0.01
	50	10	8.1	0.394	significant at p=0.05
Females	0	10	7.25	0.354	
	1	9	7.39	0.651	
	50	10	7.35	0.412	
	500	10	8	0.408	significant at p=0.01

Brain Weight to Body Weight - Interim (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	0.4442	0.0604	
	1	10	0.4971	0.0638	
	50	10	0.4659	0.1041	
	500	10	0.5426	0.0864	significant at p=0.05

Kidney Weight to Body Weight - Interim (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	0.6308	0.0383	
	1	10	0.6753	0.0867	
	50	10	0.6828	0.1139	
	500	10	0.7855	0.1085	significant at p=0.01

Kidney Weight - Terminal (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	16	3.103	0.348	
	1	21	3.185	0.407	
	50	14	3.247	0.352	
	500	18	3.517	0.573	significant at p=0.05

Kidney Weight to Body Weight - Terminal (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	16	0.6839	0.1033	
	1	21	0.6664	0.1256	
	50	14	0.6352	0.1018	
	500	18	0.779	0.1023	significant at p=0.05

Liver Weight - Interim (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	13.2	2.508	
	1	10	11.961	1.57	
	50	10	14.754	3.576	
	500	10	17.589	2.58	significant at p=0.01

Liver Weight to Body Weight - Interim (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	10	3.2228	0.2974	
	0.1	10	3.3174	0.259	
	1	10	3.2789	0.1849	
	50	10	3.6912	0.3955	significant at p=0.01
Females	0	10	2.9249	0.2519	
	1	10	2.9744	0.3031	
	50	10	3.3096	0.3748	
	500	10	4.8773	0.5557	significant at p=0.01

Liver Weight to Brain Weight - Interim (ratio)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	6.7391	1.4803	
	1	10	6.0364	0.7165	
	50	10	7.4088	1.8336	
	500	10	9.1168	1.2927	significant at p=0.01

Liver Weight - Terminal (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	16	16.379	3.783	
	1	22	15.802	4.257	
	50	15	17.215	3.041	
	500	18	23.232	8.181	significant at p=0.01

Liver Weight to Body Weight - Terminal (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	16	3.5154	0.4327	
	1	22	3.304	0.6869	
	50	15	3.3387	0.5578	
	500	18	4.9782	0.8934	significant at p=0.01

Liver Weight to Brain Weight - Terminal (ratio)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	16	8.2118	1.8579	
	1	22	7.8181	2.2269	
	50	15	8.6551	1.2959	
	500	18	11.0377	4.3882	significant at p=0.05

Spleen Weight - Interim (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	0.694	0.086	
	1	10	0.613	0.063	
	50	10	0.614	0.11	
	500	10	0.566	0.08	significant at p=0.01

Spleen Weight to Brain Weight - Interim (ratio)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	0.3536	0.0498	
	1	10	0.3098	0.0312	
	50	10	0.3083	0.0576	
	500	10	0.2936	0.0413	significant at p=0.05

Thyroid/Parathyroid Gland Weight to Body Weight - Interim (%)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	10	0.0063	0.0011	
	1	10	0.0063	0.0008	
	50	10	0.007	0.0016	
	500	10	0.0081	0.0014	significant at p=0.01

Cataracts - Terminal				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	No significant differences			
Females	0	69	0	
	1	48	0	
	50	55	0	
	500	70	3	sig; 2 mild, 1 moderate

Kidney Dilatation, Tubular - Terminal				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	No significant differences			
Females	0	70	4	3 minimal, 1 mild
	1	70	2	2 mild
	50	70	5	5 mild
	500	70	28	sig; 11 minimal, 15 mild, 2 moderate

Kidney Edema, Papilla - Terminal				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	No significant differences			
Females	0	70	4	1 minimal, 3 mild
	1	70	1	minimal
	50	70	2	2 minimal
	500	70	43	sig; 23 minimal, 20 mild, 1 severe

Kidney Hyperplasia, Transitional Cell - Terminal				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	No significant differences			
Females	0	70	6	5 minimal, 1 mild
	1	70	3	2 minimal, 1 mild
	50	70	12	11 minimal, 1 mild
	500	70	33	sig; 29 minimal, 4 mild

Kidney Mineralization, Pelvic - Terminal				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	No significant differences			
Females	0	70	52	47 minimal, 5 mild
	1	70	63	sig; 52 minimal, 11 mild
	50	70	58	54 minimal, 4 mild
	500	70	63	sig; 51 minimal, 12 mild

Kidney Mineralization, Tubular - Terminal				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	No significant differences			
Females	0	70	25	25 minimal
	1	70	32	31 minimal, 1 mild
	50	70	28	28 minimal
	500	70	42	sig; 37 minimal, 5 mild

Kidney Necrosis, Papillary - Terminal				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	No significant differences			
Females	0	70	0	
	1	70	0	
	50	70	0	
	500	70	16	sig; 1 minimal, 3 mild, 6 moderate, 6 severe

Kidney Nephropathy, Chronic Progressive - Interim				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	No significant differences			
Females	0	10	6	5 minimal, 1 moderate
	1	10	4	3 minimal, 1 mild
	50	10	6	4 minimal, 2 mild
	500	10	9	3 minimal, 6 mild

Kidney Nephropathy, Chronic Progressive - Terminal				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	No significant differences			
Females	0	70	39	29 minimal, 9 mild, 1 moderate
	1	70	40	32 minimal, 6 mild, 2 moderate
	50	70	41	32 minimal, 8 mild, 1 moderate
	500	70	64	sig; 15 minimal, 45 mild, 4 moderate

Liver Angiectasis - Terminal				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	No significant differences			
Females	0	70	1	minimal
	1	70	0	
	50	70	3	3 mild
	500	70	5	sig; 3 minimal, 2 mild

Liver Degeneration, Cystic, Focal - Interim				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	0	10	0	
	0.1	10	0	
	1	10	0	
	50	10	3	sig; minimal
Females	No significant differences			

Liver Degeneration, Cystic, Focal - Terminal				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	0	70	24	18 minimal, 5 mild, 1 moderate
	0.1	70	24	20 minimal, 4 mild
	1	70	19	18 minimal, 1 mild
	50	70	42	sig; 27 minimal, 15 mild
Females	0	70	2	2 minimal
	1	70	2	2 minimal
	50	70	2	2 minimal
	500	70	14	sig; 12 minimal, 2 mild

Hypertrophy, Hepatocyte, Centrilobular - Interim				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	No significant differences			
Females	0	10	0	
	1	10	0	
	50	10	0	
	500	10	10	sig; 5 minimal, 5 mild

Hypertrophy, Hepatocyte, Centrilobular - Terminal				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	0	70	0	
	0.1	70	0	
	1	70	0	
	50	70	7	sig; 7 minimal
Females	0	70	0	
	1	70	0	
	50	70	3	3 minimal
	500	70	65	sig; 52 minimal, 13 mild

Hypertrophy, Hepatocyte, Panlobular - Terminal				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	No significant differences			
Females	0	70	0	
	1	70	0	
	50	70	0	
	500	70	3	sig; 3 mild

Necrosis, Hepatocytes, Centrilobular - Terminal				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	0	70	1	moderate
	0.1	70	0	
	1	70	1	severe
	50	70	5	sig; 1 minimal, 1 moderate, 3 severe
Females	0	70	1	minimal
	1	70	1	severe
	50	70	4	1 mild, 2 moderate, 1 severe
	500	70	7	sig; 3 mild, 4 moderate

Necrosis, Individual Hepatocyte - Terminal				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	No significant differences			
Females	0	70	0	
	1	70	0	
	50	70	0	
	500	70	3	sig; 1 minimal, 2 mild

Alveolar Histiocytosis - Terminal				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	No significant differences			
Females	0	70	22	20 minimal, 2 mild
	1	70	20	20 minimal
	50	70	21	21 minimal
	500	70	42	sig; 34 minimal, 8 mild

Pancreatic Acinar Cell Hyperplasia - Terminal				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	No significant differences			
Females	0	70	0	
	1	70	2	1 minimal, 1 mild
	50	70	5	sig; 3 minimal, 1 mild, 1 moderate
	500	70	5	sig; 2 minimal, 2 mild, 1 moderate
NOTE: Statistically significant in females by Cochran-Armitage Trend test, but not by Fisher Exact test				

Alopecia/Hypotrichosis - Terminal				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	No significant differences			
Females	0	70	1	1 mild
	1	48	2	2 moderate
	50	55	5	5 mild
	500	70	9	sig; 6 mild, 3 moderate

Stomach, Nonglandular Hyperplasia, Epithelia, Limiting Ridge - Terminal				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	No significant differences			
Females	0	70	0	
	1	70	0	
	50	70	0	
	500	70	9	sig; 8 minimal, 1 moderate

Tongue Hyperplasia, Squamous Cell - Terminal				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	No significant differences			
Females	0	70	2	1 mild, 1 moderate
	1	70	8	4 mild, 4 moderate
	50	70	4	1 mild, 3 moderate
	500	70	13	sig; 1 minimal, 5 mild, 7 moderate

Tongue Inflammation, Subacute/Chronic - Terminal				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	No significant differences			
Females	0	70	3	1 minimal, 1 mild, 1 moderate
	1	70	8	1 minimal, 7 mild
	50	70	4	4 mild
	500	70	13	sig; 1 minimal, 11 mild, 1 moderate

H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Notes on Data Presented

1) Neoplastic findings not presented here.
2) Body weight and body weight changes were statistically significant at variable timepoints. Due to the variable response of this endpoint, this data is not presented here. See section 4.2.3 of study report for more information.

An Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice

Summary Tables

An Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice

Continuous Data (F_0 Body Weight)

Final Body Weight (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	25	37.2	3.19	
	0.1	24	38.4	4.06	
	0.5	24	37.2	3.29	
	5	24	40.5	3.92	significant at p=0.01
Females	0	21	34.9	2.24	
	0.1	18	35.2	2.57	
	0.5	23	37	3.11	
	5	20	39.8	3.9	significant at p=0.01

An Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice

Continuous Data (F_0 Organ Weights)

Brain Weight to Final Body Weight (g/100g final body weight)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	25	1.314	0.1215	
	0.1	24	1.301	0.1316	
	0.5	24	1.329	0.1138	
	5	24	1.217	0.1173	significant at p=0.05
Females	0	21	1.413	0.0831	
	0.1	18	1.426	0.1259	
	0.5	23	1.357	0.1257	
	5	20	1.253	0.1145	significant at p=0.01

Epididymis Weight to Final Body Weight (g/100g final body weight)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males (left testis)	0	25	0.132	0.0227	
	0.1	24	0.128	0.0159	
	0.5	24	0.128	0.0161	
	5	24	0.116	0.0147	significant at p=0.01
Males (right testis)	0	25	0.135	0.0253	
	0.1	24	0.134	0.017	
	0.5	24	0.131	0.0155	
	5	24	0.119	0.0153	significant at p=0.01
Note: These paired organs were weighed separately.					

Kidney Weight (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	21	0.4773	0.04412	
	0.1	18	0.5013	0.03868	
	0.5	23	0.5046	0.04599	
	5	20	0.5771	0.04995	significant at p=0.01

Kidney Weight to Final Body Weight (g/100g final body weight)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	21	1.367	0.0981	
	0.1	18	1.427	0.0628	
	0.5	23	1.367	0.1173	
	5	20	1.456	0.1042	significant at p=0.05

Kidney Weight to Brain Weight (g/100g brain weight)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	21	97.006	8.2431	
	0.1	18	100.797	9.5287	
	0.5	23	101.248	9.5233	
	5	20	116.698	8.4777	significant at p=0.01

Liver Weight (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	25	1.8076	0.17079	
	0.1	24	1.9649	0.28554	
	0.5	24	2.2836	0.30454	significant at p=0.01
	5	24	4.372	0.87308	significant at p=0.01
Females	0	21	2.1026	0.27466	
	0.1	18	2.2687	0.21414	
	0.5	23	2.6128	0.39338	significant at p=0.01
	5	20	4.2703	0.48662	significant at p=0.01

An Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice

Continuous Data (F_0 Organ Weights)

Liver Weight to Final Body Weight (g/100g final body weight)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	25	4.862	0.3034	
	0.1	24	5.104	0.3888	
	0.5	24	6.134	0.6197	significant at p=0.01
	5	24	10.752	1.6364	significant at p=0.01
Females	0	21	6.006	0.5457	
	0.1	18	6.456	0.4066	
	0.5	23	7.05	0.8027	significant at p=0.01
	5	20	10.767	1.0681	significant at p=0.01

Liver Weight to Brain Weight (g/100g brain weight)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	25	372.934	41.0786	
	0.1	24	396.618	54.4874	
	0.5	24	465.278	63.5695	significant at p=0.01
	5	24	893.709	169.7741	significant at p=0.01
Females	0	21	427.097	51.1989	
	0.1	18	455.91	46.8862	
	0.5	23	526.053	94.2293	significant at p=0.01
	5	20	863.983	93.4767	significant at p=0.01

An Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice

Continuous Data (F_1 Body Weight)

Offspring Weight (litter as experimental unit) - PND4 (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	22	3.17	0.39	
	0.1	21	3.11	0.43	
	0.5	24	3.3	0.421	
	5	21	2.57	0.359	significant at p=0.01
Females	0	22	3.04	0.392	
	0.1	21	3.05	0.473	
	0.5	24	3.17	0.338	
	5	20	2.59	0.34	significant at p=0.01

Offspring Weight (litter as experimental unit) - PND7 (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	22	5.27	0.384	
	0.1	21	5.29	0.485	
	0.5	24	5.53	0.534	
	5	21	4.02	0.741	significant at p=0.01
Females	0	22	5.12	0.4	
	0.1	21	5.14	0.533	
	0.5	24	5.46	0.455	
	5	20	4.02	0.748	significant at p=0.01

Offspring Weight (litter as experimental unit) - PND14 (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	22	8.68	0.814	
	0.1	21	8.8	0.742	
	0.5	23	8.66	0.657	
	5	21	7	0.98	significant at p=0.01
Females	0	22	8.62	0.867	
	0.1	21	8.62	0.768	
	0.5	23	8.7	0.597	
	5	20	6.98	1.379	significant at p=0.01

An Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice

Continuous Data (F_1 Body Weight)

Offspring Weight (litter as experimental unit) - PND21 (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	21	13.52	1.376	
	0.1	18	13.78	1.37	
	0.5	23	13.87	1.284	
	5	20	10.56	1.908	significant at p=0.01
Females	0	21	13.04	1.149	
	0.1	18	13.22	1.258	
	0.5	23	13.45	1.127	
	5	18	10.73	1.54	significant at p=0.01

Offspring Weight Change (litter as experimental unit) - PND 1-4 (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	22	1.26	0.289	
	0.1	21	1.24	0.307	
	0.5	24	1.38	0.287	
	5	21	0.77	0.272	significant at p=0.01
Females	0	22	1.22	0.266	
	0.1	21	1.23	0.32	
	0.5	24	1.33	0.23	
	5	20	0.83	0.268	significant at p=0.01

Offspring Weight Change (litter as experimental unit) - PND 4-7 (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	22	2.1	0.298	
	0.1	21	2.14	0.305	
	0.5	24	2.26	0.255	
	5	21	1.43	0.531	significant at p=0.01
Females	0	22	2.09	0.29	
	0.1	21	2.09	0.292	
	0.5	24	2.26	0.248	
	5	20	1.45	0.549	significant at p=0.01

An Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice

Continuous Data (F_1 Body Weight)

Offspring Weight Change (litter as experimental unit) - PND 7-14 (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	22	3.41	0.622	
	0.1	21	3.51	0.613	
	0.5	23	3.18	0.408	
	5	21	2.99	0.462	significant at p=0.05
Females	0	22	3.51	0.689	
	0.1	21	3.49	0.597	
	0.5	23	3.28	0.419	
	5	20	2.96	0.818	significant at p=0.05

Offspring Weight Change (litter as experimental unit) - PND 14-21 (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	21	4.87	1.027	
	0.1	18	4.92	0.839	
	0.5	23	5.21	0.807	
	5	20	3.52	0.982	significant at p=0.01
Females	0	21	4.44	0.973	
	0.1	18	4.53	0.666	
	0.5	23	4.76	0.701	
	5	18	3.48	0.787	significant at p=0.01

An Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice

Continuous Data (F_1 Balanopreputial Separation)

Balanopreputial Separation (Postnatal Day)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	21	27.5	1.4	
	0.1	18	27.6	1.72	
	0.5	23	27.7	1.61	
	5	19	30.1	1.27	significant at p=0.01

An Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice

Continuous Data (F_1 Vaginal Patency)

Vaginal Patency (Postnatal Day)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	20	26.6	2.63	
	0.1	18	27.6	3.16	
	0.5	23	26	3.15	
	5	18	30	2.52	significant at p=0.01

An Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice

Continuous Data (F_1 Post-Weaning Body Weight)

Body Weight - PND21 (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	21	13.5	1.42	
	0.1	18	13.8	1.52	
	0.5	23	13.7	1.32	
	5	20	10.4	1.94	significant at p=0.01
Females	0	21	12.6	1.43	
	0.1	18	13.5	1.44	
	0.5	23	13.3	1.26	
	5	18	10.4	1.79	significant at p=0.01

Body Weight - PND28 (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	21	22.8	2.2	
	0.1	18	23.2	2.07	
	0.5	23	22.9	2.12	
	5	19	18.4	2.95	significant at p=0.01
Females	0	20	18.2	1.66	
	0.1	18	19.7	2.32	significant at p=0.05
	0.5	23	19.3	1.82	
	5	18	16.5	2.04	significant at p=0.05

Body Weight - PND35 (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	21	28.2	2.49	
	0.1	18	28.3	1.87	
	0.5	23	28.3	2.47	
	5	19	25.3	2.37	significant at p=0.01
Females	No significant differences				

An Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice

Continuous Data (F_1 Post-Weaning Body Weight)

Body Weight - PND40 (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	21	29.6	2.77	
	0.1	18	29.8	2.07	
	0.5	23	30	2.86	
	5	19	27.2	2.3	significant at p=0.01
Females	No significant differences				

Body Weight Change - PND 21-28 (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	21	9.2	1.29	
	0.1	18	9.3	1.01	
	0.5	23	9.2	1.12	
	5	19	7.8	1.67	significant at p=0.01
Females	No significant differences				

Body Weight Change - PND 28-35 (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	21	5.4	1.26	
	0.1	18	5.1	1.33	
	0.5	23	5.4	1.15	
	5	19	6.9	1.47	significant at p=0.01
Females	0	20	4.4	0.74	
	0.1	18	3.4	1.17	significant at p=0.05
	0.5	23	3.7	1.06	
	5	18	5.5	1.28	significant at p=0.01

An Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice

Continuous Data (F_1 Post-Weaning Body Weight)

Body Weight Change - PND 21-40 (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	No significant differences				
Females	0	20	11.2	1.29	
	0.1	18	10.4	1.34	
	0.5	23	10.7	1.14	
	5	18	12.9	1.93	significant at p=0.01

An Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice

Continuous Data (F_1 Food Consumption)

Food Consumption - PND 28-35 (g/animal/day)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	21	5	0.44	
	0.1	16	5	0.32	
	0.5	21	5.1	0.5	
	5	16	4.6	0.42	significant at p=0.05
Females	No significant differences				

Food Consumption - PND 35-40 (g/kg/day)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Males	0	21	166.3	17.97	
	0.1	17	168.6	22.62	
	0.5	21	185	33.46	
	5	17	192.4	43.94	significant at p=0.05
Females	No significant differences				

Kidney - Chronic Progressive Nephropathy				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	0	25	2	2 minimal
	0.1	24	1	1 minimal
	0.5	24	4	3 minimal, 1 mild
	5	24	5	5 minimal
Females	No apparent trend			

Kidney - Hypertrophy, tubular cell				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	0	25	1	1 minimal
	0.1	24	0	
	0.5	24	6	6 minimal
	5	24	18	18 minimal
Females	No apparent trend			

Hepatocellular hypertrophy, centrilobular/diffuse				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	0	25	0	
	0.1	24	0	
	0.5	24	12	7 minimal, 5 mild
	5	24	24	2 mild, 22 moderate
Females	0	24	0	
	0.1	22	0	
	0.5	24	14	14 minimal
	5	24	24	1 minimal, 10 mild, 13 moderate

Liver - mitotic figures increased				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	0	25	0	
	0.1	24	0	
	0.5	24	0	
	5	24	18	4 minimal, 14 mild
Females	0	24	0	
	0.1	22	0	
	0.5	24	0	
	5	24	5	5 minimal

Liver - necrosis, focal/multifocal				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	0	25	0	
	0.1	24	0	
	0.5	24	1	1 minimal
	5	24	1	1 minimal
Females	0	24	1	1 minimal
	0.1	22	0	
	0.5	24	3	3 minimal
	5	24	5	5 minimal

Liver - necrosis, single cell				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	0	25	1	1 minimal
	0.1	24	1	1 minimal
	0.5	24	5	5 minimal
	5	24	24	4 minimal, 17 mild, 3 moderate
Females	0	24	1	1 minimal
	0.1	22	3	3 minimal
	0.5	24	2	2 minimal
	5	24	21	17 minimal, 4 mild

An Oral (Gavage) Reproduction/Developmental Toxicity Screening Study of H-28548 in Mice

Dichotomous Data (F_0 Microscopic)

Liver - pigment, increased				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Males	0	25	0	
	0.1	24	0	
	0.5	24	0	
	5	24	21	21 minimal
Females	0	24	0	
	0.1	22	0	
	0.5	24	0	
	5	24	5	5 minimal

An Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats

Summary Tables

An Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats

Continuous Data (Maternal Body Weight)

Maternal Body Weight During Gestation - Day 20 (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	411	28.6	
	10	21	409	17.3	
	100	21	410	20.7	
	1000	21	392	20.3	significant at p=0.05

Maternal Body Weight During Gestation - Day 21/Terminal Body Weight (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	431	31.6	
	10	21	428	19	
	100	17	426	19	
	1000	14	395	22.3	significant at p=0.01

Maternal Body Weight Change During Gestation - Day 6-7 (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	4	3.4	
	10	21	4	3.7	
	100	21	2	4.2	
	1000	22	-5	7.1	significant at p=0.01

Maternal Body Weight Change During Gestation - Day 19-20 (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	18	3.5	
	10	21	18	3.7	
	100	21	18	4.1	
	1000	21	9	5.5	significant at p=0.01

An Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats

Continuous Data (Maternal Body Weight)

Maternal Body Weight Change During Gestation - Day 20-21 (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	20	6	
	10	21	19	5.2	
	100	17	17	6.2	
	1000	14	4	9.8	significant at p=0.01

Maternal Body Weight Change During Gestation - Day 6-9 (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	13	4.8	
	10	21	12	4.2	
	100	21	11	4.5	
	1000	22	2	13.4	significant at p=0.01

Maternal Body Weight Change During Gestation - Day 18-21 (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	55	9.5	
	10	21	54	7.8	
	100	17	53	7.6	
	1000	14	29	10.9	significant at p=0.01

Maternal Body Weight Change During Gestation - Day 6-21 (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	145	18.4	
	10	21	141	13.1	
	100	17	139	13.9	
	1000	14	109	17.7	significant at p=0.01

An Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats

Continuous Data (Gravid Uterine Weight)

Gravid Uterine Weight (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	116.3	20.22	
	10	21	114.7	9.22	
	100	17	104.4	13.3	significant at p=0.05
	1000	12	87.1	6.6	significant at p=0.01

An Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats

Continuous Data (Food Consumption)

Food Consumption During Gestation - Day 6-7 (g/animal/day)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	21	2.6	
	10	21	21	2	
	100	21	20	3.4	
	1000	22	14	4.9	significant at p=0.01

Food Consumption During Gestation - Day 7-8 (g/animal/day)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	22	3.3	
	10	21	21	2.8	
	100	21	21	3.2	
	1000	22	17	5.1	significant at p=0.01

Food Consumption During Gestation - Day 8-9 (g/animal/day)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	22	3.9	
	10	21	21	2.8	
	100	21	22	2.8	
	1000	22	17	4.9	significant at p=0.01

Food Consumption During Gestation - Day 9-10 (g/animal/day)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	22	3.8	
	10	21	22	2.4	
	100	21	22	2.9	
	1000	22	18	2.4	significant at p=0.01

An Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats

Continuous Data (Food Consumption)

Food Consumption During Gestation - Day 10-11 (g/animal/day)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	23	4	
	10	21	23	2.7	
	100	21	23	2.8	
	1000	22	20	4.7	significant at p=0.05

Food Consumption During Gestation - Day 12-13 (g/animal/day)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	21	22	3.3	
	10	21	23	2.4	
	100	21	24	2.8	
	1000	22	20	4	significant at p=0.05

Food Consumption During Gestation - Day 20-21 (g/animal/day)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	26	3.8	
	10	21	25	4	
	100	17	26	3.4	
	1000	14	21	5.5	significant at p=0.01

Food Consumption During Gestation - Day 6-9 (g/animal/day)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	22	2.7	
	10	21	21	1.8	
	100	21	21	2.1	
	1000	22	16	4.5	significant at p=0.01

An Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats

Continuous Data (Food Consumption)

Food Consumption During Gestation - Day 9-12 (g/animal/day)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	23	2.8	
	10	21	22	1.9	
	100	21	23	2.4	
	1000	22	19	2.5	significant at p=0.01

Food Consumption During Gestation - Day 6-21 (g/animal/day)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	23	2.4	
	10	21	23	1.8	
	100	21	24	1.9	
	1000	21	21	1.8	significant at p=0.01

Food Consumption During Gestation - Day 6-7 (g/kg/day)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	74	7.3	
	10	21	73	7	
	100	21	70	11.1	
	1000	22	50	17	significant at p=0.01

Food Consumption During Gestation - Day 7-8 (g/kg/day)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	74	9.5	
	10	21	71	8.6	
	100	21	73	9.9	
	1000	22	58	17.2	significant at p=0.01

An Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats

Continuous Data (Food Consumption)

Food Consumption During Gestation - Day 8-9 (g/kg/day)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	74	10.5	
	10	21	72	9.9	
	100	21	74	9.3	
	1000	22	60	16.2	significant at p=0.01

Food Consumption During Gestation - Day 9-10 (g/kg/day)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	73	10.2	
	10	21	72	6.4	
	100	21	73	8.3	
	1000	22	60	6.6	significant at p=0.01

Food Consumption During Gestation - Day 20-21 (g/kg/day)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	61	7	
	10	21	61	8.6	
	100	17	63	7.5	
	1000	14	53	12.6	significant at p=0.05

Food Consumption During Gestation - Day 6-9 (g/kg/day)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	74	6.3	
	10	21	72	5.9	
	100	21	73	6.4	
	1000	22	56	14.9	significant at p=0.01

An Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats

Continuous Data (Food Consumption)

Food Consumption During Gestation - Day 9-12 (g/kg/day)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	74	5.9	
	10	21	73	5.4	
	100	21	74	6.2	
	1000	22	65	9	significant at p=0.01

Food Consumption During Gestation - Day 6-21 (g/kg/day)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	69	4.3	
	10	21	70	4.4	
	100	17	71	3.7	
	1000	14	63	3.4	significant at p=0.01

An Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats

Dichotomous Data (Maternal Macroscopic)

Early Deliveries on Gestation Day 21				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Females	0	22	0	
	10	22	0	
	100	22	4	
	1000	22	9	

An Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats

Continuous Data (Organ Weights)

Maternal Liver Weight (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	14.82	1.552	
	10	21	14.93	1.308	
	100	21	16.61	1.946	significant at p=0.01
	1000	21	19.88	1.689	significant at p=0.01

Maternal Kidney Weight (g)					
Sex	**Dose (mg/kg/day)**	**N**	**Mean**	**St. Dev**	**Notes**
Females	0	22	2.07	0.225	
	10	21	2.1	0.118	
	100	21	2.15	0.187	
	1000	21	2.28	0.173	significant at p=0.01

An Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats

Dichotomous Data (Maternal Microscopic)

Hepatocellular Hypertrophy				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Females	0	22	0	
	10	22	0	
	100	22	0	
	1000	22	19	18 minimal, 1 mild

Liver Necrosis, Focal				
Sex	**Dose (mg/kg/day)**	**N**	**Incidence (#)**	**Notes**
Females	0	22	0	
	10	22	0	
	100	22	2	2 minimal
	1000	22	5	4 minimal, 1 moderate

An Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats

Continuous Data (Laparohysterectomy Data)

Combined Fetal Weights (g)				
Dose (mg/kg/day)	**N (# of litters)**	**Mean**	**St. Dev**	**Notes**
0	22	5.7	0.38	
10	21	5.6	0.24	
100	21	5.2	0.24	significant at p=0.01
1000	21	4.1	0.29	significant at p=0.01

Male Fetal Weights (g)				
Dose (mg/kg/day)	**N (# of litters)**	**Mean**	**St. Dev**	**Notes**
0	21	5.9	0.3	
10	21	5.8	0.28	
100	21	5.3	0.21	significant at p=0.01
1000	21	4.2	0.31	significant at p=0.01

Female Fetal Weights (g)				
Dose (mg/kg/day)	**N (# of litters)**	**Mean**	**St. Dev**	**Notes**
0	22	5.5	0.41	
10	21	5.5	0.22	
100	21	5.1	0.28	significant at p=0.01
1000	21	4	0.27	significant at p=0.01

Percent Male Offspring (%)				
Dose (mg/kg/day)	**N (# of litters)**	**Mean**	**St. Dev**	**Notes**
0	22	55	16.19	
10	21	48.5	13.56	
100	21	48.9	10.52	
1000	21	46.8	9.57	significant at p=0.05

An Oral (Gavage) Prenatal Developmental Toxicity Study of H-28548 in Rats

Continuous Data (Laparohysterectomy Data)

Percent Female Offspring (%)				
Dose (mg/kg/day)	**N (# of litters)**	**Mean**	**St. Dev**	**Notes**
0	22	45	16.19	
10	21	51.5	13.56	
100	21	51.1	10.52	
1000	21	53.2	9.57	significant at p=0.05

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Continuous Data (Fetal Morphology)

Percent Per Litter with Skeletal Variations (%)				
Dose (mg/kg/day)	**N (# of litters)**	**Mean**	**St. Dev**	**Notes**
0	22	10.6	14.17	
10	21	11.6	10.9	
100	21	14.7	10.42	
1000	21	30.3	27.49	significant at p=0.05, 14th rudimentary rib, 7th cervical rib

Total Percent Per Litter with Variations (%)				
Dose (mg/kg/day)	**N (# of litters)**	**Mean**	**St. Dev**	**Notes**
0	22	11.9	14.31	
10	21	12.8	10.92	
100	21	15.3	9.86	
1000	21	30.6	27.22	significant at p=0.05, 14th rudimentary rib, 7th cervical rib

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Notes on Data Presented

1) One female in the 1000 mg/kg/day group was found dead on gestation day 20. This death was reported as test-substance related.
2) Four females in the 100 mg/kg/day group and nine females in the 1000 mg/kg/day group delivered early on gestation day 21 prior to necropsy.