

Toxicology Research Laboratory

UIC The University of Illinois
at Chicago

Department of Pharmacology (M/C 868)
1940 W. Taylor St.
Chicago, Illinois 60612-7353

20100915248

DRAFT

Title Page

Draft Report for Task Order No. UIC-9
Volume 2 of 2

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

Sponsor: US Army Medical Materiel
Development Activity

Test Article: WR238605 Succinate

Contract No.: DAMD17-92-C-2001

Study Director

Barry S. Levine, D.Sc., D.A.B.T.

In-Life Phase Completed On

July 18, 1997

Performing Laboratory

TOXICOLOGY RESEARCH LABORATORY (TRL)
University of Illinois at Chicago (UIC)
Department of Pharmacology
1940 W. Taylor St.
Chicago, IL 60612-7353

The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other documentation.

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APPENDIX D
Individual Body Weights and Body Weight Gains

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 219 GROUP: 1-M SEX: MALE
DOSE: 0 (mg/kg)

ANIMAL #	DAY -2	DAY 6	DAY 13	DAY 20	DAY 27	DAY 34	DAY 41	DAY 48	DAY 55	DAY 62	DAY 69	DAY 76
8922	9.9	9.9	10.1	10.2	10.2	10.3	10.2	10.4	11.0	11.1	11.6	11.7
8915	11.3	11.1	11.2	11.3	11.2	11.4	11.2	11.3	11.4	11.4	11.6	11.6
8911	12.2	12.0	12.0	12.2	12.0	12.3	12.3	12.5	12.6	12.6	12.8	12.7
8909	13.1	13.1	13.0	12.9	12.9	13.1	13.0	13.0	13.1	12.9	12.9	12.5
MEAN	11.6	11.5	11.6	11.7	11.6	11.8	11.7	11.8	12.0	12.0	12.2	12.1
S.D.	1.36	1.36	1.23	1.17	1.15	1.20	1.23	1.17	0.99	0.88	0.72	0.56
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 1-M SEX: MALE
DOSE: 0 (mg/kg)

ANIMAL #	DAY 83	DAY 90	DAY 97	DAY 104	DAY 111	DAY 118	DAY 125	DAY 132	DAY 139	DAY 146	DAY 153	DAY 160
8922	11.7	11.5	11.4	11.5	11.5	11.7	11.6	11.7	12.0	12.1	12.3	12.3
8915	11.8	11.7	11.6	11.7	11.8	11.8	11.3	11.6	11.7	11.7	11.7	11.6
8911	12.8	12.5	12.6	12.7	12.7	13.1	12.9	12.7	12.8	12.9	13.1	13.3
8909	12.7	12.8	12.7	12.8	12.8	12.9	12.8	12.8	12.9	13.1	13.1	12.9
MEAN	12.3	12.1	12.1	12.2	12.2	12.4	12.2	12.2	12.4	12.5	12.6	12.5
S.D.	0.58	0.62	0.67	0.67	0.65	0.73	0.82	0.64	0.59	0.66	0.68	0.74
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 1-M SEX: MALE
DOSE: 0 (mg/kg)

ANIMAL #	DAY 167	DAY 174	DAY 181	DAY 188	DAY 195	DAY 202	DAY 209	DAY 216	DAY 223	DAY 230	DAY 237	DAY 244
8922	12.9	12.1	12.1	12.1	11.7	11.9	11.9	12.0	12.4	12.1	11.9	12.7
8915	12.1	11.7	11.9	12.0	11.9	11.9	11.8	12.1	12.0	11.8	12.2	12.3
8911	13.4	13.0	13.2	12.9	13.0	13.0	13.1	12.9	12.8	12.9	13.3	13.6
8909	13.5	13.0	12.8	12.8	13.0	12.8	12.9	13.0	12.8	12.8	12.6	13.2
MEAN	13.0	12.5	12.5	12.5	12.4	12.4	12.4	12.5	12.5	12.4	12.5	13.0
S.D.	0.64	0.66	0.61	0.47	0.70	0.58	0.67	0.52	0.38	0.54	0.61	0.57
N	4	4	4	4	4	4	4	4	4	4	4	4

---: Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 219

GROUP: 1-M
DOSE: 0 (mg/kg)

SEX: MALE

ANIMAL #	DAY 251	DAY 258	DAY 265	DAY 272	DAY 279	DAY 286	DAY 293	DAY 300	DAY 307	DAY 314	DAY 321	DAY 328
8922	12.5	12.6	12.5	12.6	12.2	12.3	12.3	12.3	12.3	12.3	12.6	12.8
8915	12.5	12.5	12.6	13.2	13.2	12.8	12.8	12.8	12.9	12.9	13.3	13.0
8911	13.3	13.3	13.4	14.1	14.0	13.6	13.5	13.4	13.4	13.7	13.9	13.8
8909	13.2	13.2	13.4	14.3	13.9	13.7	13.6	13.5	14.0	13.9	14.6	14.5
MEAN	12.9	12.9	13.0	13.6	13.3	13.1	13.1	13.0	13.2	13.2	13.6	13.5
S.D.	0.43	0.41	0.49	0.79	0.83	0.67	0.61	0.56	0.72	0.74	0.85	0.78
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 1-M
DOSE: 0 (mg/kg)

SEX: MALE

ANIMAL #	DAY 335	DAY 342	DAY 349	DAY 356	DAY 363
8922	12.6	12.5	12.6	13.0	12.4
8915	13.2	13.4	13.3	13.3	13.0
8911	13.7	13.7	14.0	14.4	14.0
8909	14.5	14.3	14.4	14.7	14.2
MEAN	13.5	13.5	13.6	13.9	13.4
S.D.	0.80	0.75	0.79	0.83	0.85
N	4	4	4	4	4

--: Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 219 GROUP: 2-M SEX: MALE
DOSE: 0.1 (mg/kg)

ANIMAL #	DAY -2	DAY 6	DAY 13	DAY 20	DAY 27	DAY 34	DAY 41	DAY 48	DAY 55	DAY 62	DAY 69	DAY 76
8923	11.2	11.0	11.2	10.8	11.0	11.0	10.7	10.7	10.9	10.9	11.0	11.0
8907	11.5	11.0	11.0	11.1	10.6	11.0	10.9	11.1	11.4	11.4	11.4	11.4
8919	12.1	11.8	11.7	12.1	11.6	11.5	11.5	11.4	11.4	11.5	11.3	11.5
8924	12.6	12.3	12.0	12.0	11.8	12.0	11.8	11.6	11.9	11.8	11.8	12.0
MEAN	11.9	11.5	11.5	11.5	11.3	11.4	11.2	11.2	11.4	11.4	11.4	11.5
S.D.	0.62	0.64	0.46	0.65	0.55	0.48	0.51	0.39	0.41	0.37	0.33	0.41
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 2-M SEX: MALE
DOSE: 0.1 (mg/kg)

ANIMAL #	DAY 83	DAY 90	DAY 97	DAY 104	DAY 111	DAY 118	DAY 125	DAY 132	DAY 139	DAY 146	DAY 153	DAY 160
8923	11.5	11.5	11.0	11.2	11.1	11.0	10.8	11.0	11.0	11.3	11.5	11.7
8907	11.6	11.5	11.6	11.8	11.8	12.0	12.3	12.3	12.2	12.5	12.4	12.4
8919	11.8	11.2	11.2	11.4	11.6	11.7	11.5	11.5	11.7	11.6	11.7	11.7
8924	12.0	11.9	11.8	12.0	11.9	11.7	11.5	11.7	11.8	11.8	11.9	12.0
MEAN	11.7	11.5	11.4	11.6	11.6	11.6	11.5	11.6	11.7	11.8	11.9	12.0
S.D.	0.22	0.29	0.37	0.37	0.36	0.42	0.61	0.54	0.50	0.51	0.39	0.33
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 2-M SEX: MALE
DOSE: 0.1 (mg/kg)

ANIMAL #	DAY 167	DAY 174	DAY 181	DAY 188	DAY 195	DAY 202	DAY 209	DAY 216	DAY 223	DAY 230	DAY 237	DAY 244
8923	12.0	11.7	11.7	11.9	11.8	11.9	11.9	11.8	11.8	11.4	11.8	12.1
8907	12.8	12.6	12.1	12.3	11.9	12.3	12.3	12.5	12.5	12.6	12.3	12.6
8919	12.2	11.9	11.7	12.0	11.6	11.9	11.7	11.8	11.4	11.3	11.6	11.9
8924	12.5	12.2	12.4	12.6	12.9	12.9	13.0	13.0	13.1	13.1	13.6	13.7
MEAN	12.4	12.1	12.0	12.2	12.1	12.3	12.2	12.3	12.2	12.1	12.3	12.6
S.D.	0.35	0.39	0.34	0.32	0.58	0.47	0.57	0.59	0.75	0.89	0.90	0.81
N	4	4	4	4	4	4	4	4	4	4	4	4

--: Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 219

GROUP: 2-M
DOSE: 0.1 (mg/kg)

SEX: MALE

ANIMAL #	DAY 251	DAY 258	DAY 265	DAY 272	DAY 279	DAY 286	DAY 293	DAY 300	DAY 307	DAY 314	DAY 321	DAY 328
8923	12.5	12.5	12.6	13.2	13.2	12.6	12.2	12.3	12.4	12.4	12.6	12.6
8907	12.8	12.9	12.9	13.5	12.7	12.7	12.5	12.4	12.7	12.9	13.1	13.4
8919	11.9	12.0	12.0	12.3	12.1	12.1	12.1	12.2	12.2	12.3	12.5	12.6
8924	13.6	13.5	14.0	14.2	14.3	14.2	14.0	14.4	14.6	14.4	14.2	14.2
MEAN	12.7	12.7	12.9	13.3	13.1	12.9	12.7	12.8	13.0	13.0	13.1	13.2
S.D.	0.71	0.63	0.84	0.79	0.93	0.91	0.88	1.05	1.10	0.97	0.78	0.77
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 2-M
DOSE: 0.1 (mg/kg)

SEX: MALE

ANIMAL #	DAY 335	DAY 342	DAY 349	DAY 356	DAY 363
8923	12.9	12.4	12.5	12.7	12.5
8907	13.3	13.4	13.6	13.6	13.0
8919	12.5	12.3	12.3	12.3	12.1
8924	14.1	14.3	14.3	14.6	14.6
MEAN	13.2	13.1	13.2	13.3	13.1
S.D.	0.68	0.94	0.94	1.02	1.10
N	4	4	4	4	4

---: Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 219 GROUP: 3-M SEX: MALE
DOSE: 1.0 (mg/kg)

ANIMAL #	DAY -2	DAY 6	DAY 13	DAY 20	DAY 27	DAY 34	DAY 41	DAY 48	DAY 55	DAY 62	DAY 69	DAY 76
8917	11.0	11.1	11.3	11.4	11.3	11.4	11.3	11.1	11.4	11.3	11.4	11.8
8910	11.6	11.4	11.2	11.1	10.8	10.9	10.8	10.9	11.0	11.0	11.1	11.2
8913	12.0	11.6	11.5	11.2	10.9	10.8	10.8	10.7	11.0	11.1	11.2	11.4
8914	12.3	12.2	12.0	12.0	12.0	11.9	11.9	11.8	12.1	12.0	12.0	12.0
MEAN	11.7	11.6	11.5	11.4	11.3	11.3	11.2	11.1	11.4	11.4	11.4	11.6
S.D.	0.56	0.46	0.36	0.40	0.54	0.51	0.52	0.48	0.52	0.45	0.40	0.37
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 3-M SEX: MALE
DOSE: 1.0 (mg/kg)

ANIMAL #	DAY 83	DAY 90	DAY 97	DAY 104	DAY 111	DAY 118	DAY 125	DAY 132	DAY 139	DAY 146	DAY 153	DAY 160
8917	11.9	11.7	11.9	12.0	11.8	11.9	11.7	11.6	11.8	12.1	12.0	11.9
8910	11.2	11.2	11.2	11.1	11.0	11.0	10.9	10.9	11.1	11.0	11.1	11.0
8913	11.3	11.0	11.1	11.1	10.9	10.6	10.6	10.3	10.8	10.7	10.5	10.4
8914	12.0	11.9	12.0	12.1	12.1	11.8	11.9	11.7	11.7	11.8	12.0	12.0
MEAN	11.6	11.5	11.6	11.6	11.5	11.3	11.3	11.1	11.4	11.4	11.4	11.3
S.D.	0.41	0.42	0.47	0.55	0.59	0.63	0.62	0.66	0.48	0.66	0.73	0.76
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 3-M SEX: MALE
DOSE: 1.0 (mg/kg)

ANIMAL #	DAY 167	DAY 174	DAY 181	DAY 188	DAY 195	DAY 202	DAY 209	DAY 216	DAY 223	DAY 230	DAY 237	DAY 244
8917	12.4	12.3	12.0	12.0	12.0	12.5	12.4	12.5	12.5	12.4	12.1	12.5
8910	11.7	11.3	11.1	11.0	8.5	10.9	10.9	11.0	10.9	10.9	11.3	11.2
8913	11.1	10.7	10.5	10.7	10.6	10.6	10.4	10.5	10.5	9.7	10.2	10.5
8914	12.6	12.4	12.3	12.4	12.6	12.5	12.5	12.7	12.7	12.6	13.1	13.2
MEAN	12.0	11.7	11.5	11.5	10.9	11.6	11.6	11.7	11.7	11.4	11.7	11.9
S.D.	0.69	0.82	0.83	0.81	1.82	1.02	1.06	1.09	1.11	1.36	1.23	1.22
N	4	4	4	4	4	4	4	4	4	4	4	4

--- Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 219

GROUP: 3-M
DOSE: 1.0 (mg/kg)

SEX: MALE

ANIMAL #	DAY 251	DAY 258	DAY 265	DAY 272	DAY 279	DAY 286	DAY 293	DAY 300	DAY 307	DAY 314	DAY 321	DAY 328
8917	12.0	12.6	12.8	12.7	12.6	12.8	12.3	12.4	12.5	12.5	12.8	12.8
8910	11.5	11.5	11.4	12.0	11.6	11.5	11.5	11.4	11.4	11.5	11.9	11.7
8913	10.6	10.7	10.8	11.7	11.1	11.1	10.8	10.5	10.8	10.6	10.9	11.0
8914	13.1	13.0	13.3	13.8	13.4	13.1	13.1	13.1	13.3	12.7	13.0	13.2
MEAN	11.8	12.0	12.1	12.6	12.2	12.1	11.9	11.9	12.0	11.8	12.2	12.2
S.D.	1.04	1.05	1.17	0.93	1.03	0.97	0.99	1.14	1.12	0.97	0.96	1.01
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 3-M
DOSE: 1.0 (mg/kg)

SEX: MALE

ANIMAL #	DAY 335	DAY 342	DAY 349	DAY 356	DAY 363
8917	13.0	12.8	12.7	12.6	12.5
8910	11.6	11.4	11.3	11.5	11.5
8913	11.3	11.0	11.1	11.5	11.0
8914	13.0	13.0	13.2	13.5	13.0
MEAN	12.2	12.1	12.1	12.3	12.0
S.D.	0.90	1.00	1.03	0.97	0.91
N	4	4	4	4	4

--: Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 219 GROUP: 4-M SEX: MALE
DOSE: 4.0 (mg/kg)

ANIMAL #	OAY -2	DAY 6	DAY 13	DAY 20	OAY 27	OAY 34	OAY 41	OAY 48	OAY 55	DAY 62	DAY 69	OAY 76
8918	10.8	10.8	10.7	10.6	10.3	10.7	10.8	10.8	10.9	10.8	10.9	11.2
8908	11.8	11.7	11.6	11.7	11.5	11.5	11.5	11.6	11.7	11.7	11.8	11.9
8926	12.0	11.5	11.6	11.5	11.3	11.3	11.2	11.2	11.2	11.4	11.6	11.6
8921	12.3	12.1	12.0	11.8	11.6	11.6	11.5	11.6	11.6	11.7	11.8	11.8
MEAN	11.7	11.5	11.5	11.4	11.2	11.3	11.3	11.3	11.4	11.4	11.5	11.6
S.D.	0.65	0.54	0.55	0.55	0.60	0.40	0.33	0.38	0.37	0.42	0.43	0.31
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 4-M SEX: MALE
DOSE: 4.0 (mg/kg)

ANIMAL #	DAY 83	DAY 90	DAY 97	DAY 104	DAY 111	DAY 118	OAY 125	DAY 132	DAY 139	DAY 146	DAY 153	DAY 160
8918	11.2	11.1	11.2	11.3	11.3	11.3	11.1	11.2	11.3	11.3	11.4	11.3
8908	11.9	11.7	11.6	11.7	11.5	11.5	11.3	11.2	11.2	11.0	11.0	11.2
8926	11.6	11.3	11.0	11.3	11.2	11.1	11.1	11.0	11.0	11.0	11.1	11.0
8921	11.8	11.7	11.4	11.6	11.5	11.0	11.0	10.9	11.3	11.3	11.3	11.4
MEAN	11.6	11.5	11.3	11.5	11.4	11.2	11.1	11.1	11.2	11.2	11.2	11.2
S.D.	0.31	0.30	0.26	0.21	0.15	0.22	0.13	0.15	0.14	0.17	0.18	0.17
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 4-M SEX: MALE
DOSE: 4.0 (mg/kg)

ANIMAL #	DAY 167	DAY 174	DAY 181	DAY 188	DAY 195	DAY 202	DAY 209	DAY 216	DAY 223	DAY 230	OAY 237	DAY 244
8918	11.6	11.4	11.1	11.0	11.0	11.2	11.2	11.3	11.3	11.4	11.0	11.2
8908	11.8	11.4	11.2	11.4	10.8	11.0	10.8	10.9	10.9	11.0	11.1	11.2
8926	11.0	10.2	10.4	10.5	10.5	10.4	10.4	10.6	10.7	10.4	10.2	10.7
8921	11.8	11.4	11.5	11.8	11.9	11.9	12.0	12.1	12.1	12.1	12.5	12.6
MEAN	11.6	11.1	11.1	11.2	11.1	11.1	11.1	11.2	11.3	11.2	11.2	11.4
S.D.	0.38	0.60	0.47	0.56	0.60	0.62	0.68	0.65	0.62	0.71	0.96	0.82
N	4	4	4	4	4	4	4	4	4	4	4	4

---: Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL BODY WEIGHTS (kilograms)

STUDY: 219

GROUP: 4-M
DOSE: 4.0 (mg/kg)

SEX: MALE

ANIMAL #	DAY 251	DAY 258	DAY 265	DAY 272	DAY 279	DAY 286	DAY 293	DAY 300	DAY 307	DAY 314	DAY 321	DAY 328
8918	11.0	11.3	11.5	11.6	11.6	11.4	11.3	11.2	11.3	11.4	11.5	11.8
8908	11.3	11.3	11.3	12.0	11.5	11.6	11.7	11.6	11.7	11.8	12.0	12.1
8926	10.7	10.8	11.3	11.9	11.4	11.4	11.4	11.5	11.6	11.6	12.0	11.9
8921	12.4	12.6	12.8	13.1	12.8	12.8	12.6	12.8	13.0	12.8	12.8	13.1
MEAN	11.4	11.5	11.7	12.2	11.8	11.8	11.8	11.8	11.9	11.9	12.1	12.2
S.D.	0.74	0.77	0.72	0.66	0.66	0.67	0.59	0.70	0.75	0.62	0.54	0.60
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 4-M
DOSE: 4.0 (mg/kg)

SEX: MALE

ANIMAL #	DAY 335	DAY 342	DAY 349	DAY 356	DAY 363
8918	11.6	11.6	11.4	11.6	11.3
8908	11.9	11.7	11.6	11.7	11.6
8926	12.0	11.8	12.0	11.9	11.4
8921	12.9	12.9	13.0	13.2	13.0
MEAN	12.1	12.0	12.0	12.1	11.8
S.D.	0.56	0.61	0.71	0.74	0.79
N	4	4	4	4	4

---: Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 219 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg/kg)

ANIMAL #	DAY -2	DAY 6	DAY 13	DAY 20	DAY 27	DAY 34	DAY 41	DAY 48	DAY 55	DAY 62	DAY 69	DAY 76
8929	8.0	8.0	7.7	8.1	8.1	8.4	7.9	8.2	8.5	8.3	8.2	8.3
8942	9.0	8.9	8.8	8.7	8.5	8.8	8.6	8.6	9.0	9.0	9.3	9.2
8930	10.5	10.5	10.5	11.0	11.0	11.4	11.3	11.4	11.4	11.3	11.5	11.4
8938	11.2	11.1	11.0	11.2	11.0	11.5	11.4	11.5	11.9	11.7	11.5	11.4
MEAN	9.7	9.6	9.5	9.8	9.7	10.0	9.8	9.9	10.2	10.1	10.1	10.1
S.D.	1.45	1.43	1.53	1.58	1.57	1.65	1.81	1.77	1.70	1.68	1.65	1.57
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg/kg)

ANIMAL #	DAY 83	DAY 90	DAY 97	DAY 104	DAY 111	DAY 118	DAY 125	DAY 132	DAY 139	DAY 146	DAY 153	DAY 160
8929	8.2	7.8	7.4	7.4	7.3	7.5	7.5	7.3	7.2	7.3	7.3	7.3
8942	9.2	9.3	9.1	9.2	9.0	9.3	9.3	9.2	9.3	9.2	9.1	9.2
8930	11.6	11.4	11.5	11.3	11.0	11.0	10.9	10.8	11.0	11.1	11.1	11.0
8938	11.4	11.1	11.1	11.0	11.2	11.4	11.4	11.3	11.5	11.6	11.6	11.9
MEAN	10.1	9.9	9.8	9.7	9.6	9.8	9.8	9.7	9.8	9.8	9.8	9.9
S.D.	1.67	1.68	1.90	1.81	1.84	1.78	1.76	1.80	1.94	1.96	1.97	2.04
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg/kg)

ANIMAL #	DAY 167	DAY 174	DAY 181	DAY 188	DAY 195	DAY 202	DAY 209	DAY 216	DAY 223	DAY 230	DAY 237	DAY 244
8929	7.8	7.6	7.6	7.6	7.6	7.7	7.8	8.0	8.0	8.0	7.9	8.2
8942	9.4	9.3	9.1	9.1	9.1	9.2	9.2	9.3	9.3	9.3	9.0	9.2
8930	11.2	11.0	11.0	10.9	10.9	11.0	11.1	11.1	11.2	11.4	10.8	11.5
8938	12.0	11.8	11.7	11.6	11.8	11.9	12.1	12.0	12.1	12.0	12.0	11.8
MEAN	10.1	9.9	9.9	9.8	9.9	10.0	10.1	10.1	10.2	10.2	9.9	10.2
S.D.	1.88	1.87	1.86	1.81	1.87	1.87	1.92	1.79	1.85	1.86	1.83	1.76
N	4	4	4	4	4	4	4	4	4	4	4	4

--: Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 219 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg/kg)

ANIMAL #	DAY 251	DAY 258	DAY 265	DAY 272	DAY 279	DAY 286	DAY 293	DAY 300	DAY 307	DAY 314	DAY 321	DAY 328
8929	8.2	8.7	8.6	8.8	8.8	8.6	8.4	8.3	8.4	7.8	7.9	7.9
8942	9.2	9.4	9.7	10.0	9.7	9.7	9.7	9.5	9.8	9.7	9.8	9.8
8930	11.1	11.1	11.3	12.0	11.8	11.6	11.7	11.6	11.4	11.2	11.5	11.5
8938	11.4	11.7	11.8	12.3	12.1	12.0	12.0	12.1	12.6	12.6	12.9	13.2
MEAN	10.0	10.2	10.4	10.8	10.6	10.5	10.5	10.4	10.6	10.3	10.5	10.6
S.D.	1.53	1.41	1.47	1.67	1.61	1.60	1.71	1.78	1.84	2.06	2.16	2.27
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 1-F
DOSE: 0 (mg/kg)

SEX: FEMALE

ANIMAL # DAY 335 DAY 342 DAY 349 DAY 356 DAY 363

8929	7.7	7.5	7.4	7.8	7.7
8942	9.8	9.5	9.5	9.6	9.8
8930	11.7	11.5	11.6	11.4	11.4
8938	13.0	12.6	13.0	12.8	12.8
MEAN	10.6	10.3	10.4	10.4	10.4
S.D.	2.31	2.25	2.45	2.17	2.19
N	4	4	4	4	4

--: Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 219 GROUP: 2-F SEX: FEMALE
DOSE: 0.1 (mg/kg)

ANIMAL #	DAY -2	DAY 6	OAY 13	OAY 20	DAY 27	OAY 34	DAY 41	OAY 48	OAY 55	DAY 62	DAY 69	DAY 76
8935	8.2	8.5	8.7	8.8	8.8	9.1	9.2	9.5	9.9	9.8	9.7	9.8
8937	9.5	9.9	9.9	9.7	9.6	9.7	9.7	9.8	9.9	9.9	10.0	10.1
8934	9.8	10.2	10.0	10.0	9.9	10.1	9.8	10.0	10.2	10.3	10.7	10.6
8945	11.4	11.3	11.3	11.5	11.3	11.6	11.5	11.8	12.1	12.1	12.3	12.6
MEAN	9.7	10.0	10.0	10.0	9.9	10.1	10.1	10.3	10.5	10.5	10.7	10.8
S.D.	1.31	1.15	1.06	1.12	1.04	1.07	1.00	1.04	1.06	1.07	1.16	1.26
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 2-F SEX: FEMALE
DOSE: 0.1 (mg/kg)

ANIMAL #	DAY 83	OAY 90	OAY 97	DAY 104	DAY 111	DAY 118	DAY 125	OAY 132	DAY 139	OAY 146	OAY 153	OAY 160
8935	10.2	10.1	10.3	10.5	10.6	10.6	10.7	10.7	11.0	10.9	10.9	10.7
8937	10.2	10.1	10.1	10.2	10.3	10.2	10.0	10.4	10.4	10.5	10.8	10.2
8934	11.1	11.0	10.8	10.9	10.8	10.7	10.6	10.7	10.8	10.8	10.6	10.7
8945	13.0	12.8	12.8	13.0	12.9	13.1	13.1	13.0	13.3	13.6	13.9	13.2
MEAN	11.1	11.0	11.0	11.2	11.2	11.2	11.1	11.2	11.4	11.5	11.6	11.2
S.D.	1.32	1.27	1.24	1.27	1.18	1.32	1.37	1.21	1.31	1.44	1.57	1.35
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 2-F SEX: FEMALE
DOSE: 0.1 (mg/kg)

ANIMAL #	DAY 167	DAY 174	DAY 181	DAY 188	DAY 195	DAY 202	DAY 209	DAY 216	DAY 223	DAY 230	DAY 237	DAY 244
8935	10.9	10.7	10.5	10.5	10.6	10.7	10.8	11.0	10.7	10.8	11.0	11.0
8937	10.6	10.6	10.6	10.3	10.4	10.5	10.4	10.6	10.6	10.7	10.6	10.5
8934	10.9	10.7	10.7	10.8	10.8	10.8	10.6	10.7	10.6	10.6	10.8	11.2
8945	14.0	13.6	14.0	13.9	14.0	14.0	14.0	14.2	14.4	14.4	14.7	15.0
MEAN	11.6	11.4	11.5	11.4	11.5	11.5	11.5	11.6	11.6	11.6	11.8	11.9
S.D.	1.61	1.47	1.70	1.70	1.71	1.67	1.71	1.73	1.88	1.85	1.96	2.07
N	4	4	4	4	4	4	4	4	4	4	4	4

--- Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 219

GROUP: 2-F
DOSE: 0.1 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 251	DAY 258	DAY 265	DAY 272	DAY 279	DAY 286	DAY 293	DAY 300	DAY 307	DAY 314	DAY 321	DAY 328
8935	11.1	11.1	11.3	11.6	11.5	11.6	11.6	11.6	11.6	11.5	11.8	11.8
8937	10.6	10.9	11.0	11.0	11.1	11.3	11.1	11.2	11.1	11.5	11.1	11.4
8934	11.5	11.3	11.4	11.6	11.3	11.3	11.4	11.6	11.8	11.7	12.1	12.2
8945	15.2	15.4	15.6	16.5	16.0	16.1	16.2	16.4	16.2	16.4	17.0	17.1
MEAN	12.1	12.2	12.3	12.7	12.5	12.6	12.6	12.7	12.7	12.8	13.0	13.1
S.D.	2.10	2.16	2.19	2.57	2.36	2.35	2.43	2.47	2.37	2.42	2.70	2.67
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 2-F
DOSE: 0.1 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 335	DAY 342	DAY 349	DAY 356	DAY 363
8935	12.2	12.2	12.3	12.7	12.6
8937	11.7	11.9	11.7	11.7	11.6
8934	12.0	11.9	11.7	12.0	12.0
8945	16.9	16.3	16.3	16.5	16.3
MEAN	13.2	13.1	13.0	13.2	13.1
S.D.	2.48	2.15	2.22	2.22	2.16
N	4	4	4	4	4

---: Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 219 GROUP: 3-F SEX: FEMALE
DOSE: 1.0 (mg/kg)

ANIMAL #	DAY -2	DAY 6	DAY 13	DAY 20	DAY 27	DAY 34	DAY 41	DAY 48	DAY 55	DAY 62	DAY 69	DAY 76
8928	8.4	8.6	8.7	8.5	8.4	8.4	8.4	8.4	8.4	8.7	8.7	8.7
8940	9.3	8.9	8.9	8.8	8.4	8.6	8.5	8.6	8.7	8.7	8.7	8.8
8931	10.1	10.1	10.1	9.9	9.6	10.0	9.6	9.4	9.6	9.6	9.7	9.8
8943	10.5	10.4	10.2	10.4	10.0	10.2	10.1	10.1	10.4	10.3	10.3	10.5
MEAN	9.6	9.5	9.5	9.4	9.1	9.3	9.2	9.1	9.3	9.3	9.4	9.5
S.D.	0.93	0.88	0.78	0.90	0.82	0.93	0.83	0.78	0.91	0.78	0.79	0.86
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 3-F SEX: FEMALE
DOSE: 1.0 (mg/kg)

ANIMAL #	DAY 83	DAY 90	DAY 97	DAY 104	DAY 111	DAY 118	DAY 125	DAY 132	DAY 139	DAY 146	DAY 153	DAY 160
8928	8.6	8.3	8.2	8.3	8.4	8.5	8.3	8.8	9.0	9.0	8.9	8.8
8940	8.8	8.6	8.4	8.7	8.9	8.9	8.8	9.0	9.3	9.2	9.1	9.0
8931	9.1	8.7	8.5	8.6	8.6	8.4	8.5	8.6	8.5	8.8	8.5	8.5
8943	10.5	10.5	10.6	10.7	10.9	11.1	11.1	10.9	11.1	11.2	11.2	11.2
MEAN	9.3	9.0	8.9	9.1	9.2	9.2	9.2	9.3	9.5	9.6	9.4	9.4
S.D.	0.86	1.00	1.12	1.10	1.15	1.27	1.30	1.06	1.13	1.11	1.21	1.23
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 3-F SEX: FEMALE
DOSE: 1.0 (mg/kg)

ANIMAL #	DAY 167	DAY 174	DAY 181	DAY 188	DAY 195	DAY 202	DAY 209	DAY 216	DAY 223	DAY 230	DAY 237	DAY 244
8928	9.5	9.5	9.0	9.0	10.8	8.8	8.8	9.0	9.1	9.4	9.1	9.1
8940	9.0	9.0	8.6	8.5	8.4	8.8	8.8	8.8	9.0	9.0	8.8	9.2
8931	8.7	8.5	8.5	8.7	8.3	8.5	8.5	8.5	8.7	8.6	8.7	9.2
8943	11.9	11.2	11.4	11.6	11.6	11.8	11.6	11.7	11.7	11.7	12.3	12.4
MEAN	9.8	9.6	9.4	9.5	9.8	9.5	9.4	9.5	9.6	9.7	9.7	10.0
S.D.	1.45	1.17	1.37	1.45	1.68	1.56	1.46	1.48	1.39	1.39	1.73	1.62
N	4	4	4	4	4	4	4	4	4	4	4	4

--- Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 219

GROUP: 3-F

SEX: FEMALE

DOSE: 1.0 (mg/kg)

ANIMAL #	DAY 251	DAY 258	DAY 265	DAY 272	DAY 279	DAY 286	DAY 293	DAY 300	DAY 307	DAY 314	DAY 321	DAY 328
8928	9.0	9.1	9.1	9.3	9.2	9.3	9.3	9.4	9.4	9.1	9.4	9.8
8940	9.2	9.4	9.3	9.8	9.2	9.5	9.6	9.8	9.7	9.7	9.5	9.6
8931	9.0	8.9	9.1	9.6	9.8	9.2	9.0	9.3	9.4	9.6	9.8	9.9
8943	12.4	12.3	13.0	13.7	13.3	12.8	13.1	13.1	14.0	13.7	14.6	14.8
MEAN	9.9	9.9	10.1	10.6	10.4	10.2	10.3	10.4	10.6	10.5	10.8	11.0
S.D.	1.67	1.60	1.92	2.08	1.97	1.74	1.92	1.81	2.25	2.13	2.52	2.52
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 3-F

SEX: FEMALE

DOSE: 1.0 (mg/kg)

ANIMAL # DAY 335 DAY 342 DAY 349 DAY 356 DAY 363

8928	9.5	9.7	9.4	9.3	9.2
8940	9.5	9.5	9.3	9.2	9.2
8931	9.8	9.8	9.9	9.9	9.9
8943	14.5	14.0	14.2	14.5	14.0
MEAN	10.8	10.8	10.7	10.7	10.6
S.D.	2.45	2.17	2.35	2.54	2.31
N	4	4	4	4	4

--: Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 219 GROUP: 4-F SEX: FEMALE
DOSE: 4.0 (mg/kg)

ANIMAL #	DAY -2	DAY 6	DAY 13	DAY 20	DAY 27	DAY 34	DAY 41	DAY 48	DAY 55	DAY 62	DAY 69	DAY 76
8941	8.2	8.1	8.3	8.5	8.3	8.3	8.2	8.3	8.3	8.4	8.4	8.5
8933	9.1	9.1	9.5	9.2	9.0	9.3	9.1	9.4	9.6	9.6	9.8	9.5
8936	9.6	9.3	9.7	9.6	9.5	9.5	9.6	9.6	9.8	9.8	10.0	10.0
8944	11.0	11.0	11.1	11.1	11.0	11.0	10.7	11.1	11.4	11.4	11.6	11.6
MEAN	9.5	9.4	9.7	9.6	9.5	9.5	9.4	9.6	9.8	9.8	10.0	9.9
S.D.	1.17	1.20	1.15	1.10	1.14	1.11	1.04	1.15	1.27	1.23	1.31	1.29
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 4-F SEX: FEMALE
DOSE: 4.0 (mg/kg)

ANIMAL #	DAY 83	DAY 90	DAY 97	DAY 104	DAY 111	DAY 118	DAY 125	DAY 132	DAY 139	DAY 146	DAY 153	DAY 160
8941	8.6	8.5	8.6	8.4	8.3	8.2	8.3	8.1	8.3	8.3	8.2	8.0
8933	9.5	9.5	9.4	9.4	9.3	9.3	9.2	9.3	9.2	9.4	9.6	9.7
8936	10.2	10.1	9.7	9.8	9.6	9.6	9.7	9.5	9.7	9.6	9.8	9.5
8944	11.6	11.3	11.3	11.4	11.3	11.3	11.2	11.0	11.3	11.2	11.1	11.2
MEAN	10.0	9.9	9.8	9.8	9.6	9.6	9.6	9.5	9.6	9.6	9.7	9.6
S.D.	1.27	1.17	1.13	1.25	1.25	1.28	1.21	1.19	1.26	1.20	1.19	1.31
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 4-F SEX: FEMALE
DOSE: 4.0 (mg/kg)

ANIMAL #	DAY 167	DAY 174	DAY 181	DAY 188	DAY 195	DAY 202	DAY 209	DAY 216	DAY 223	DAY 230	DAY 237	DAY 244
8941	8.1	8.3	8.0	8.1	8.1	8.2	8.2	8.4	8.3	8.5	8.5	8.8
8933	9.7	9.8	9.4	9.4	9.4	10.0	9.6	10.1	10.2	10.4	10.1	10.5
8936	10.2	9.7	9.8	9.8	9.7	10.0	9.9	9.9	10.1	10.0	10.0	10.5
8944	11.3	11.4	11.1	11.2	11.1	11.3	11.4	11.3	11.4	11.2	11.3	11.8
MEAN	9.8	9.8	9.6	9.6	9.6	9.9	9.8	9.9	10.0	10.0	10.0	10.4
S.D.	1.33	1.27	1.28	1.28	1.23	1.27	1.31	1.19	1.28	1.13	1.15	1.23
N	4	4	4	4	4	4	4	4	4	4	4	4

---: Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 219

GROUP: 4-F

SEX: FEMALE

DOSE: 4.0 (mg/kg)

ANIMAL # DAY 251 DAY 258 DAY 265 DAY 272 DAY 279 DAY 286 DAY 293 DAY 300 DAY 307 DAY 314 DAY 321 DAY 328

8941	8.9	9.0	8.9	9.3	9.1	9.3	9.3	9.2	9.1	9.6	9.6	9.4
8933	10.2	10.2	10.1	10.3	10.1	10.3	10.2	10.2	10.2	10.3	10.4	10.5
8936	10.3	10.7	10.5	11.0	10.6	10.6	10.6	10.5	10.3	10.2	10.4	10.5
8944	11.6	11.6	11.7	12.1	11.6	11.6	11.4	11.6	11.9	12.0	12.0	12.0
MEAN	10.3	10.4	10.3	10.7	10.4	10.5	10.4	10.4	10.4	10.5	10.6	10.6
S.D.	1.10	1.08	1.15	1.18	1.04	0.95	0.87	0.99	1.15	1.03	1.01	1.07
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 4-F

SEX: FEMALE

DOSE: 4.0 (mg/kg)

ANIMAL # DAY 335 DAY 342 DAY 349 DAY 356 DAY 363

8941	9.5	9.5	9.4	9.7	9.8
8933	10.5	10.3	10.5	10.6	10.3
8936	10.4	10.2	10.2	10.4	10.3
8944	12.1	11.8	11.9	11.8	11.6
MEAN	10.6	10.5	10.5	10.6	10.5
S.D.	1.08	0.97	1.04	0.87	0.77
N	4	4	4	4	4

--: Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 219

GROUP: 1-M
DOSE: 0 (mg/kg)

SEX: MALE

ANIMAL #	DAY 6 ^b	DAY 13	DAY 20	DAY 27	DAY 34	DAY 41	DAY 48	DAY 55	DAY 62	DAY 69	DAY 76
8922	0.0	0.2	0.1	0.0	0.1	-0.1	0.2	0.6	0.1	0.5	0.1
8915	-0.2	0.1	0.1	-0.1	0.2	-0.2	0.1	0.1	0.0	0.2	0.0
8911	-0.2	0.0	0.2	-0.2	0.3	0.0	0.2	0.1	0.0	0.2	-0.1
8909	0.0	-0.1	-0.1	0.0	0.2	-0.1	0.0	0.1	-0.2	0.0	-0.4
MEAN	-0.1	0.1	0.1	-0.1	0.2	-0.1	0.1	0.2	0.0	0.2	-0.1
S.D.	0.12	0.13	0.13	0.10	0.08	0.08	0.10	0.25	0.13	0.21	0.22
N	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 1-M
DOSE: 0 (mg/kg)

SEX: MALE

ANIMAL #	DAY 83	DAY 90	DAY 97	DAY 104	DAY 111	DAY 118	DAY 125	DAY 132	DAY 139	DAY 146	DAY 153
8922	0.0	-0.2	-0.1	0.1	0.0	0.2	-0.1	0.1	0.3	0.1	0.2
8915	0.2	-0.1	-0.1	0.1	0.1	0.0	-0.5	0.3	0.1	0.0	0.0
8911	0.1	-0.3	0.1	0.1	0.0	0.4	-0.2	-0.2	0.1	0.1	0.2
8909	0.2	0.1	-0.1	0.1	0.0	0.1	-0.1	0.0	0.1	0.2	0.0
MEAN	0.1	-0.1	-0.1	0.1	0.0	0.2	-0.2	0.1	0.2	0.1	0.1
S.O.	0.10	0.17	0.10	0.00	0.05	0.17	0.19	0.21	0.10	0.08	0.12
N	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 1-M
DOSE: 0 (mg/kg)

SEX: MALE

ANIMAL #	DAY 160	DAY 167	DAY 174	DAY 181	DAY 188	DAY 195	DAY 202	DAY 209	DAY 216	DAY 223	DAY 230
8922	0.0	0.6	-0.8	0.0	0.0	-0.4	0.2	0.0	0.1	0.4	-0.3
8915	-0.1	0.5	-0.4	0.2	0.1	-0.1	0.0	-0.1	0.3	-0.1	-0.2
8911	0.2	0.1	-0.4	0.2	-0.3	0.1	0.0	0.1	-0.2	-0.1	0.1
8909	-0.2	0.6	-0.5	-0.2	0.0	0.2	-0.2	0.1	0.1	-0.2	0.0
MEAN	0.0	0.5	-0.5	0.1	-0.1	-0.1	0.0	0.0	0.1	0.0	-0.1
S.O.	0.17	0.24	0.19	0.19	0.17	0.26	0.16	0.10	0.21	0.27	0.18
N	4	4	4	4	4	4	4	4	4	4	4

---: Data Unavailable

^aWeight gains compared to the previous period
^bBaseline is Day -2

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 219

GROUP: 1-M
DOSE: 0 (mg/kg)

SEX: MALE

ANIMAL #	DAY 237	DAY 244	DAY 251	DAY 258	DAY 265	DAY 272	DAY 279	DAY 286	DAY 293	DAY 300	DAY 307
8922	-0.2	0.8	-0.2	0.1	-0.1	0.1	-0.4	0.1	0.0	0.0	0.0
8915	0.4	0.1	0.2	0.0	-0.1	0.6	0.0	-0.4	0.0	0.0	0.1
8911	0.4	0.3	-0.3	0.0	0.1	0.7	-0.1	-0.4	-0.1	-0.1	0.0
8909	-0.2	0.6	0.0	0.0	0.2	0.9	-0.4	-0.2	-0.1	-0.1	0.5
MEAN	0.1	0.5	-0.1	0.0	0.1	0.6	-0.2	-0.2	-0.1	-0.1	0.2
S.D.	0.35	0.31	0.22	0.05	0.13	0.34	0.21	0.24	0.06	0.06	0.24
N	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 1-M
DOSE: 0 (mg/kg)

SEX: MALE

ANIMAL #	DAY 314	DAY 321	DAY 328	DAY 335	DAY 342	DAY 349	DAY 356	DAY 363	TOTAL GAIN
8922	0.0	0.3	0.2	-0.2	-0.1	0.1	0.4	-0.6	2.5
8915	0.0	0.4	-0.3	0.2	0.2	-0.1	0.0	-0.3	1.7
8911	0.3	0.2	-0.1	-0.1	0.0	0.3	0.4	-0.4	1.8
8909	-0.1	0.7	-0.1	0.0	-0.2	0.1	0.3	-0.5	1.1
MEAN	0.1	0.4	-0.1	0.0	0.0	0.1	0.3	-0.5	1.8
S.D.	0.17	0.22	0.21	0.17	0.17	0.16	0.19	0.13	0.57
N	4	4	4	4	4	4	4	4	4

--- Data Unavailable

^aWeight gains compared to the previous period

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL WEIGHT GAIN (kilograms)^a

STUDY: 219

GROUP: 2-M
DOSE: 0.1 (mg/kg)

SEX: MALE

ANIMAL #	DAY 6 ^b	DAY 13	DAY 20	DAY 27	DAY 34	DAY 41	DAY 48	DAY 55	DAY 62	DAY 69	DAY 76
8923	-0.2	0.2	-0.4	0.2	0.0	-0.3	0.0	0.2	0.0	0.1	0.0
8907	-0.5	0.0	0.1	-0.5	0.4	-0.1	0.2	0.3	0.0	0.0	0.0
8919	-0.3	-0.1	0.4	-0.5	-0.1	0.0	-0.1	0.0	0.1	-0.2	0.2
8924	-0.3	-0.3	0.0	-0.2	0.2	-0.2	-0.2	0.3	-0.1	0.0	0.2
MEAN	-0.3	-0.1	0.0	-0.3	0.1	-0.2	0.0	0.2	0.0	0.0	0.1
S.D.	0.13	0.21	0.33	0.33	0.22	0.13	0.17	0.14	0.08	0.13	0.12
N	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 2-M
DOSE: 0.1 (mg/kg)

SEX: MALE

ANIMAL #	DAY 83	DAY 90	DAY 97	DAY 104	DAY 111	DAY 118	DAY 125	DAY 132	DAY 139	DAY 146	DAY 153
8923	0.5	0.0	-0.5	0.2	-0.1	-0.1	-0.2	0.2	0.0	0.3	0.2
8907	0.2	-0.1	0.1	0.2	0.0	0.2	0.3	0.0	-0.1	0.3	-0.1
8919	0.3	-0.6	0.0	0.2	0.2	0.1	-0.2	0.0	0.2	-0.1	0.1
8924	0.0	-0.1	-0.1	0.2	-0.1	-0.2	-0.2	0.2	0.1	0.0	0.1
MEAN	0.3	-0.2	-0.1	0.2	0.0	0.0	-0.1	0.1	0.1	0.1	0.1
S.D.	0.21	0.27	0.26	0.00	0.14	0.18	0.25	0.12	0.13	0.21	0.13
N	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 2-M
DOSE: 0.1 (mg/kg)

SEX: MALE

ANIMAL #	DAY 160	DAY 167	DAY 174	DAY 181	DAY 188	DAY 195	DAY 202	DAY 209	DAY 216	DAY 223	DAY 230
8923	0.2	0.3	-0.3	0.0	0.2	-0.1	0.1	0.0	-0.1	0.0	-0.4
8907	0.0	0.4	-0.2	-0.5	0.2	-0.4	0.4	0.0	0.2	0.0	0.1
8919	0.0	0.5	-0.3	-0.2	0.3	-0.4	0.3	-0.2	0.1	-0.4	-0.1
8924	0.1	0.5	-0.3	0.2	0.2	0.3	0.0	0.1	0.0	0.1	0.0
MEAN	0.1	0.4	-0.3	-0.1	0.2	-0.2	0.2	0.0	0.1	-0.1	-0.1
S.D.	0.10	0.10	0.05	0.30	0.05	0.33	0.18	0.13	0.13	0.22	0.22
N	4	4	4	4	4	4	4	4	4	4	4

---: Data Unavailable

^aWeight gains compared to the previous period
^bBaseline is Day -2

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL WEIGHT GAIN (kilograms)^a

STUDY: 219 GROUP: 2-M SEX: MALE
DOSE: 0.1 (mg/kg)

ANIMAL #	DAY 237	DAY 244	DAY 251	DAY 258	DAY 265	DAY 272	DAY 279	DAY 286	DAY 293	DAY 300	DAY 307
8923	0.4	0.3	0.4	0.0	0.1	0.6	0.0	-0.6	-0.4	0.1	0.1
8907	-0.3	0.3	0.2	0.1	0.0	0.6	-0.8	0.0	-0.2	-0.1	0.3
8919	0.3	0.3	0.0	0.1	0.0	0.3	-0.2	0.0	0.0	0.1	0.0
8924	0.5	0.1	-0.1	-0.1	0.5	0.2	0.1	-0.1	-0.2	0.4	0.2
MEAN	0.2	0.3	0.1	0.0	0.2	0.4	-0.2	-0.2	-0.2	0.1	0.2
S.D.	0.36	0.10	0.22	0.10	0.24	0.21	0.40	0.29	0.16	0.21	0.13
N	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 2-M SEX: MALE
DOSE: 0.1 (mg/kg)

ANIMAL #	DAY 314	DAY 321	DAY 328	DAY 335	DAY 342	DAY 349	DAY 356	DAY 363	TOTAL GAIN
8923	0.0	0.2	0.0	0.3	-0.5	0.1	0.2	-0.2	1.3
8907	0.2	0.2	0.3	-0.1	0.1	0.2	0.0	-0.6	1.5
8919	0.1	0.2	0.1	-0.1	-0.2	0.0	0.0	-0.2	0.0
8924	-0.2	-0.2	0.0	-0.1	0.2	0.0	0.3	0.0	2.0
MEAN	0.0	0.1	0.1	0.0	-0.1	0.1	0.1	-0.3	1.2
S.D.	0.17	0.20	0.14	0.20	0.32	0.10	0.15	0.25	0.85
N	4	4	4	4	4	4	4	4	4

--: Data Unavailable

^aWeight gains compared to the previous period

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 219

GROUP: 3-M
DOSE: 1.0 (mg/kg)

SEX: MALE

ANIMAL #	OAY 6 ^b	OAY 13	DAY 20	OAY 27	OAY 34	OAY 41	OAY 48	OAY 55	OAY 62	OAY 69	OAY 76
8917	0.1	0.2	0.1	-0.1	0.1	-0.1	-0.2	0.3	-0.1	0.1	0.4
8910	-0.2	-0.2	-0.1	-0.3	0.1	-0.1	0.1	0.1	0.0	0.1	0.1
8913	-0.4	-0.1	-0.3	-0.3	-0.1	0.0	-0.1	0.3	0.1	0.1	0.2
8914	-0.1	-0.2	0.0	0.0	-0.1	0.0	-0.1	0.3	-0.1	0.0	0.0
MEAN	-0.2	-0.1	-0.1	-0.2	0.0	-0.1	-0.1	0.3	0.0	0.1	0.2
S.O.	0.21	0.19	0.17	0.15	0.12	0.06	0.13	0.10	0.10	0.05	0.17
N	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 3-M
DOSE: 1.0 (mg/kg)

SEX: MALE

ANIMAL #	OAY 83	OAY 90	OAY 97	OAY 104	OAY 111	OAY 118	OAY 125	DAY 132	OAY 139	OAY 146	OAY 153
8917	0.1	-0.2	0.2	0.1	-0.2	0.1	-0.2	-0.1	0.2	0.3	-0.1
8910	0.0	0.0	0.0	-0.1	-0.1	0.0	-0.1	0.0	0.2	-0.1	0.1
8913	-0.1	-0.3	0.1	0.0	-0.2	-0.3	0.0	-0.3	0.5	-0.1	-0.2
8914	0.0	-0.1	0.1	0.1	0.0	-0.3	0.1	-0.2	0.0	0.1	0.2
MEAN	0.0	-0.2	0.1	0.0	-0.1	-0.1	-0.1	-0.2	0.2	0.1	0.0
S.O.	0.08	0.13	0.08	0.10	0.10	0.21	0.13	0.13	0.21	0.19	0.18
N	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 3-M
DOSE: 1.0 (mg/kg)

SEX: MALE

ANIMAL #	DAY 160	OAY 167	DAY 174	DAY 181	OAY 188	OAY 195	OAY 202	DAY 209	DAY 216	OAY 223	DAY 230
8917	-0.1	0.5	-0.1	-0.3	0.0	0.0	0.5	-0.1	0.1	0.0	-0.1
8910	-0.1	0.7	-0.4	-0.2	-0.1	-2.5	2.4	0.0	0.1	-0.1	0.0
8913	-0.1	0.7	-0.4	-0.2	0.2	-0.1	0.0	-0.2	0.1	0.0	-0.8
8914	0.0	0.6	-0.2	-0.1	0.1	0.2	-0.1	0.0	0.2	0.0	-0.1
MEAN	-0.1	0.6	-0.3	-0.2	0.1	-0.6	0.7	-0.1	0.1	0.0	-0.3
S.O.	0.05	0.10	0.15	0.08	0.13	1.27	1.16	0.10	0.05	0.05	0.37
N	4	4	4	4	4	4	4	4	4	4	4

---: Data Unavailable

^aWeight gains compared to the previous period
^bBaseline is Day -2

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL WEIGHT GAIN (kilograms)^a

STUDY: 219 GROUP: 3-M SEX: MALE
DOSE: 1.0 (mg/kg)

ANIMAL #	DAY 237	DAY 244	DAY 251	DAY 258	DAY 265	DAY 272	DAY 279	DAY 286	DAY 293	DAY 300	DAY 307
8917	-0.3	0.4	-0.5	0.6	0.2	-0.1	-0.1	0.2	-0.5	0.1	0.1
8910	0.4	-0.1	0.3	0.0	-0.1	0.6	-0.4	-0.1	0.0	-0.1	0.0
8913	0.5	0.3	0.1	0.1	0.1	0.9	-0.6	0.0	-0.3	-0.3	0.3
8914	0.5	0.1	-0.1	-0.1	0.3	0.5	-0.4	-0.3	0.0	0.0	0.2
MEAN	0.3	0.2	-0.1	0.2	0.1	0.5	-0.4	-0.1	-0.2	-0.1	0.2
S.D.	0.39	0.22	0.34	0.31	0.17	0.42	0.21	0.21	0.24	0.17	0.13
N	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 3-M SEX: MALE
DOSE: 1.0 (mg/kg)

ANIMAL #	DAY 314	DAY 321	DAY 328	DAY 335	DAY 342	DAY 349	DAY 356	DAY 363	TOTAL GAIN
8917	0.0	0.3	0.0	0.2	-0.2	-0.1	-0.1	-0.1	1.5
8910	0.1	0.4	-0.2	-0.1	-0.2	-0.1	0.2	0.0	-0.1
8913	-0.2	0.3	0.1	0.3	-0.3	0.1	0.4	-0.5	-1.0
8914	-0.6	0.3	0.2	-0.2	0.0	0.2	0.3	-0.5	0.7
MEAN	-0.2	0.3	0.0	0.1	-0.2	0.0	0.2	-0.3	0.3
S.D.	0.31	0.05	0.17	0.24	0.13	0.15	0.22	0.26	1.07
N	4	4	4	4	4	4	4	4	4

--: Data Unavailable

^aWeight gains compared to the previous period

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL WEIGHT GAIN (kilograms)^a

STUDY: 219

GROUP: 4-M
DOSE: 4.0 (mg/kg)

SEX: MALE

ANIMAL #	DAY 6 ^b	DAY 13	DAY 20	DAY 27	DAY 34	DAY 41	DAY 48	DAY 55	DAY 62	DAY 69	DAY 76
8918	0.0	-0.1	-0.1	-0.3	0.4	0.1	0.0	0.1	-0.1	0.1	0.3
8908	-0.1	-0.1	0.1	-0.2	0.0	0.0	0.1	0.1	0.0	0.1	0.1
8926	-0.5	0.1	-0.1	-0.2	0.0	-0.1	0.0	0.0	0.2	0.2	0.0
8921	-0.2	-0.1	-0.2	-0.2	0.0	-0.1	0.1	0.0	0.1	0.1	0.0
MEAN	-0.2	-0.1	-0.1	-0.2	0.1	0.0	0.1	0.1	0.1	0.1	0.1
S.D.	0.22	0.10	0.13	0.05	0.20	0.10	0.06	0.06	0.13	0.05	0.14
N	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 4-M
DOSE: 4.0 (mg/kg)

SEX: MALE

ANIMAL #	DAY 83	DAY 90	DAY 97	DAY 104	DAY 111	DAY 118	DAY 125	DAY 132	DAY 139	DAY 146	DAY 153
8918	0.0	-0.1	0.1	0.1	0.0	0.0	-0.2	0.1	0.1	0.0	0.1
8908	0.0	-0.2	-0.1	0.1	-0.2	0.0	-0.2	-0.1	0.0	-0.2	0.0
8926	0.0	-0.3	-0.3	0.3	-0.1	-0.1	0.0	-0.1	0.0	0.0	0.1
8921	0.0	-0.1	-0.3	0.2	-0.1	-0.5	0.0	-0.1	0.4	0.0	0.0
MEAN	0.0	-0.2	-0.2	0.2	-0.1	-0.2	-0.1	-0.1	0.1	-0.1	0.1
S.D.	0.00	0.10	0.19	0.10	0.08	0.24	0.12	0.10	0.19	0.10	0.06
N	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 4-M
DOSE: 4.0 (mg/kg)

SEX: MALE

ANIMAL #	DAY 160	DAY 167	DAY 174	DAY 181	DAY 188	DAY 195	DAY 202	DAY 209	DAY 216	DAY 223	DAY 230
8918	-0.1	0.3	-0.2	-0.3	-0.1	0.0	0.2	0.0	0.1	0.0	0.1
8908	0.2	0.6	-0.4	-0.2	0.2	-0.6	0.2	-0.2	0.1	0.0	0.1
8926	-0.1	0.0	-0.8	0.2	0.1	0.0	-0.1	0.0	0.2	0.1	-0.3
8921	0.1	0.4	-0.4	0.1	0.3	0.1	0.0	0.1	0.1	0.0	0.0
MEAN	0.0	0.3	-0.5	-0.1	0.1	-0.1	0.1	0.0	0.1	0.0	0.0
S.D.	0.15	0.25	0.25	0.24	0.17	0.32	0.15	0.13	0.05	0.05	0.19
N	4	4	4	4	4	4	4	4	4	4	4

--: Data Unavailable

^aWeight gains compared to the previous period
^bBaseline is Day -2

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 219

GROUP: 4-M
DOSE: 4.0 (mg/kg)

SEX: MALE

ANIMAL #	DAY 237	DAY 244	DAY 251	DAY 258	DAY 265	DAY 272	DAY 279	DAY 286	DAY 293	DAY 300	DAY 307
8918	-0.4	0.2	-0.2	0.3	0.2	0.1	0.0	-0.2	-0.1	-0.1	0.1
8908	0.1	0.1	0.1	0.0	0.0	0.7	-0.5	0.1	0.1	-0.1	0.1
8926	-0.2	0.5	0.0	0.1	0.5	0.6	-0.5	0.0	0.0	0.1	0.1
8921	0.4	0.1	-0.2	0.2	0.2	0.3	-0.3	0.0	-0.2	0.2	0.2
MEAN	0.0	0.2	-0.1	0.2	0.2	0.4	-0.3	0.0	-0.1	0.0	0.1
S.D.	0.35	0.19	0.15	0.13	0.21	0.28	0.24	0.13	0.13	0.15	0.05
N	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 4-M
DOSE: 4.0 (mg/kg)

SEX: MALE

ANIMAL #	DAY 314	DAY 321	DAY 328	DAY 335	DAY 342	DAY 349	DAY 356	DAY 363	TOTAL GAIN
8918	0.1	0.1	0.3	-0.2	0.0	-0.2	0.2	-0.3	0.5
8908	0.1	0.2	0.1	-0.2	-0.2	-0.1	0.1	-0.1	-0.2
8926	0.0	0.4	-0.1	0.1	-0.2	0.2	-0.1	-0.5	-0.6
8921	-0.2	0.0	0.3	-0.2	0.0	0.1	0.2	-0.2	0.7
MEAN	0.0	0.2	0.2	-0.1	-0.1	0.0	0.1	-0.3	0.1
S.D.	0.14	0.17	0.19	0.15	0.12	0.18	0.14	0.17	0.61
N	4	4	4	4	4	4	4	4	4

---: Data Unavailable

^aWeight gains compared to the previous period

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 219 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg/kg)

ANIMAL #	DAY 6 ^b	DAY 13	DAY 20	DAY 27	DAY 34	DAY 41	DAY 48	DAY 55	DAY 62	DAY 69	DAY 76
8929	0.0	-0.3	0.4	0.0	0.3	-0.5	0.3	0.3	-0.2	-0.1	0.1
8942	-0.1	-0.1	-0.1	-0.2	0.3	-0.2	0.0	0.4	0.0	0.3	-0.1
8930	0.0	0.0	0.5	0.0	0.4	-0.1	0.1	0.0	-0.1	0.2	-0.1
8938	-0.1	-0.1	0.2	-0.2	0.5	-0.1	0.1	0.4	-0.2	-0.2	-0.1
MEAN	-0.1	-0.1	0.3	-0.1	0.4	-0.2	0.1	0.3	-0.1	0.1	-0.1
S.D.	0.06	0.13	0.26	0.12	0.10	0.19	0.13	0.19	0.10	0.24	0.10
N	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg/kg)

ANIMAL #	DAY 83	DAY 90	DAY 97	DAY 104	DAY 111	DAY 118	DAY 125	DAY 132	DAY 139	DAY 146	DAY 153
8929	-0.1	-0.4	-0.4	0.0	-0.1	0.2	0.0	-0.2	-0.1	0.1	0.0
8942	0.0	0.1	-0.2	0.1	-0.2	0.3	0.0	-0.1	0.1	-0.1	-0.1
8930	0.2	-0.2	0.1	-0.2	-0.3	0.0	-0.1	-0.1	0.2	0.1	0.0
8938	0.0	-0.3	0.0	-0.1	0.2	0.2	0.0	-0.1	0.2	0.1	0.0
MEAN	0.0	-0.2	-0.1	-0.1	-0.1	0.2	0.0	-0.1	0.1	0.1	0.0
S.O.	0.13	0.22	0.22	0.13	0.22	0.13	0.05	0.05	0.14	0.10	0.05
N	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg/kg)

ANIMAL #	DAY 160	DAY 167	DAY 174	DAY 181	DAY 188	DAY 195	DAY 202	DAY 209	DAY 216	DAY 223	DAY 230
8929	0.0	0.5	-0.2	0.0	0.0	0.0	0.1	0.1	0.2	0.0	0.0
8942	0.1	0.2	-0.1	-0.2	0.0	0.0	0.1	0.0	0.1	0.0	0.0
8930	-0.1	0.2	-0.2	0.0	-0.1	0.0	0.1	0.1	0.0	0.1	0.2
8938	0.3	0.1	-0.2	-0.1	-0.1	0.2	0.1	0.2	-0.1	0.1	-0.1
MEAN	0.1	0.3	-0.2	-0.1	-0.1	0.1	0.1	0.1	0.1	0.1	0.0
S.O.	0.17	0.17	0.05	0.10	0.06	0.10	D.DD	0.08	D.13	0.06	0.13
N	4	4	4	4	4	4	4	4	4	4	4

---: Data Unavailable

^aWeight gains compared to the previous period
^bBaseline is Day -2

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL WEIGHT GAIN (kilograms)^a

STUDY: 219

GROUP: 1-F
DOSE: 0 (mg/kg)

SEX: FEMALE

ANIMAL # DAY 237 DAY 244 DAY 251 DAY 258 DAY 265 DAY 272 DAY 279 DAY 286 DAY 293 DAY 300 DAY 307

8929	-0.1	0.3	0.0	0.5	-0.1	0.2	0.0	-0.2	-0.2	-0.1	0.1
8942	-0.3	0.2	0.0	0.2	0.3	0.3	-0.3	0.0	0.0	-0.2	0.3
8930	-0.6	0.7	-0.4	0.0	0.2	0.7	-0.2	-0.2	0.1	-0.1	-0.2
8938	0.0	-0.2	-0.4	0.3	0.1	0.5	-0.2	-0.1	0.0	0.1	0.5
MEAN	-0.3	0.3	-0.2	0.3	0.1	0.4	-0.2	-0.1	0.0	-0.1	0.2
S.D.	0.26	0.37	0.23	0.21	0.17	0.22	0.13	0.10	0.13	0.13	0.30
N	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 1-F
DOSE: 0 (mg/kg)

SEX: FEMALE

ANIMAL # DAY 314 DAY 321 DAY 328 DAY 335 DAY 342 DAY 349 DAY 356 DAY 363 TOTAL GAIN

8929	-0.6	0.1	0.0	-0.2	-0.2	-0.1	0.4	-0.1	-0.3
8942	-0.1	0.1	0.0	0.0	-0.3	0.0	0.1	0.2	0.8
8930	-0.2	0.3	0.0	0.2	-0.2	0.1	-0.2	0.0	0.9
8938	0.0	0.3	0.3	-0.2	-0.4	0.4	-0.2	0.0	1.6
MEAN	-0.2	0.2	0.1	-0.1	-0.3	0.1	0.0	0.0	0.8
S.D.	0.26	0.12	0.15	0.19	0.10	0.22	0.29	0.13	0.79
N	4	4	4	4	4	4	4	4	4

---: Data Unavailable

^aWeight gains compared to the previous period

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 219 GROUP: 2-F SEX: FEMALE
DOSE: 0.1 (mg/kg)

ANIMAL #	DAY 6 ^b	DAY 13	DAY 20	DAY 27	DAY 34	DAY 41	DAY 48	DAY 55	DAY 62	DAY 69	DAY 76
8935	0.3	0.2	0.1	0.0	0.3	0.1	0.3	0.4	-0.1	-0.1	0.1
8937	0.4	0.0	-0.2	-0.1	0.1	0.0	0.1	0.1	0.0	0.1	0.1
8934	0.4	-0.2	0.0	-0.1	0.2	-0.3	0.2	0.2	0.1	0.4	-0.1
8945	-0.1	0.0	0.2	-0.2	0.3	-0.1	0.3	0.3	0.0	0.2	0.3
MEAN	0.3	0.0	0.0	-0.1	0.2	-0.1	0.2	0.3	0.0	0.2	0.1
S.D.	0.24	0.16	0.17	0.08	0.10	0.17	0.10	0.13	0.08	0.21	0.16
N	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 2-F SEX: FEMALE
DOSE: 0.1 (mg/kg)

ANIMAL #	DAY 83	DAY 90	DAY 97	DAY 104	DAY 111	DAY 118	DAY 125	DAY 132	DAY 139	DAY 146	DAY 153
8935	0.4	-0.1	0.2	0.2	0.1	0.0	0.1	0.0	0.3	-0.1	0.0
8937	0.1	-0.1	0.0	0.1	0.1	-0.1	-0.2	0.4	0.0	0.1	0.3
8934	0.5	-0.1	-0.2	0.1	-0.1	-0.1	-0.1	0.1	0.1	0.0	-0.2
8945	0.4	-0.2	0.0	0.2	-0.1	0.2	0.0	-0.1	0.3	0.3	0.3
MEAN	0.4	-0.1	0.0	0.2	0.0	0.0	-0.1	0.1	0.2	0.1	0.1
S.D.	0.17	0.05	0.16	0.06	0.12	0.14	0.13	0.22	0.15	0.17	0.24
N	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 2-F SEX: FEMALE
DOSE: 0.1 (mg/kg)

ANIMAL #	DAY 160	DAY 167	DAY 174	DAY 181	DAY 188	DAY 195	DAY 202	DAY 209	DAY 216	DAY 223	DAY 230
8935	-0.2	0.2	-0.2	-0.2	0.0	0.1	0.1	0.1	0.2	-0.3	0.1
8937	-0.6	0.4	0.0	0.0	-0.3	0.1	0.1	-0.1	0.2	0.0	0.1
8934	0.1	0.2	-0.2	0.0	0.1	0.0	0.0	-0.2	0.1	-0.1	0.0
8945	-0.7	0.8	-0.4	0.4	-0.1	0.1	0.0	0.0	0.2	0.2	0.0
MEAN	-0.4	0.4	-0.2	0.1	-0.1	0.1	0.1	-0.1	0.2	-0.1	0.1
S.D.	0.37	0.28	0.16	0.25	0.17	0.05	0.06	0.13	0.05	0.21	0.06
N	4	4	4	4	4	4	4	4	4	4	4

---: Data Unavailable

^aWeight gains compared to the previous period
^bBaseline is Day -2

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 219 GROUP: 2-F SEX: FEMALE
DOSE: 0.1 (mg/kg)

ANIMAL #	DAY 237	DAY 244	DAY 251	DAY 258	DAY 265	DAY 272	DAY 279	DAY 286	DAY 293	DAY 300	DAY 307
8935	0.2	0.0	0.1	0.0	0.2	0.3	-0.1	0.1	0.0	0.0	0.0
8937	-0.1	-0.1	0.1	0.3	0.1	0.0	0.1	0.2	-0.2	0.1	-0.1
8934	0.2	0.4	0.3	-0.2	0.1	0.2	-0.3	0.0	0.1	0.2	0.2
8945	0.3	0.3	0.2	0.2	0.2	0.9	-0.5	0.1	0.1	0.2	-0.2
MEAN	0.2	0.2	0.2	0.1	0.2	0.4	-0.2	0.1	0.0	0.1	0.0
S.D.	0.17	0.24	0.10	0.22	0.06	0.39	0.26	0.08	0.14	0.10	0.17
N	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 2-F SEX: FEMALE
DOSE: 0.1 (mg/kg)

ANIMAL #	DAY 314	DAY 321	DAY 328	DAY 335	DAY 342	DAY 349	DAY 356	DAY 363	TOTAL GAIN
8935	-0.1	0.3	0.0	0.4	0.0	0.1	0.4	-0.1	4.4
8937	0.4	-0.4	0.3	0.3	0.2	-0.2	0.0	-0.1	2.1
8934	-0.1	0.4	0.1	-0.2	-0.1	-0.2	0.3	0.0	2.2
8945	0.2	0.6	0.1	-0.2	-0.6	0.0	0.2	-0.2	4.9
MEAN	0.1	0.2	0.1	0.1	-0.1	-0.1	0.2	-0.1	3.4
S.D.	0.24	0.43	0.13	0.32	0.34	0.15	0.17	0.08	1.46
N	4	4	4	4	4	4	4	4	4

---: Data Unavailable

^aWeight gains compared to the previous period

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL WEIGHT GAIN (kilograms)^a

STUDY: 219 GROUP: 3-F SEX: FEMALE
DOSE: 1.0 (mg/kg)

ANIMAL #	DAY 6 ^b	DAY 13	DAY 20	DAY 27	DAY 34	DAY 41	DAY 48	DAY 55	DAY 62	DAY 69	DAY 76
8928	0.2	0.1	-0.2	-0.1	0.0	0.0	0.0	0.0	0.3	0.0	0.0
8940	-0.4	0.0	-0.1	-0.4	0.2	-0.1	0.1	0.1	0.0	0.0	0.1
8931	0.0	0.0	-0.2	-0.3	0.4	-0.4	-0.2	0.2	0.0	0.1	0.1
8943	-0.1	-0.2	0.2	-0.4	0.2	-0.1	0.0	0.3	-0.1	0.0	0.2
MEAN	-0.1	0.0	-0.1	-0.3	0.2	-0.2	0.0	0.2	0.1	0.0	0.1
S.D.	0.25	0.13	0.19	0.14	0.16	0.17	0.13	0.13	0.17	0.05	0.08
N	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 3-F SEX: FEMALE
DOSE: 1.0 (mg/kg)

ANIMAL #	DAY 83	DAY 90	DAY 97	DAY 104	DAY 111	DAY 118	DAY 125	DAY 132	DAY 139	DAY 146	DAY 153
8928	-0.1	-0.3	-0.1	0.1	0.1	0.1	-0.2	0.5	0.2	0.0	-0.1
8940	0.0	-0.2	-0.2	0.3	0.2	0.0	-0.1	0.2	0.3	-0.1	-0.1
8931	-0.7	-0.4	-0.2	0.1	0.0	-0.2	0.1	0.1	-0.1	0.3	-0.3
8943	0.0	0.0	0.1	0.1	0.2	0.2	0.0	-0.2	0.2	0.1	0.0
MEAN	-0.2	-0.2	-0.1	0.2	0.1	0.0	-0.1	0.2	0.2	0.1	-0.1
S.D.	0.34	0.17	0.14	0.10	0.10	0.17	0.13	0.29	0.17	0.17	0.13
N	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 3-F SEX: FEMALE
DOSE: 1.0 (mg/kg)

ANIMAL #	DAY 160	DAY 167	DAY 174	DAY 181	DAY 188	DAY 195	DAY 202	DAY 209	DAY 216	DAY 223	DAY 230
8928	-0.1	0.7	0.0	-0.5	0.0	1.8	-2.0	0.0	0.2	0.1	0.3
8940	-0.1	0.0	0.0	-0.4	-0.1	-0.1	0.4	0.0	0.0	0.2	0.0
8931	0.0	0.2	-0.2	0.0	0.2	-0.4	0.2	0.0	0.0	0.2	-0.1
8943	0.0	0.7	-0.7	0.2	0.2	0.0	0.2	-0.2	0.1	0.0	0.0
MEAN	-0.1	0.4	-0.2	-0.2	0.1	0.3	-0.3	-0.1	0.1	0.1	0.1
S.D.	0.06	0.36	0.33	0.33	0.15	1.00	1.14	0.10	0.10	0.10	0.17
N	4	4	4	4	4	4	4	4	4	4	4

---: Data Unavailable

^aWeight gains compared to the previous period
^bBaseline is Day -2

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 219

GROUP: 3-F
DOSE: 1.0 (mg/kg)

SEX: FEMALE

ANIMAL # DAY 237 DAY 244 DAY 251 DAY 258 DAY 265 DAY 272 DAY 279 DAY 286 DAY 293 DAY 300 DAY 307

8928	-0.3	0.0	-0.1	0.1	0.0	0.2	-0.1	0.1	0.0	0.1	0.0
8940	-0.2	0.4	0.0	0.2	-0.1	0.5	-0.6	0.3	0.1	0.2	-0.1
8931	0.1	0.5	-0.2	-0.1	0.2	0.5	0.2	-0.6	-0.2	0.3	0.1
8943	0.6	0.1	0.0	-0.1	0.7	0.7	-0.4	-0.5	0.3	0.0	0.9
MEAN	0.1	0.3	-0.1	0.0	0.2	0.5	-0.2	-0.2	0.1	0.2	0.2
S.D.	0.40	0.24	0.10	0.15	0.36	0.21	0.35	0.44	0.21	0.13	0.46
N	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 3-F
DOSE: 1.0 (mg/kg)

SEX: FEMALE

ANIMAL # DAY 314 DAY 321 DAY 328 DAY 335 DAY 342 DAY 349 DAY 356 DAY 363 TOTAL GAIN

8928	-0.3	0.3	0.4	-0.3	0.2	-0.3	-0.1	-0.1	0.8
8940	0.0	-0.2	0.1	-0.1	0.0	-0.2	-0.1	0.0	-0.1
8931	0.2	0.2	0.1	-0.1	0.0	0.1	0.0	0.0	-0.2
8943	-0.3	0.9	0.2	-0.3	-0.5	0.2	0.3	-0.5	3.5
MEAN	-0.1	0.3	0.2	-0.2	-0.1	-0.1	0.0	-0.2	1.0
S.D.	0.24	0.45	0.14	0.12	0.30	0.24	0.19	0.24	1.73
N	4	4	4	4	4	4	4	4	4

--: Data Unavailable

^aWeight gains compared to the previous period

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL WEIGHT GAIN (kilograms)^a

STUDY: 219

GROUP: 4-F
DOSE: 4.0 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 6 ^b	DAY 13	DAY 20	DAY 27	DAY 34	DAY 41	DAY 48	DAY 55	DAY 62	DAY 69	DAY 76
8941	-0.1	0.2	0.2	-0.2	0.0	-0.1	0.1	0.0	0.1	0.0	0.1
8933	0.0	0.4	-0.3	-0.2	0.3	-0.2	0.3	0.2	0.0	0.2	-0.3
8936	-0.3	0.4	-0.1	-0.1	0.0	0.1	0.0	0.2	0.0	0.2	0.0
8944	0.0	0.1	0.0	-0.1	0.0	-0.3	0.4	0.3	0.0	0.2	0.0
MEAN	-0.1	0.3	-0.1	-0.2	0.1	-0.1	0.2	0.2	0.0	0.2	-0.1
S.D.	0.14	0.15	0.21	0.06	0.15	0.17	0.18	0.13	0.05	0.10	0.17
N	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 4-F
DOSE: 4.0 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 83	DAY 90	DAY 97	DAY 104	DAY 111	DAY 118	DAY 125	DAY 132	DAY 139	DAY 146	DAY 153
8941	0.1	-0.1	0.1	-0.2	-0.1	-0.1	0.1	-0.2	0.2	0.0	-0.1
8933	0.0	0.0	-0.1	0.0	-0.1	0.0	-0.1	0.1	-0.1	0.2	0.2
8936	0.2	-0.1	-0.4	0.1	-0.2	0.0	0.1	-0.2	0.2	-0.1	0.2
8944	0.0	-0.3	0.0	0.1	-0.1	0.0	-0.1	-0.2	0.3	-0.1	-0.1
MEAN	0.1	-0.1	-0.1	0.0	-0.1	0.0	0.0	-0.1	0.2	0.0	0.1
S.O.	0.10	0.13	0.22	0.14	0.05	0.05	0.12	0.15	0.17	0.14	0.17
N	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 4-F
DOSE: 4.0 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 160	DAY 167	DAY 174	DAY 181	DAY 188	DAY 195	DAY 202	DAY 209	DAY 216	DAY 223	DAY 230
8941	-0.2	0.1	0.2	-0.3	0.1	0.0	0.1	0.0	0.2	-0.1	0.2
8933	0.1	0.0	0.1	-0.4	0.0	0.0	0.6	-0.4	0.5	0.1	0.2
8936	-0.3	0.7	-0.5	0.1	0.0	-0.1	0.3	-0.1	0.0	0.2	-0.1
8944	0.1	0.1	0.1	-0.3	0.1	-0.1	0.2	0.1	-0.1	0.1	-0.2
MEAN	-0.1	0.2	0.0	-0.2	0.1	-0.1	0.3	-0.1	0.2	0.1	0.0
S.D.	0.21	0.32	0.32	0.22	0.06	0.06	0.22	0.22	0.26	0.13	0.21
N	4	4	4	4	4	4	4	4	4	4	4

---: Data Unavailable

^aWeight gains compared to the previous period
^bBaseline is Day -2

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 219 GROUP: 4-F SEX: FEMALE
DOSE: 4.0 (mg/kg)

ANIMAL #	DAY 237	DAY 244	DAY 251	DAY 258	DAY 265	DAY 272	DAY 279	DAY 286	DAY 293	DAY 300	DAY 307
8941	0.0	0.3	0.1	0.1	-0.1	0.4	-0.2	0.2	0.0	-0.1	-0.1
8933	-0.3	0.4	-0.3	0.0	-0.1	0.2	-0.2	0.2	-0.1	0.0	0.0
8936	0.0	0.5	-0.2	0.4	-0.2	0.5	-0.4	0.0	0.0	-0.1	-0.2
8944	0.1	0.5	-0.2	0.0	0.1	0.4	-0.5	0.0	-0.2	0.2	0.3
MEAN	-0.1	0.4	-0.2	0.1	-0.1	0.4	-0.3	0.1	-0.1	0.0	0.0
S.D.	0.17	0.10	0.17	0.19	0.13	0.13	0.15	0.12	0.10	0.14	0.22
N	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 4-F SEX: FEMALE
DOSE: 4.0 (mg/kg)

ANIMAL #	DAY 314	DAY 321	DAY 328	DAY 335	DAY 342	DAY 349	DAY 356	DAY 363	TOTAL GAIN
8941	0.5	0.0	-0.2	0.1	0.0	-0.1	0.3	0.1	1.6
8933	0.1	0.1	0.1	0.0	-0.2	0.2	0.1	-0.3	1.2
8936	-0.1	0.2	0.1	-0.1	-0.2	0.0	0.2	-0.1	0.7
8944	0.1	0.0	0.0	0.1	-0.3	0.1	-0.1	-0.2	0.6
MEAN	0.2	0.1	0.0	0.0	-0.2	0.1	0.1	-0.1	1.0
S.D.	0.25	0.10	0.14	0.10	0.13	0.13	0.17	0.17	0.46
N	4	4	4	4	4	4	4	4	4

--: Data Unavailable

^aWeight gains compared to the previous period

DRAFT

APPENDIX E
Individual Food Consumption Data

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 219 GROUP: 1-M SEX: MALE
DOSE: 0 (mg/kg)

ANIMAL #	DAY -15	DAY -9	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70
8922	390	400	400	400	400	400	400	400	400	400	400	400
8915	400	400	291	400	400	400	400	400	400	400	400	400
8911	400	400	400	400	400	400	400	400	400	400	400	400
8909	360	400	400	400	400	400	400	400	400	400	400	400
MEAN	388	400	373	400	400	400	400	400	400	400	400	400
S.O.	18.9	0.0	54.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 1-M SEX: MALE
DOSE: 0 (mg/kg)

ANIMAL #	DAY 77	DAY 84	DAY 91	DAY 98	DAY 105	DAY 112	DAY 119	DAY 126	DAY 133	DAY 140	DAY 147	DAY 154
8922	400	400	400	400	400	400	400	400	400	400	400	400
8915	400	400	400	400	400	400	400	400	400	400	400	400
8911	400	400	400	400	400	400	400	400	400	400	400	400
8909	400	400	400	400	400	400	400	400	400	400	400	400
MEAN	400	400	400	400	400	400	400	400	400	400	400	400
S.O.	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 1-M SEX: MALE
DOSE: 0 (mg/kg)

ANIMAL #	DAY 161	DAY 169	DAY 175	DAY 182	DAY 189	DAY 196	DAY 203	DAY 210	DAY 217	DAY 224	DAY 231	DAY 238
8922	400	400	400	400	400	400	400	400	400	400	400	400
8915	400	400	400	400	400	400	400	400	400	400	400	400
8911	400	400	400	400	400	400	400	400	150	400	400	400
8909	400	400	400	400	400	400	400	400	400	400	400	400
MEAN	400	400	400	400	400	400	400	400	338	400	400	400
S.O.	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	125.0	0.0	0.0	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

--- Data Unavailable

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 219

GROUP: 1-M
DOSE: 0 (mg/kg)

SEX: MALE

ANIMAL #	DAY 245	DAY 252	DAY 259	DAY 266	DAY 273	DAY 280	DAY 287	DAY 294	DAY 301	DAY 308	DAY 315	DAY 322
8922	400	400	400	400	400	400	400	400	400	400	400	400
8915	400	400	400	400	400	400	400	400	400	400	400	400
8911	400	400	400	400	400	400	400	400	400	400	400	400
8909	400	400	400	400	400	400	400	400	400	400	400	400
MEAN	400	400	400	400	400	400	400	400	400	400	400	400
S.D.	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 1-M
DOSE: 0 (mg/kg)

SEX: MALE

ANIMAL #	DAY 329	DAY 336	DAY 343	DAY 350	DAY 357	DAY 364
8922	400	400	400	400	400	400
8915	400	400	400	400	400	400
8911	400	400	400	400	400	400
8909	400	400	400	400	400	400
MEAN	400	400	400	400	400	400
S.O.	0.0	0.0	0.0	0.0	0.0	0.0
N	4	4	4	4	4	4

--: Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 219

GROUP: 2-M
DOSE: 0.1 (mg/kg)

SEX: MALE

ANIMAL #	OAY -15	DAY -9	OAY 7	OAY 14	DAY 21	OAY 28	OAY 35	OAY 42	DAY 49	DAY 56	DAY 63	OAY 70
8923	106	400	400	400	400	400	400	400	400	400	400	400
8907	400	400	400	400	400	400	400	400	400	400	400	400
8919	362	400	400	400	400	400	400	400	400	400	400	400
8924	266	367	339	400	400	400	400	400	400	400	400	400
MEAN	284	392	385	400	400	400	400	400	400	400	400	400
S.D.	131.1	16.5	30.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 2-M
DOSE: 0.1 (mg/kg)

SEX: MALE

ANIMAL #	OAY 77	OAY 84	OAY 91	OAY 98	OAY 105	OAY 112	OAY 119	OAY 126	OAY 133	OAY 140	OAY 147	DAY 154
8923	400	400	400	400	400	400	400	400	400	400	400	400
8907	400	400	400	400	400	400	400	400	400	400	400	400
8919	400	400	400	400	400	400	400	400	400	400	400	400
8924	400	400	400	400	400	400	400	400	400	400	400	400
MEAN	400	400	400	400	400	400	400	400	400	400	400	400
S.O.	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 2-M
DOSE: 0.1 (mg/kg)

SEX: MALE

ANIMAL #	OAY 161	OAY 169	OAY 175	OAY 182	OAY 189	OAY 196	OAY 203	OAY 210	OAY 217	OAY 224	OAY 231	OAY 238
8923	400	400	400	400	400	400	400	400	400	400	400	400
8907	400	400	400	400	400	400	400	362	400	400	400	400
8919	400	400	400	400	400	400	400	400	400	400	400	400
8924	400	400	400	400	400	400	400	400	400	400	400	400
MEAN	400	400	400	400	400	400	400	391	400	400	400	400
S.O.	0.0	0.0	0.0	0.0	0.0	0.0	0.0	19.0	0.0	0.0	0.0	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

--: Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 219

GROUP: 2-M

SEX: MALE

DOSE: 0.1 (mg/kg)

ANIMAL #	DAY 245	DAY 252	DAY 259	DAY 266	DAY 273	DAY 280	DAY 287	DAY 294	DAY 301	DAY 308	DAY 315	DAY 322
8923	400	400	400	400	400	400	400	400	400	400	400	400
8907	400	400	400	400	400	400	400	400	400	400	400	400
8919	400	400	400	400	400	400	400	400	400	400	400	400
8924	400	400	400	400	400	400	400	400	400	400	400	400
MEAN	400	400	400	400	400	400	400	400	400	400	400	400
S.D.	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 2-M

SEX: MALE

DOSE: 0.1 (mg/kg)

ANIMAL #	DAY 329	DAY 336	DAY 343	DAY 350	DAY 357	DAY 364
8923	400	400	400	400	400	400
8907	400	400	400	400	400	400
8919	400	400	400	400	400	400
8924	400	400	400	400	400	400
MEAN	400	400	400	400	400	400
S.D.	0.0	0.0	0.0	0.0	0.0	0.0
N	4	4	4	4	4	4

--- Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 219

GROUP: 3-M
DOSE: 1.0 (mg/kg)

SEX: MALE

ANIMAL #	DAY -15	DAY -9	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70
8917	367	400	400	400	384	375	400	400	400	400	329	400
8910	347	400	400	400	400	400	400	400	400	400	400	400
8913	346	191	281	400	400	400	400	400	400	400	400	400
8914	400	400	400	400	400	400	400	400	400	400	400	400
MEAN	365	348	370	400	396	394	400	400	400	400	382	400
S.D.	25.3	104.5	59.5	0.0	8.0	12.5	0.0	0.0	0.0	0.0	35.5	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 3-M
DOSE: 1.0 (mg/kg)

SEX: MALE

ANIMAL #	DAY 77	DAY 84	DAY 91	DAY 98	DAY 105	DAY 112	DAY 119	DAY 126	DAY 133	DAY 140	DAY 147	DAY 154
8917	400	400	337	400	400	400	385	400	400	400	400	400
8910	400	400	400	400	400	400	400	400	400	400	400	400
8913	400	400	400	400	400	400	400	400	400	400	400	400
8914	400	400	400	400	400	400	400	400	400	400	400	400
MEAN	400	400	384	400	400	400	396	400	400	400	400	400
S.D.	0.0	0.0	31.5	0.0	0.0	0.0	7.5	0.0	0.0	0.0	0.0	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 3-M
DOSE: 1.0 (mg/kg)

SEX: MALE

ANIMAL #	DAY 161	DAY 169	DAY 175	DAY 182	DAY 189	DAY 196	DAY 203	DAY 210	DAY 217	DAY 224	DAY 231	DAY 238
8917	400	400	314	333	400	400	400	400	400	400	400	400
8910	400	400	400	400	301	400	400	400	400	400	400	400
8913	400	400	400	400	400	400	400	400	400	400	400	400
8914	400	400	400	400	400	400	400	400	400	400	400	400
MEAN	400	400	379	383	375	400	400	400	400	400	400	400
S.D.	0.0	0.0	43.0	33.5	49.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

--: Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 219

GROUP: 3-M
DOSE: 1.0 (mg/kg)

SEX: MALE

ANIMAL # DAY 245 DAY 252 DAY 259 DAY 266 DAY 273 DAY 280 DAY 287 DAY 294 DAY 301 DAY 308 DAY 315 DAY 322

8917	400	400	400	400	400	234	400	400	400	400	400	400
8910	400	400	400	400	400	400	400	400	400	400	400	400
8913	400	400	400	400	400	400	400	400	400	400	400	400
8914	400	400	400	400	400	400	400	400	400	400	400	400
MEAN	400	400	400	400	400	359	400	400	400	400	400	400
S.D.	0.0	0.0	0.0	0.0	0.0	83.0	0.0	0.0	0.0	0.0	0.0	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 3-M
DOSE: 1.0 (mg/kg)

SEX: MALE

ANIMAL # DAY 329 DAY 336 DAY 343 DAY 350 DAY 357 DAY 364

8917	400	400	400	400	400	400
8910	400	400	400	400	400	400
8913	400	400	400	400	400	400
8914	400	400	400	400	400	400
MEAN	400	400	400	400	400	400
S.D.	0.0	0.0	0.0	0.0	0.0	0.0
N	4	4	4	4	4	4

---: Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 219 GROUP: 4-M SEX: MALE
DOSE: 4.0 (mg/kg)

ANIMAL #	DAY -15	DAY -9	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70
8918	287	400	400	400	400	400	400	400	400	400	400	400
8908	400	400	400	400	400	400	400	400	400	400	400	400
8926	356	400	400	400	400	400	400	400	400	400	400	400
8921	229	400	400	400	400	400	400	400	400	400	400	400
MEAN	318	400	400	400	400	400	400	400	400	400	400	400
S.D.	75.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 4-M SEX: MALE
DOSE: 4.0 (mg/kg)

ANIMAL #	DAY 77	DAY 84	DAY 91	DAY 98	DAY 105	DAY 112	DAY 119	DAY 126	DAY 133	DAY 140	DAY 147	DAY 154
8918	400	400	400	400	400	400	400	400	400	400	400	400
8908	400	400	400	400	400	400	400	400	400	400	400	400
8926	400	400	400	400	400	400	400	400	400	400	400	400
8921	400	400	400	400	400	400	400	400	400	400	400	400
MEAN	400	400	400	400	400	400	400	400	400	400	400	400
S.D.	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 4-M SEX: MALE
DOSE: 4.0 (mg/kg)

ANIMAL #	DAY 161	DAY 169	DAY 175	DAY 182	DAY 189	DAY 196	DAY 203	DAY 210	DAY 217	DAY 224	DAY 231	DAY 238
8918	400	400	400	400	400	400	400	400	400	400	400	400
8908	400	400	400	400	400	400	400	400	400	400	400	400
8926	400	400	400	400	400	400	400	400	400	400	400	400
8921	400	400	400	400	400	400	400	400	400	400	400	400
MEAN	400	400	400	400	400	400	400	400	400	400	400	400
S.D.	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 219 GROUP: 4-M SEX: MALE
DOSE: 4.0 (mg/kg)

ANIMAL #	DAY 245	DAY 252	DAY 259	DAY 266	DAY 273	DAY 280	DAY 287	DAY 294	DAY 301	DAY 308	DAY 315	DAY 322
8918	400	400	400	400	400	400	400	400	400	400	400	400
8908	400	400	400	400	400	400	400	400	400	400	400	400
8926	400	400	400	400	400	400	400	400	400	400	400	400
8921	400	400	400	400	400	400	400	400	400	400	400	400
MEAN	400	400	400	400	400	400	400	400	400	400	400	400
S.D.	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 4-M SEX: MALE
DOSE: 4.0 (mg/kg)

ANIMAL #	DAY 329	DAY 336	DAY 343	DAY 350	DAY 357	DAY 364
8918	400	400	400	400	400	400
8908	400	400	400	400	400	400
8926	400	400	400	400	400	400
8921	400	400	400	400	400	400
MEAN	400	400	400	400	400	400
S.D.	0.0	0.0	0.0	0.0	0.0	0.0
N	4	4	4	4	4	4

--: Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 219 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg/kg)

ANIMAL #	DAY -15	DAY -9	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70
8929	172	192	375	384	395	400	400	400	400	400	400	400
8942	380	319	400	400	400	400	400	400	400	400	400	400
8930	255	400	400	400	400	400	400	400	400	400	400	400
8938	227	216	400	400	400	400	400	400	400	400	400	400
MEAN	259	282	394	396	399	400	400	400	400	400	400	400
S.D.	88.0	96.2	12.5	8.0	2.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg/kg)

ANIMAL #	DAY 77	DAY 84	DAY 91	DAY 98	DAY 105	DAY 112	DAY 119	DAY 126	DAY 133	DAY 140	DAY 147	DAY 154
8929	400	400	400	400	400	400	400	400	400	400	400	400
8942	400	400	400	400	400	400	400	400	400	400	400	400
8930	400	400	400	400	400	400	400	400	400	400	400	400
8938	400	400	400	400	400	400	400	400	400	400	400	400
MEAN	400	400	400	400	400	400	400	400	400	400	400	400
S.D.	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg/kg)

ANIMAL #	DAY 161	DAY 169	DAY 175	DAY 182	DAY 189	DAY 196	DAY 203	DAY 210	DAY 217	DAY 224	DAY 231	DAY 238
8929	400	400	400	400	400	400	400	400	400	400	400	400
8942	400	400	400	400	400	400	400	400	400	400	400	400
8930	400	400	400	400	400	400	400	400	400	400	400	400
8938	400	400	400	400	400	400	400	400	400	400	400	400
MEAN	400	400	400	400	400	400	400	400	400	400	400	400
S.D.	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

---: Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 219

GROUP: 1-F
DOSE: 0 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 245	DAY 252	DAY 259	DAY 266	DAY 273	DAY 280	DAY 287	DAY 294	DAY 301	DAY 308	DAY 315	DAY 322
8929	400	400	400	400	400	400	268	400	400	400	183	175
8942	400	400	400	400	400	400	400	400	400	400	400	400
8930	400	400	400	400	400	400	400	400	400	400	400	400
8938	400	400	400	400	400	400	400	400	400	400	400	400
MEAN	400	400	400	400	400	400	367	400	400	400	346	344
S.D.	0.0	0.0	0.0	0.0	0.0	0.0	66.0	0.0	0.0	0.0	108.5	112.5
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 1-F
DOSE: 0 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 329	DAY 336	DAY 343	DAY 350	DAY 357	DAY 364
8929	248	400	400	400	400	400
8942	400	400	400	400	400	400
8930	400	400	400	400	400	400
8938	400	400	400	400	400	400
MEAN	362	400	400	400	400	400
S.D.	76.0	0.0	0.0	0.0	0.0	0.0
N	4	4	4	4	4	4

--: Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 219

GROUP: 2-F
DOSE: 0.1 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY -15	DAY -9	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70
8935	43	253	400	221	389	354	400	400	336	400	257	191
8937	340	321	400	192	337	271	278	328	400	254	249	183
8934	158	338	400	211	400	400	400	400	400	400	400	400
8945	247	331	400	400	258	400	400	400	400	400	400	400
MEAN	197	311	400	256	346	356	370	382	384	364	327	294
S.O.	126.7	39.1	0.0	96.8	64.8	60.8	61.0	36.0	32.0	73.0	84.9	123.0
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 2-F
DOSE: 0.1 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 77	DAY 84	DAY 91	DAY 98	DAY 105	DAY 112	DAY 119	DAY 126	DAY 133	DAY 140	DAY 147	DAY 154
8935	290	400	400	400	400	400	400	400	400	400	400	400
8937	215	370	400	347	400	356	342	400	400	275	258	243
8934	400	400	400	400	400	400	400	400	400	400	400	400
8945	400	400	400	400	400	400	400	400	400	400	400	174
MEAN	326	393	400	387	400	389	386	400	400	369	365	304
S.D.	90.5	15.0	0.0	26.5	0.0	22.0	29.0	0.0	0.0	62.5	71.0	114.1
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 2-F
DOSE: 0.1 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 161	DAY 169	DAY 175	DAY 182	DAY 189	DAY 196	DAY 203	DAY 210	DAY 217	DAY 224	DAY 231	DAY 238
8935	400	400	59	400	400	400	400	400	400	400	400	400
8937	316	277	240	211	400	264	229	400	375	262	242	400
8934	400	400	400	400	400	400	400	400	400	400	400	400
8945	322	400	400	400	400	400	400	400	400	400	400	400
MEAN	360	369	275	353	400	366	357	400	394	366	361	400
S.D.	46.8	61.5	162.4	94.5	0.0	68.0	85.5	0.0	12.5	69.0	79.0	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

---: Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 219

GROUP: 2-F
DOSE: 0.1 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 245	DAY 252	DAY 259	DAY 266	DAY 273	DAY 280	DAY 287	DAY 294	DAY 301	DAY 308	DAY 315	DAY 322
8935	400	400	400	400	400	400	400	400	400	400	400	400
8937	321	329	315	119	52	188	118	279	400	400	400	286
8934	400	400	400	400	400	400	400	400	400	400	400	400
8945	400	400	400	400	400	400	400	400	400	223	400	400
MEAN	380	382	379	330	313	347	330	370	400	356	400	372
S.D.	39.5	35.5	42.5	140.5	174.0	106.0	141.0	60.5	0.0	88.5	0.0	57.0
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 2-F
DOSE: 0.1 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 329	DAY 336	DAY 343	DAY 350	DAY 357	DAY 364
8935	400	400	400	400	400	400
8937	166	297	400	400	400	90
8934	400	400	400	400	400	400
8945	400	400	400	400	400	400
MEAN	342	374	400	400	400	323
S.D.	117.0	51.5	0.0	0.0	0.0	155.0
N	4	4	4	4	4	4

---: Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 219 GROUP: 3-F SEX: FEMALE
DOSE: 1.0 (mg/kg)

ANIMAL #	OAY -15	OAY -9	OAY 7	OAY 14	OAY 21	OAY 28	OAY 35	DAY 42	DAY 49	OAY 56	OAY 63	OAY 70
8928	400	333	389	363	400	389	400	338	400	400	400	400
8940	357	88	400	400	400	400	400	400	400	400	400	400
8931	376	372	400	186	268	306	281	338	384	400	400	400
8943	224	400	400	400	400	400	400	400	400	400	400	400
MEAN	339	298	397	337	367	374	370	369	396	400	400	400
S.O.	78.8	142.8	5.5	102.3	66.0	45.5	59.5	35.8	8.0	0.0	0.0	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 3-F SEX: FEMALE
DOSE: 1.0 (mg/kg)

ANIMAL #	OAY 77	OAY 84	OAY 91	OAY 98	OAY 105	OAY 112	DAY 119	OAY 126	OAY 133	OAY 140	OAY 147	DAY 154
8928	368	400	400	400	400	400	400	400	400	400	400	400
8940	400	400	400	400	400	400	400	400	400	400	400	400
8931	400	400	400	400	400	400	400	400	400	400	400	400
8943	400	400	400	400	400	400	400	400	400	400	400	400
MEAN	392	400	400	400	400	400	400	400	400	400	400	400
S.O.	16.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 3-F SEX: FEMALE
DOSE: 1.0 (mg/kg)

ANIMAL #	OAY 161	OAY 169	OAY 175	OAY 182	OAY 189	OAY 196	OAY 203	OAY 210	DAY 217	DAY 224	OAY 231	OAY 238
8928	400	400	400	400	400	281	189	400	258	331	299	400
8940	400	400	400	400	400	400	400	400	400	400	400	400
8931	400	400	400	400	400	400	400	400	400	400	400	400
8943	400	400	400	400	400	400	400	400	400	400	400	400
MEAN	400	400	400	400	400	370	347	400	365	383	375	400
S.D.	0.0	0.0	0.0	0.0	0.0	59.5	105.5	0.0	71.0	34.5	50.5	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

---: Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 219

GROUP: 3-F
DOSE: 1.0 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 245	DAY 252	DAY 259	DAY 266	DAY 273	DAY 280	DAY 287	DAY 294	DAY 301	DAY 308	DAY 315	DAY 322
8928	144	400	400	400	400	178	400	400	400	400	400	400
8940	400	400	400	400	400	400	400	400	400	400	400	400
8931	400	400	400	400	400	400	400	400	400	400	400	400
8943	400	400	400	400	400	400	400	400	400	400	400	400
MEAN	336	400	400	400	400	345	400	400	400	400	400	400
S.D.	128.0	0.0	0.0	0.0	0.0	111.0	0.0	0.0	0.0	0.0	0.0	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 3-F
DOSE: 1.0 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 329	DAY 336	DAY 343	DAY 350	DAY 357	DAY 364
8928	400	400	400	400	400	268
8940	400	400	400	400	400	400
8931	400	400	400	400	400	400
8943	400	400	400	400	400	400
MEAN	400	400	400	400	400	367
S.D.	0.0	0.0	0.0	0.0	0.0	66.0
N	4	4	4	4	4	4

--: Data Unavailable

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 219 GROUP: 4-F SEX: FEMALE
DOSE: 4.0 (mg/kg)

ANIMAL #	DAY -15	DAY -9	DAY 7	OAY 14	OAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	OAY 70
8941	263	214	248	387	400	359	400	400	400	400	400	400
8933	293	355	400	224	373	400	262	400	400	351	400	218
8936	400	400	400	400	400	390	400	400	400	400	400	400
8944	328	293	309	355	204	297	400	400	400	318	400	365
MEAN	321	316	339	342	344	362	366	400	400	367	400	346
S.D.	59.0	80.6	74.4	80.6	94.4	46.4	69.0	0.0	0.0	40.1	0.0	86.8
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 4-F SEX: FEMALE
DOSE: 4.0 (mg/kg)

ANIMAL #	DAY 77	DAY 84	OAY 91	DAY 98	DAY 105	DAY 112	DAY 119	DAY 126	DAY 133	DAY 140	OAY 147	DAY 154
8941	400	400	400	400	400	400	400	400	400	400	400	400
8933	231	286	249	211	157	212	343	400	319	400	400	400
8936	400	400	400	400	400	400	400	400	400	400	400	400
8944	400	400	400	400	400	400	400	400	400	400	400	400
MEAN	358	372	362	353	339	353	386	400	380	400	400	400
S.D.	84.5	57.0	75.5	94.5	121.5	94.0	28.5	0.0	40.5	0.0	0.0	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219 GROUP: 4-F SEX: FEMALE
DOSE: 4.0 (mg/kg)

ANIMAL #	DAY 161	OAY 169	OAY 175	OAY 182	DAY 189	DAY 196	OAY 203	DAY 210	DAY 217	DAY 224	DAY 231	DAY 238
8941	400	400	400	400	400	400	400	400	400	400	400	400
8933	400	400	215	400	400	400	400	400	326	260	327	400
8936	400	400	400	400	400	400	400	400	400	400	400	400
8944	400	400	400	400	400	400	400	400	400	400	400	400
MEAN	400	400	354	400	400	400	400	400	382	365	382	400
S.D.	0.0	0.0	92.5	0.0	0.0	0.0	0.0	0.0	37.0	70.0	36.5	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

---: Data Unavailable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 219 GROUP: 4-F SEX: FEMALE
DOSE: 4.0 (mg/kg)

ANIMAL #	DAY 245	DAY 252	DAY 259	DAY 266	DAY 273	DAY 280	DAY 287	DAY 294	DAY 301	DAY 308	DAY 315	DAY 322
8941	400	400	400	400	400	400	400	400	400	400	400	400
8933	373	350	76	216	400	227	241	141	186	400	400	400
8936	400	400	400	400	400	400	400	400	400	400	400	400
8944	400	400	400	400	400	400	400	400	400	400	400	400
MEAN	393	388	319	354	400	357	360	335	347	400	400	400
S.D.	13.5	25.0	162.0	92.0	0.0	86.5	79.5	129.5	107.0	0.0	0.0	0.0
N	4	4	4	4	4	4	4	4	4	4	4	4

STUDY: 219

GROUP: 4-F
DOSE: 4.0 (mg/kg)

SEX: FEMALE

ANIMAL #	DAY 329	DAY 336	DAY 343	DAY 350	DAY 357	DAY 364
8941	400	400	400	400	400	400
8933	267	400	400	400	252	330
8936	400	400	400	400	400	400
8944	400	400	400	400	400	400
MEAN	367	400	400	400	363	383
S.D.	66.5	0.0	0.0	0.0	74.0	35.0
N	4	4	4	4	4	4

--: Data Unavailable

DRAFT

APPENDIX F
Individual Clinical Chemistry Data

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

Clinical Chemistry Test Directory

STUDY: UIC-9

NO.	ABBR. UNITS	DESCRIPTION PRECISION	CALCULATED	OPERAND A	OPERAND B	---LOWER LIMIT---		---UPPER LIMIT---	
						MALE	FEMALE	MALE	FEMALE
1.	ALT IU/L	Alanine Aminotransferase Integer	NO			20	20	50	50
2.	AST IU/L	Aspartate Aminotransferase Integer	NO			20	20	50	50
3.	TP g/dL	Total Protein 0.0	NO			5.5	5.5	7.5	7.5
4.	ALB g/dL	Albumin 0.0	NO			2.7	2.7	4.0	4.0
5.	TBILI mg/dL	Total Bilirubin 0.00	NO			0.00	0.00	0.50	0.50
6.	ALKP IU/L	Alkaline Phosphatase Integer	NO			50	50	200	150
7.	GGT IU/L	Gamma Glutamyl Transferase 0.0	NO			0	0	10	10
8.	CHOL mg/dL	Cholesterol Integer	NO			150	150	250	250
9.	TRIG mg/dL	Triglycerides Integer	NO			20	20	70	70
10.	LDH IU/L	Lactate Dehydrogenase Integer	NO			25	25	150	150
11.	CK IU/L	Creatine Kinase Integer	NO			100	100	400	400
12.	BUN mg/dL	Blood Urea Nitrogen 0.0	NO			8.0	8.0	20.0	20.0
13.	CREAT mg/dL	Creatinine 0.00	NO			0.50	0.50	1.00	1.00
14.	NA mEq/L	Sodium Integer	NO			140	140	150	150
15.	K mEq/L	Potassium 0.00	NO			4.00	4.00	5.25	5.25

(REPORT CONTINUED)

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

Clinical Chemistry Test Directory

STUDY: UIC-9

NO.	ABBR. UNITS	DESCRIPTION PRECISION	CALCULATED	OPERAND A	OPERAND B	---LOWER LIMIT---		---UPPER LIMIT---	
						MALE	FEMALE	MALE	FEMALE
16.	CL mEq/L	Chloride 0.0	NO			110	110	130	130
17.	CA mg/dL	Calcium 0.0	NO			9.0	9.0	12.0	12.0
18.	IP mg/dL	Inorganic Phosphorus 0.0	NO			4.0	4.0	8.0	8.0
19.	GLU mg/dL	Glucose Integer	NO			90	90	140	140
20.	HAPT mg/dL	Haptoglobin 0.0	NO			0.0	0.0	200.0	200.0
21.	GLOB g/dL	Globulin 0.0	Operand A - Operand B TP		ALB	2.7	2.7	4.0	4.0
22.	A/G -	A/G Ratio 0.00	Operand A / Operand B ALB		GLOB	0.70	0.70	1.50	1.50
23.	PH -	pH Integer	NO			6.3	6.8	7	7
24.	SG g/ml	Specific Gravity 0.000	NO			1.04	1.035	1.065	1.065

(END OF REPORT)

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK -3

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	ALT IU/L	AST IU/L	TP g/dL	ALB g/dL	GLOB g/dL	A/G -	TBILI mg/dL	ALKP IU/L
GROUP: 1-M:0 mg base/kg/day								
8915	41	42	6.5	3.4	3.1	1.10	0.12	96
8911	38	30	6.6	3.5	3.1	1.13	0.13	131
8909	66	23	6.9	3.9	3.0	1.30	0.13	115
8922	34	36	6.2	3.2	3.0	1.07	0.13	123
MEAN	45	33	6.6	3.5	3.1	1.15	0.13	116
SD	14.5	8.1	0.29	0.29	0.06	0.103	0.005	15.0
N	4	4	4	4	4	4	4	4
GROUP: 2-M:0.1 mg base/kg/day								
8923	32	34	6.3	3.1	3.2	0.97	0.10	122
8907	37	23	7.3	3.7	3.6	1.03	0.15	105
8919	26	21	7.0	3.8	3.2	1.19	0.12	70
8924	27	30	6.2	3.4	2.8	1.21	0.13	93
MEAN	31	27	6.7	3.5	3.2	1.10	0.13	98
SD	5.1	6.1	0.54	0.32	0.33	0.118	0.021	21.9
N	4	4	4	4	4	4	4	4
GROUP: 3-M:1.0 mg base/kg/day								
8917	34	25	6.5	3.1	3.4	0.91	0.10	100
8910	29	26	7.2	3.8	3.4	1.12	0.10	106
8913	31	31	6.3	3.5	2.8	1.25	0.10	97
8914	37	31	6.6	3.6	3.0	1.20	0.12	126
MEAN	33	28	6.7	3.5	3.2	1.12	0.11	107
SD	3.5	3.2	0.39	0.29	0.30	0.150	0.010	13.0
N	4	4	4	4	4	4	4	4
GROUP: 4-M:4.0 mg base/kg/day								
8908	46	25	6.6	3.4	3.2	1.06	0.13	138
8926	39	31	6.4	3.3	3.1	1.06	0.13	149
8921	59	31	6.3	3.1	3.2	0.97	0.11	190
8918	30	29	6.5	3.5	3.0	1.17	0.14	153
MEAN	44	29	6.5	3.3	3.1	1.07	0.13	158
SD	12.2	2.8	0.13	0.17	0.10	0.082	0.013	22.6
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK -3

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	GGT IU/L	CHOL mg/dL	TRIG mg/dL	LDH IU/L	CK IU/L	BUN mg/dL	CREAT mg/dL	NA mEq/L
GROUP: 1-M:0 mg base/kg/day								
8915	4.4	203	61	169	299	12.9	0.59	145
8911	5.8	217	51	31	262	7.9	0.64	144
8909	6.5	304	53	33	161	13.1	0.66	147
8922	3.3	201	42	43	380	13.9	0.89	146
MEAN	5.0	231	52	69	276	12.0	0.70	146
SD	1.43	49.0	7.8	66.9	90.9	2.73	0.133	1.3
N	4	4	4	4	4	4	4	4

GROUP: 2-M:0.1 mg base/kg/day								
8923	7.0	213	34	41	353	8.0	0.72	144
8907	5.8	313	65	51	149	11.3	0.65	145
8919	4.8	258	29	17	146	16.5	0.80	148
8924	6.2	179	51	37	334	9.6	0.68	144
MEAN	6.0	241	45	37	246	11.4	0.71	145
SD	0.91	58.0	16.5	14.3	113.4	3.69	0.065	1.9
N	4	4	4	4	4	4	4	4

GROUP: 3-M:1.0 mg base/kg/day								
8917	6.2	220	39	43	258	15.1	0.72	144
8910	3.7	302	43	43	167	18.0	0.69	148
8913	3.1	260	60	69	224	11.9	0.75	142
8914	4.4	253	82	49	197	15.4	0.72	145
MEAN	4.4	259	56	51	212	15.1	0.72	145
SD	1.34	33.7	19.6	12.3	38.8	2.50	0.024	2.5
N	4	4	4	4	4	4	4	4

GROUP: 4-M:4.0 mg base/kg/day								
8908	7.7	251	68	43	202	15.7	0.66	145
8926	5.5	335	57	53	350	12.7	0.71	146
8921	4.4	187	44	38	313	13.3	0.66	144
8918	5.5	214	32	38	316	17.4	0.73	148
MEAN	5.8	247	50	43	295	14.8	0.69	146
SD	1.38	64.4	15.6	7.1	64.4	2.18	0.036	1.7
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP PERIOD: WEEK -3

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	K mEq/L	CL mEq/L	CA mg/dL	IP mg/dL	GLU mg/dL	HAPT mg/dL
GROUP: 1-M:0 mg base/kg/day						
8915	4.79	115.0	10.9	6.9	121	-- B
8911	4.44	110.0	11.1	6.8	119	50.1
8909	4.55	113.5	11.3	7.3	125	42.5
8922	4.79	115.3	10.5	4.8	118	-- B
MEAN	4.64	113.5	11.0	6.5	121	46.3
SD	0.176	2.43	0.34	1.12	3.1	5.37
N	4	4	4	4	4	2
GROUP: 2-M:0.1 mg base/kg/day						
8923	4.37	116.0	11.4	6.7	120	22.0
8907	4.54	112.2	11.1	6.6	121	73.9
8919	4.54	111.7	11.4	5.9	119	75.6
8924	4.74	112.2	10.7	6.7	111	83.4
MEAN	4.55	113.0	11.2	6.5	118	63.7
SD	0.151	2.00	0.33	0.39	4.6	28.12
N	4	4	4	4	4	4
GROUP: 3-M:1.0 mg base/kg/day						
8917	4.60	114.9	10.9	6.3	110	76.9
8910	4.55	112.4	11.5	7.9	109	65.7
8913	4.54	116.0	10.8	6.9	108	18.8
8914	4.38	114.0	11.2	6.8	118	36.3
MEAN	4.52	114.3	11.1	7.0	111	49.4
SD	0.095	1.52	0.32	0.67	4.6	26.65
N	4	4	4	4	4	4
GROUP: 4-M:4.0 mg base/kg/day						
8908	4.68	116.9	11.1	7.9	106	75.0
8926	4.36	110.3	10.5	6.1	111	48.1
8921	4.47	111.5	10.8	6.9	116	63.8
8918	4.51	115.4	11.1	5.4	118	-- B
MEAN	4.51	113.5	10.9	6.6	113	62.3
SD	0.133	3.13	0.29	1.08	5.4	13.51
N	4	4	4	4	4	3

(--) - Data Unavailable

B - Below Linearity

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK -1

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	ALT IU/L	AST IU/L	TP g/dL	ALB g/dL	GLOB g/dL	A/G -	TBILI mg/dL	ALKP IU/L
GROUP: 1-M:0 mg base/kg/day								
8915	37	42	6.1	3.2	2.9	1.10	0.10	92
8911	30	48	6.3	3.4	2.9	1.17	0.17	128
8909	58	28	6.0	3.2	2.8	1.14	0.12	119
8922	37	60	5.9	3.1	2.8	1.11	0.15	119
MEAN	41	45	6.1	3.2	2.9	1.13	0.14	115
SD	12.1	13.3	0.17	0.13	0.06	0.032	0.031	15.6
N	4	4	4	4	4	4	4	4

GROUP: 2-M:0.1 mg base/kg/day								
8923	32	30	6.2	3.4	2.8	1.21	0.12	133
8907	31	31	6.4	3.5	2.9	1.21	0.14	91
8919	30	29	6.5	3.6	2.9	1.24	0.12	72
8924	26	33	6.1	3.6	2.5	1.44	0.16	92
MEAN	30	31	6.3	3.5	2.8	1.28	0.14	97
SD	2.6	1.7	0.18	0.10	0.19	0.111	0.019	25.7
N	4	4	4	4	4	4	4	4

GROUP: 3-M:1.0 mg base/kg/day								
8917	47	29	6.3	3.5	2.8	1.25	0.12	113
8910	34	34	6.6	3.5	3.1	1.13	0.15	107
8913	29	45	5.8	3.4	2.4	1.42	0.11	98
8914	33	34	6.5	3.7	2.8	1.32	0.15	129
MEAN	36	36	6.3	3.5	2.8	1.28	0.13	112
SD	7.8	6.8	0.36	0.13	0.29	0.122	0.021	13.0
N	4	4	4	4	4	4	4	4

GROUP: 4-M:4.0 mg base/kg/day								
8908	27	46	5.9	3.1	2.8	1.11	0.12	132
8926	23	33	6.1	3.2	2.9	1.10	0.15	155
8921	36	37	6.5	3.4	3.1	1.10	0.12	203
8918	26	33	6.3	3.4	2.9	1.17	0.17	147
MEAN	28	37	6.2	3.3	2.9	1.12	0.14	159
SD	5.6	6.1	0.26	0.15	0.13	0.034	0.024	30.7
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK -1

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	GGT IU/L	CHOL mg/dL	TRIG mg/dL	LDH IU/L	CK IU/L	BUN mg/dL	CREAT mg/dL	NA mEq/L
GROUP: 1-M:0 mg base/kg/day								
8915	3.6	180	52	120	381	9.9	0.61	147
8911	3.3	195	55	111	613	10.1	0.63	146
8909	4.9	205	51	27	151	10.2	0.62	144
8922	6.1	156	58	101	572	17.9	0.88	144
MEAN	4.5	184	54	90	429	12.0	0.69	145
SD	1.29	21.3	3.2	42.5	211.3	3.92	0.130	1.5
N	4	4	4	4	4	4	4	4
GROUP: 2-M:0.1 mg base/kg/day								
8923	5.4	199	47	46	217	9.7	0.64	143
8907	3.1	196	52	46	225	7.8	0.68	145
8919	4.4	151	33	35	238	13.4	0.73	146
8924	5.3	161	67	54	301	10.7	0.68	144
MEAN	4.6	177	50	45	245	10.4	0.68	145
SD	1.07	24.3	14.0	7.8	38.2	2.33	0.037	1.3
N	4	4	4	4	4	4	4	4
GROUP: 3-M:1.0 mg base/kg/day								
8917	4.1	167	51	60	207	12.3	0.69	145
8910	4.8	199	66	50	323	8.2	0.66	145
8913	4.8	212	52	88	408	10.6	0.73	145
8914	5.7	229	75	65	253	11.6	0.68	146
MEAN	4.9	202	61	66	298	10.7	0.69	145
SD	0.66	26.2	11.6	16.1	87.6	1.79	0.029	0.5
N	4	4	4	4	4	4	4	4
GROUP: 4-M:4.0 mg base/kg/day								
8908	5.6	164	41	75	266	12.8	0.67	145
8926	7.7	203	67	59	233	13.4	0.66	144
8921	4.7	160	57	73	288	14.8	0.70	145
8918	5.3	153	42	37	271	11.2	0.61	146
MEAN	5.8	170	52	61	265	13.1	0.66	145
SD	1.30	22.5	12.5	17.5	23.0	1.49	0.037	0.8
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP PERIOD: WEEK -1

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	K mEq/L	CL mEq/L	CA mg/dL	IP mg/dL	GLU mg/dL	HAPT mg/dL
GROUP: 1-M:0 mg base/kg/day						
8915	5.65	106.7	10.8	5.4	138	-- B
8911	4.43	110.4	10.7	5.3	128	-- B
8909	4.32	110.3	10.4	6.2	123	37.9
8922	4.14	116.5	10.5	4.1	109	19.0
MEAN	4.64	111.0	10.6	5.3	125	28.5
SD	0.687	4.07	0.18	0.87	12.1	13.36
N	4	4	4	4	4	2
GROUP: 2-M:0.1 mg base/kg/day						
8923	4.50	107.1	10.6	6.0	118	33.6
8907	4.42	106.3	10.5	6.1	128	73.4
8919	4.20	117.3	10.9	5.8	121	59.2
8924	4.40	111.1	10.5	7.0	114	28.3
MEAN	4.38	110.5	10.6	6.2	120	48.6
SD	0.128	5.03	0.19	0.53	5.9	21.33
N	4	4	4	4	4	4
GROUP: 3-M:1.0 mg base/kg/day						
8917	4.19	114.2	10.5	6.0	106	48.7
8910	4.53	107.7	10.8	6.1	112	55.0
8913	4.67	113.4	10.3	7.1	117	17.4
8914	4.20	118.3	11.0	5.4	131	32.3
MEAN	4.40	113.4	10.7	6.2	117	38.4
SD	0.241	4.36	0.31	0.70	10.7	16.93
N	4	4	4	4	4	4
GROUP: 4-M:4.0 mg base/kg/day						
8908	4.49	113.1	10.5	7.0	105	78.2
8926	4.30	116.4	10.2	6.2	121	42.7
8921	4.67	116.8	10.7	6.2	120	49.4
8918	4.34	108.0	10.5	6.6	124	30.6
MEAN	4.45	113.6	10.5	6.5	118	50.2
SD	0.168	4.07	0.21	0.38	8.5	20.21
N	4	4	4	4	4	4

(--) - Data Unavailable

B - Below Linearity

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK 4

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	ALT IU/L	AST IU/L	TP g/dL	ALB g/dL	GLOB g/dL	A/G -	TBILI mg/dL	ALKP IU/L
GROUP: 1-M:0 mg base/kg/day								
8915	31	38	6.0	3.2	2.8	1.14	0.13	81
8911	29	32	6.8	3.5	3.3	1.06	0.15	119
8909	52	27	6.0	3.3	2.7	1.22	0.13	96
8922	31	31	5.9	2.9	3.0	0.97	0.12	120
MEAN	36	32	6.2	3.2	3.0	1.10	0.13	104
SD	10.9	4.5	0.42	0.25	0.26	0.107	0.013	18.9
N	4	4	4	4	4	4	4	4

GROUP: 2-M:0.1 mg base/kg/day								
8923	38	40	6.4	3.2	3.2	1.00	0.08	111
8907	34	25	6.1	3.3	2.8	1.18	0.10	82
8919	26	25	6.5	3.2	3.3	0.97	0.13	73
8924	29	32	6.0	3.3	2.7	1.22	0.13	83
MEAN	32	31	6.3	3.3	3.0	1.09	0.11	87
SD	5.3	7.1	0.24	0.06	0.29	0.126	0.024	16.5
N	4	4	4	4	4	4	4	4

GROUP: 3-M:1.0 mg base/kg/day								
8917	26	26	6.4	3.4	3.0	1.13	0.13	92
8910	26	34	6.4	3.4	3.0	1.13	0.10	88
8913	26	39	5.9	3.1	2.8	1.11	0.13	81
8914	32	32	6.0	3.3	2.7	1.22	0.11	104
MEAN	28	33	6.2	3.3	2.9	1.15	0.12	91
SD	3.0	5.4	0.26	0.14	0.15	0.049	0.015	9.6
N	4	4	4	4	4	4	4	4

GROUP: 4-M:4.0 mg base/kg/day								
8908	26	31	6.2	3.4	2.8	1.21	0.18	99
8926	25	29	6.3	3.2	3.1	1.03	0.27	101
8921	33	36	6.2	3.1	3.1	1.00	0.14	130
8918	21	33	6.2	3.0	3.2	0.94	0.19	81
MEAN	26	32	6.2	3.2	3.1	1.05	0.20	103
SD	5.0	3.0	0.05	0.17	0.17	0.116	0.054	20.3
N	4	4	4	4	4	4	4	4

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK 4

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	GGT IU/L	CHOL mg/dL	TRIG mg/dL	LDH IU/L	CK IU/L	BUN mg/dL	CREAT mg/dL	NA mEq/L
GROUP: 1-M:0 mg base/kg/day								
8915	1.6	171	71	146	235	13.0	0.67	145
8911	2.5	203	38	37	184	13.7	0.72	145
8909	3.7	204	45	39	107	10.7	0.67	146
8922	3.6	161	31	33	152	15.0	0.67	144
MEAN	2.9	185	46	64	170	13.1	0.68	145
SD	0.99	22.0	17.5	54.9	53.9	1.80	0.025	0.8
N	4	4	4	4	4	4	4	4

GROUP: 2-M:0.1 mg base/kg/day								
8923	3.2	196	87	72	225	16.4	0.70	145
8907	4.0	202	51	24	96	12.0	0.71	145
8919	5.5	166	45	25	205	17.0	0.77	147
8924	5.4	148	47	48	213	15.6	0.75	148
MEAN	4.5	178	58	42	185	15.3	0.73	146
SD	1.12	25.5	19.8	22.7	59.7	2.24	0.033	1.5
N	4	4	4	4	4	4	4	4

GROUP: 3-M:1.0 mg base/kg/day								
8917	3.8	168	37	41	175	18.1	0.80	145
8910	3.3	205	69	47	316	14.5	0.72	144
8913	3.2	203	69	68	153	20.1	0.75	144
8914	4.8	164	65	55	265	14.9	0.69	146
MEAN	3.8	185	60	53	227	16.9	0.74	145
SD	0.73	22.0	15.4	11.7	76.5	2.67	0.047	1.0
N	4	4	4	4	4	4	4	4

GROUP: 4-M:4.0 mg base/kg/day								
8908	4.8	174	55	81	169	17.5	0.81	147
8926	6.3	207	60	85	201	18.0	0.76	145
8921	2.6	172	48	44	190	15.5	0.83	144
8918	0.0	172	61	89	141	14.5	0.61	144
MEAN	3.4	181	56	75	175	16.4	0.75	145
SD	2.74	17.2	5.9	20.8	26.4	1.65	0.099	1.4
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK 4

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	K mEq/L	CL mEq/L	CA mg/dL	IP mg/dL	GLU mg/dL	HAPT mg/dL
GROUP: 1-M:0 mg base/kg/day						
8915	4.96	110.2	10.7	6.8	111	69.4
8911	4.85	115.4	11.2	6.1	120	62.8
8909	4.22	111.9	10.7	5.8	117	54.5
8922	4.64	110.0	11.1	6.3	113	49.3
MEAN	4.67	111.9	10.9	6.3	115	59.0
SD	0.327	2.50	0.26	0.42	4.0	8.89
N	4	4	4	4	4	4
GROUP: 2-M:0.1 mg base/kg/day						
8923	5.13	113.4	10.8	6.1	108	65.1
8907	4.22	112.1	10.3	5.3	115	89.3
8919	4.28	111.1	11.2	6.4	113	104.5
8924	4.30	113.1	10.7	5.9	111	31.5
MEAN	4.48	112.4	10.8	5.9	112	72.6
SD	0.433	1.04	0.37	0.46	3.0	31.84
N	4	4	4	4	4	4
GROUP: 3-M:1.0 mg base/kg/day						
8917	4.09	115.8	11.1	5.4	108	65.9
8910	4.71	112.3	11.0	6.7	117	67.4
8913	4.44	113.5	10.4	6.6	102	73.6
8914	4.32	110.3	10.7	5.8	115	41.3
MEAN	4.39	113.0	10.8	6.1	111	62.1
SD	0.258	2.30	0.32	0.63	6.9	14.23
N	4	4	4	4	4	4
GROUP: 4-M:4.0 mg base/kg/day						
8908	4.41	112.1	11.0	6.5	101	113.6
8926	4.24	113.6	10.7	6.4	109	125.4
8921	4.34	118.0	11.1	5.8	106	94.2
8918	4.22	110.8	10.9	4.5	113	141.5
MEAN	4.30	113.6	10.9	5.8	107	118.7
SD	0.089	3.13	0.17	0.92	5.1	19.92
N	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK 13

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	ALT IU/L	AST IU/L	TP g/dL	ALB g/dL	GLOB g/dL	A/G -	TBILI mg/dL	ALKP IU/L
GROUP: 1-M:0 mg base/kg/day								
8915	32	44	6.2	3.3	2.9	1.14	0.18	77
8911	34	41	6.4	3.6	2.8	1.29	0.19	67
8909	42	30	5.8	3.2	2.6	1.23	0.13	63
8922	37	59	5.9	3.1	2.8	1.11	0.17	89
MEAN	36	44	6.1	3.3	2.8	1.19	0.17	74
SD	4.3	12.0	0.28	0.22	0.13	0.083	0.026	11.6
N	4	4	4	4	4	4	4	4

GROUP: 2-M:0.1 mg base/kg/day								
8923	43	37	6.1	3.4	2.7	1.26	0.16	102
8907	48	41	6.3	3.4	2.9	1.17	0.16	66
8919	29	29	6.2	3.4	2.8	1.21	0.19	57
8924	33	37	6.1	3.6	2.5	1.44	0.20	60
MEAN	38	36	6.2	3.5	2.7	1.27	0.18	71
SD	8.8	5.0	0.10	0.10	0.17	0.119	0.021	20.8
N	4	4	4	4	4	4	4	4

GROUP: 3-M:1.0 mg base/kg/day								
8917	32	37	6.0	3.3	2.7	1.22	0.17	61
8910	28	41	6.4	3.3	3.1	1.06	0.18	92
8913	30	40	5.8	3.2	2.6	1.23	0.20	69
8914	29	40	6.0	3.1	2.9	1.07	0.17	87
MEAN	30	40	6.1	3.2	2.8	1.15	0.18	77
SD	1.7	1.7	0.25	0.10	0.22	0.093	0.014	14.7
N	4	4	4	4	4	4	4	4

GROUP: 4-M:4.0 mg base/kg/day								
8908	31	46	6.2	3.1	3.1	1.00	0.19	80
8926	33	54	6.0	3.1	2.9	1.07	0.21	92
8921	43	64	6.4	3.1	3.3	0.94	0.16	143
8918	30	43	6.4	3.2	3.2	1.00	0.19	78
MEAN	34	52	6.3	3.1	3.1	1.00	0.19	98
SD	6.0	9.4	0.19	0.05	0.17	0.053	0.021	30.5
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK 13

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	GGT IU/L	CHOL mg/dL	TRIG mg/dL	LDH IU/L	CK IU/L	BUN mg/dL	CREAT mg/dL	NA mEq/L
GROUP: 1-M:0 mg base/kg/day								
8915	3.0	166	49	143	211	13.7	0.66	146
8911	5.6	142	30	68	385	17.1	0.75	148
8909	3.8	177	28	41	93	15.4	0.84	148
8922	2.4	148	38	74	596	22.7	0.87	144
MEAN	3.7	158	36	82	321	17.2	0.78	147
SD	1.39	16.1	9.5	43.4	218.9	3.91	0.095	1.9
N	4	4	4	4	4	4	4	4

GROUP: 2-M:0.1 mg base/kg/day								
8923	2.5	149	31	68	164	15.6	0.73	143
8907	0.3	181	44	65	263	14.4	0.77	146
8919	4.6	138	38	69	141	21.7	0.81	144
8924	4.1	138	54	80	198	16.0	0.75	147
MEAN	2.9	152	42	71	192	16.9	0.77	145
SD	1.94	20.3	9.7	6.6	53.1	3.26	0.034	1.8
N	4	4	4	4	4	4	4	4

GROUP: 3-M:1.0 mg base/kg/day								
8917	0.9	147	34	93	186	21.7	0.91	143
8910	0.9	241	65	132	221	17.2	0.85	143
8913	0.0	200	55	152	172	19.2	0.85	143
8914	1.0	161	55	80	165	18.8	0.81	144
MEAN	0.7	187	52	114	186	19.2	0.86	143
SD	0.47	42.3	13.0	33.5	24.9	1.86	0.041	0.5
N	4	4	4	4	4	4	4	4

GROUP: 4-M:4.0 mg base/kg/day								
8908	2.5	145	70	120	283	18.7	0.92	146
8926	1.6	207	59	178	252	20.7	0.83	146
8921	0.6	185	71	114	246	22.2	0.86	141
8918	3.9	161	74	70	273	18.0	0.85	145
MEAN	2.2	175	69	121	264	19.9	0.87	145
SD	1.40	27.2	6.6	44.3	17.4	1.91	0.039	2.4
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK 13

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	K mEq/L	CL mEq/L	CA mg/dL	IP mg/dL	GLU mg/dL	HAPT mg/dL
GROUP: 1-M:0 mg base/kg/day						
8915	4.19	114.7	10.4	5.2	109	116.9
8911	4.24	109.9	10.4	4.3	111	79.6
8909	3.96	108.9	10.1	4.9	103	31.2
8922	3.99	105.6	10.3	4.4	112	41.5
MEAN	4.10	109.8	10.3	4.7	109	67.3
SD	0.141	3.76	0.14	0.42	4.0	39.07
N	4	4	4	4	4	4
GROUP: 2-M:0.1 mg base/kg/day						
8923	4.72	109.3	10.4	4.8	105	37.9
8907	4.22	103.1	10.0	4.4	112	52.7
8919	4.02	107.9	10.3	5.0	107	38.7
8924	4.14	109.6	10.1	4.6	114	94.9
MEAN	4.28	107.5	10.2	4.7	110	56.1
SD	0.308	3.01	0.18	0.26	4.2	26.78
N	4	4	4	4	4	4
GROUP: 3-M:1.0 mg base/kg/day						
8917	4.12	107.8	9.9	3.4	106	-- B
8910	3.75	111.2	9.9	5.1	102	50.6
8913	4.24	107.2	10.0	4.7	99	-- B
8914	3.76	115.0	10.1	4.1	116	30.9
MEAN	3.97	110.3	10.0	4.3	106	40.8
SD	0.250	3.59	0.10	0.74	7.4	13.93
N	4	4	4	4	4	2
GROUP: 4-M:4.0 mg base/kg/day						
8908	4.42	111.2	10.0	4.8	100	152.0
8926	3.60	106.1	9.7	3.5	89	120.4
8921	4.25	111.0	9.6	4.3	103	37.2
8918	4.10	112.0	10.4	5.4	96	127.3
MEAN	4.09	110.1	9.9	4.5	97	109.2
SD	0.353	2.68	0.36	0.80	6.1	49.90
N	4	4	4	4	4	4

(--)- Data Unavailable

B - Below Linearity

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK 26

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	ALT IU/L	AST IU/L	TP g/dL	ALB g/dL	GLOB g/dL	A/G -	TBILI mg/dL	ALKP IU/L
GROUP: 1-M:0 mg base/kg/day								
8915	28	45	5.8	3.1	2.7	1.15	0.13	80
8911	33	37	5.9	3.0	2.9	1.03	0.14	99
8909	35	30	5.7	2.8	2.9	0.97	0.15	95
8922	37	53	6.1	4.0	2.1	1.90	0.19	60
MEAN	33	41	5.9	3.2	2.7	1.26	0.15	84
SD	3.9	9.9	0.17	0.53	0.38	0.432	0.026	17.7
N	4	4	4	4	4	4	4	4
GROUP: 2-M:0.1 mg base/kg/day								
8923	39	33	6.1	3.4	2.7	1.26	0.14	97
8907	60	50	6.8	3.9	2.9	1.34	0.17	53
8919	28	38	6.5	4.1	2.4	1.71	0.14	52
8924	27	38	6.7	4.2	2.5	1.68	0.16	74
MEAN	39	40	6.5	3.9	2.6	1.50	0.15	69
SD	15.3	7.2	0.31	0.36	0.22	0.231	0.015	21.2
N	4	4	4	4	4	4	4	4
GROUP: 3-M:1.0 mg base/kg/day								
8917	27	36	5.9	2.9	3.0	0.97	0.12	79
8910	24	36	6.0	3.1	2.9	1.07	0.12	73
8913	23	34	4.9	2.6	2.3	1.13	0.12	53
8914	28	41	6.1	4.0	2.1	1.90	0.15	70
MEAN	26	37	5.7	3.2	2.6	1.27	0.13	69
SD	2.4	3.0	0.56	0.60	0.44	0.427	0.015	11.1
N	4	4	4	4	4	4	4	4
GROUP: 4-M:4.0 mg base/kg/day								
8908	28	54	6.0	3.1	2.9	1.07	0.20	90
8926	53	49	5.3	2.8	2.5	1.12	0.15	61
8921	32	46	5.7	2.9	2.8	1.04	0.12	119
8918	24	35	6.4	3.1	3.3	0.94	0.21	76
MEAN	34	46	5.9	3.0	2.9	1.04	0.17	87
SD	12.9	8.0	0.47	0.15	0.33	0.076	0.042	24.7
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK 26

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	GGT IU/L	CHOL mg/dL	TRIG mg/dL	LDH IU/L	CK IU/L	BUN mg/dL	CREAT mg/dL	NA mEq/L
GROUP: 1-M:0 mg base/kg/day								
8915	3.6	136	38	126	202	12.2	0.69	145
8911	2.1	134	38	68	263	10.5	0.78	148
8909	6.2	190	35	69	94	11.1	0.72	147
8922	3.9	160	23	99	398	24.1	0.94	147
MEAN	4.0	155	34	91	239	14.5	0.78	147
SD	1.69	26.2	7.1	27.7	126.8	6.46	0.111	1.3
N	4	4	4	4	4	4	4	4
GROUP: 2-M:0.1 mg base/kg/day								
8923	4.0	156	29	53	111	13.8	0.72	147
8907	1.3	196	41	125	153	14.6	0.80	152
8919	5.2	125	17	201	142	18.3	0.68	145
8924	4.7	154	36	80	78	14.5	0.68	146
MEAN	3.8	158	31	115	121	15.3	0.72	148
SD	1.74	29.2	10.4	64.7	33.7	2.03	0.057	3.1
N	4	4	4	4	4	4	4	4
GROUP: 3-M:1.0 mg base/kg/day								
8917	2.0	115	35	37	85	14.0	0.77	146
8910	3.8	200	35	73	140	17.1	0.77	148
8913	3.6	104	35	154	104	15.6	0.67	145
8914	4.7	146	50	55	126	15.7	0.75	146
MEAN	3.5	141	39	80	114	15.6	0.74	146
SD	1.12	43.0	7.5	51.6	24.2	1.27	0.048	1.3
N	4	4	4	4	4	4	4	4
GROUP: 4-M:4.0 mg base/kg/day								
8908	4.2	147	54	146	188	17.4	0.84	147
8926	5.6	152	47	247	183	14.8	0.76	145
8921	3.4	136	38	61	104	19.4	0.82	145
8918	4.8	144	42	45	101	21.6	0.77	148
MEAN	4.5	145	45	125	144	18.3	0.80	146
SD	0.93	6.7	6.9	92.8	48.0	2.90	0.039	1.5
N	4	4	4	4	4	4	4	4

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK 26

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	K mEq/L	CL mEq/L	CA mg/dL	IP mg/dL	GLU mg/dL	HAPT mg/dL
GROUP: 1-M:0 mg base/kg/day						
8915	4.39	111.7	10.2	4.5	101	121.3
8911	4.36	119.7	10.2	3.6	101	94.8
8909	4.21	117.3	10.0	4.5	114	49.4
8922	3.98	124.0	10.1	4.7	92	101.2
MEAN	4.24	118.2	10.1	4.3	102	91.7
SD	0.187	5.13	0.10	0.49	9.1	30.36
N	4	4	4	4	4	4
GROUP: 2-M:0.1 mg base/kg/day						
8923	4.66	107.8	10.1	4.0	105	75.2
8907	3.93	118.9	10.5	4.3	106	48.5
8919	4.32	127.7	11.1	4.9	117	-- B
8924	4.45	118.3	10.5	4.2	82	218.8
MEAN	4.34	118.2	10.6	4.4	103	114.2
SD	0.307	8.14	0.41	0.39	14.7	91.59
N	4	4	4	4	4	3
GROUP: 3-M:1.0 mg base/kg/day						
8917	4.40	118.5	9.7	3.9	89	133.2
8910	4.52	116.0	9.9	5.0	100	125.6
8913	4.31	118.2	9.2	4.5	82	110.3
8914	4.11	121.9	10.5	4.5	113	70.6
MEAN	4.34	118.7	9.8	4.5	96	109.9
SD	0.173	2.44	0.54	0.45	13.5	27.89
N	4	4	4	4	4	4
GROUP: 4-M:4.0 mg base/kg/day						
8908	4.55	113.9	10.0	4.3	74	131.9
8926	4.37	119.0	9.2	4.1	89	143.4
8921	4.00	113.1	10.0	4.9	94	94.9
8918	4.18	117.8	10.1	4.4	110	182.8
MEAN	4.28	116.0	9.8	4.4	92	138.3
SD	0.238	2.89	0.42	0.34	14.8	36.20
N	4	4	4	4	4	4

(--) - Data Unavailable

B - Below Linearity

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK 52

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	ALT IU/L	AST IU/L	TP g/dL	ALB g/dL	GLOB g/dL	A/G -	TBILI mg/dL	ALKP IU/L
GROUP: 1-M:0 mg base/kg/day								
8915	37	58	6.4	3.3	3.1	1.06	0.20	57
8911	41	48	6.3	3.3	3.0	1.10	0.20	48
8909	37	27	5.7	3.0	2.7	1.11	0.14	67
8922	35	39	6.2	3.2	3.0	1.07	0.18	67
MEAN	38	43	6.2	3.2	3.0	1.09	0.18	60
SD	2.5	13.2	0.31	0.14	0.17	0.024	0.028	9.1
N	4	4	4	4	4	4	4	4
GROUP: 2-M:0.1 mg base/kg/day								
8923	52	44	6.2	3.3	2.9	1.14	0.15	94
8907	55	40	6.4	3.5	2.9	1.21	0.20	46
8919	30	30	5.8	3.2	2.6	1.23	0.18	43
8924	25	32	6.3	3.2	3.1	1.03	0.13	52
MEAN	41	37	6.2	3.3	2.9	1.15	0.17	59
SD	15.2	6.6	0.26	0.14	0.21	0.090	0.031	23.8
N	4	4	4	4	4	4	4	4
GROUP: 3-M:1.0 mg base/kg/day								
8917	31	26	6.2	3.2	3.0	1.07	0.16	36
8910	32	47	6.7	3.3	3.4	0.97	0.15	101
8913	29	45	5.4	3.1	2.3	1.35	0.16	60
8914	30	36	5.6	3.0	2.6	1.15	0.16	65
MEAN	31	39	6.0	3.2	2.8	1.14	0.16	66
SD	1.3	9.6	0.59	0.13	0.48	0.161	0.005	26.8
N	4	4	4	4	4	4	4	4
GROUP: 4-M:4.0 mg base/kg/day								
8908	34	60	6.2	3.0	3.2	0.94	0.16	71
8926	47	50	6.3	3.1	3.2	0.97	0.26	84
8921	63	55	6.1	3.1	3.0	1.03	0.13	109
8918	26	30	6.0	3.0	3.0	1.00	0.13	46
MEAN	43	49	6.2	3.1	3.1	0.99	0.17	78
SD	16.2	13.1	0.13	0.06	0.12	0.039	0.062	26.3
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK 52

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	GGT IU/L	CHOL mg/dL	TRIG mg/dL	LDH IU/L	CK IU/L	BUN mg/dL	CREAT mg/dL	NA mEq/L
GROUP: 1-M:0 mg base/kg/day								
8915	6.5	150	43	138	870	15.8	0.83	149
8911	5.7	129	30	81	336	10.4	0.92	145
8909	4.7	168	23	41	124	11.5	0.77	149
8922	4.4	157	23	35	134	19.9	0.99	151
MEAN	5.3	151	30	74	366	14.4	0.88	149
SD	0.96	16.4	9.4	47.5	349.9	4.34	0.097	2.5
N	4	4	4	4	4	4	4	4

GROUP: 2-M:0.1 mg base/kg/day								
8923	6.5	159	32	26	137	12.4	0.83	147
8907	1.2	171	68	93	152	11.0	0.90	149
8919	6.1	125	23	72	161	18.0	0.86	149
8924	4.3	138	36	83	113	11.3	0.84	150
MEAN	4.5	148	40	69	141	13.2	0.86	149
SD	2.41	20.6	19.6	29.6	21.0	3.27	0.031	1.3
N	4	4	4	4	4	4	4	4

GROUP: 3-M:1.0 mg base/kg/day								
8917	6.7	138	36	34	69	15.6	0.96	149
8910	7.1	266	57	137	161	15.2	0.80	149
8913	4.8	163	55	212	252	22.4	0.77	147
8914	5.6	139	36	46	103	18.3	0.86	146
MEAN	6.1	177	46	107	146	17.9	0.85	148
SD	1.05	60.8	11.6	83.6	80.1	3.32	0.084	1.5
N	4	4	4	4	4	4	4	4

GROUP: 4-M:4.0 mg base/kg/day								
8908	5.2	139	56	76	122	18.6	0.89	148
8926	4.7	208	74	82	98	17.5	0.87	147
8921	6.3	175	72	114	214	18.6	0.95	146
8918	5.4	129	44	32	73	21.5	0.83	149
MEAN	5.4	163	62	76	127	19.1	0.89	148
SD	0.67	36.1	14.2	33.7	61.5	1.71	0.050	1.3
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK 52

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	K mEq/L	CL mEq/L	CA mg/dL	IP mg/dL	GLU mg/dL	HAPT mg/dL
GROUP: 1-M:0 mg base/kg/day						
8915	4.48	107.4	10.4	4.1	108	120.5
8911	4.26	106.2	9.9	3.5	106	108.4
8909	4.29	112.9	10.1	4.0	117	102.4
8922	4.16	110.8	9.9	2.9	107	103.6
MEAN	4.30	109.3	10.1	3.6	110	108.7
SD	0.134	3.08	0.24	0.55	5.1	8.27
N	4	4	4	4	4	4
GROUP: 2-M:0.1 mg base/kg/day						
8923	4.68	109.3	9.8	3.2	104	89.3
8907	4.22	106.5	9.5	2.8	112	110.5
8919	4.32	111.1	9.9	3.6	110	79.9
8924	4.58	108.2	9.8	3.1	96	317.8
MEAN	4.45	108.8	9.8	3.2	106	149.4
SD	0.216	1.93	0.17	0.33	7.2	113.01
N	4	4	4	4	4	4
GROUP: 3-M:1.0 mg base/kg/day						
8917	4.11	109.1	9.8	3.3	94	93.0
8910	4.92	108.4	10.1	4.0	89	77.6
8913	4.53	112.3	9.2	3.4	91	18.9
8914	4.29	108.4	9.6	2.9	111	60.2
MEAN	4.46	109.6	9.7	3.4	96	62.4
SD	0.350	1.86	0.38	0.45	10.0	31.96
N	4	4	4	4	4	4
GROUP: 4-M:4.0 mg base/kg/day						
8908	4.84	111.9	10.0	4.4	97	161.7
8926	4.73	106.9	9.0	2.5	95	194.0
8921	5.32	108.0	9.4	4.7	84	122.9
8918	4.26	109.6	10.2	5.2	107	225.1
MEAN	4.79	109.1	9.7	4.2	96	175.9
SD	0.435	2.17	0.55	1.18	9.4	43.81
N	4	4	4	4	4	4

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK -3

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	ALT IU/L	AST IU/L	TP g/dL	ALB g/dL	GLOB g/dL	A/G -	TBILI mg/dL	ALKP IU/L
GROUP: 1-F:0 mg base/kg/day								
8929	31	24	6.0	3.5	2.5	1.40	0.12	89
8942	47	25	6.0	3.8	2.2	1.73	0.11	133
8930	41	29	5.7	3.5	2.2	1.59	0.14	98
8938	37	30	5.9	3.6	2.3	1.57	0.13	116
MEAN	39	27	5.9	3.6	2.3	1.57	0.13	109
SD	6.7	2.9	0.14	0.14	0.14	0.135	0.013	19.5
N	4	4	4	4	4	4	4	4
GROUP: 2-F:0.1 mg base/kg/day								
8935	40	29	6.0	3.4	2.6	1.31	0.11	113
8937	26	27	5.7	3.6	2.1	1.71	0.13	94
8934	25	34	5.7	3.6	2.1	1.71	0.10	189
8945	39	41	5.8	4.8	1.0	4.80	0.15	115
MEAN	33	33	5.8	3.9	2.0	2.38	0.12	128
SD	8.1	6.2	0.14	0.64	0.68	1.623	0.022	41.9
N	4	4	4	4	4	4	4	4
GROUP: 3-F:1.0 mg base/kg/day								
8928	35	30	6.0	3.5	2.5	1.40	0.13	118
8940	38	46	5.8	3.5	2.3	1.52	0.13	104
8931	26	21	5.8	3.6	2.2	1.64	0.10	86
8943	50	39	6.3	3.9	2.4	1.63	0.13	229
MEAN	37	34	6.0	3.6	2.4	1.55	0.12	134
SD	9.9	10.9	0.24	0.19	0.13	0.112	0.015	64.5
N	4	4	4	4	4	4	4	4
GROUP: 4-F:4.0 mg base/kg/day								
8941	32	29	6.3	3.9	2.4	1.63	0.13	68
8933	19	30	5.7	3.4	2.3	1.48	0.10	139
8936	37	31	6.0	3.3	2.7	1.22	0.14	150
8944	45	31	6.6	3.2	3.4	0.94	0.14	161
MEAN	33	30	6.2	3.5	2.7	1.32	0.13	130
SD	10.9	1.0	0.39	0.31	0.50	0.303	0.019	42.0
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK -3

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	GGT IU/L	CHOL mg/dL	TRIG mg/dL	LDH IU/L	CK IU/L	BUN mg/dL	CREAT mg/dL	NA mEq/L
GROUP: 1-F:0 mg base/kg/day								
8929	5.1	203	50	35	208	12.9	0.70	148
8942	5.5	213	43	47	141	12.2	0.62	146
8930	4.7	212	48	41	165	12.0	0.67	143
8938	5.3	201	72	60	200	10.5	0.78	145
MEAN	5.2	207	53	46	179	11.9	0.69	146
SD	0.34	6.1	12.8	10.7	31.2	1.01	0.067	2.1
N	4	4	4	4	4	4	4	4

GROUP: 2-F:0.1 mg base/kg/day								
8935	3.9	212	69	77	329	16.2	0.69	149
8937	2.3	215	42	46	287	12.2	0.76	145
8934	3.3	165	35	112	169	10.5	0.56	146
8945	3.0	172	49	65	555	9.9	0.71	143
MEAN	3.1	191	49	75	335	12.2	0.68	146
SD	0.67	26.2	14.7	27.8	161.6	2.84	0.085	2.5
N	4	4	4	4	4	4	4	4

GROUP: 3-F:1.0 mg base/kg/day								
8928	2.7	239	59	36	221	11.0	0.78	146
8940	3.7	160	43	99	355	10.1	0.71	144
8931	3.0	231	50	30	122	15.0	0.72	147
8943	4.9	253	54	122	442	21.5	0.74	147
MEAN	3.6	221	52	72	285	14.4	0.74	146
SD	0.98	41.5	6.8	45.8	141.7	5.19	0.031	1.4
N	4	4	4	4	4	4	4	4

GROUP: 4-F:4.0 mg base/kg/day								
8941	3.4	331	49	41	214	12.2	0.71	147
8933	4.4	187	37	18	196	12.8	0.71	144
8936	3.9	167	46	44	192	8.8	0.67	144
8944	2.8	259	63	53	272	12.4	0.81	146
MEAN	3.6	236	49	39	219	11.6	0.73	145
SD	0.68	74.6	10.8	14.9	36.9	1.85	0.060	1.5
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK -3

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	K mEq/L	CL mEq/L	CA mg/dL	IP mg/dL	GLU mg/dL	HAPT mg/dL
GROUP: 1-F:0 mg base/kg/day						
8929	4.31	119.1	11.4	6.6	113	16.8
8942	4.43	122.0	11.0	7.5	122	70.0
8930	4.42	118.3	10.9	6.3	124	-- B
8938	4.41	118.9	11.2	6.6	117	-- B
MEAN	4.39	119.6	11.1	6.8	119	43.4
SD	0.056	1.65	0.22	0.52	5.0	37.62
N	4	4	4	4	4	2
GROUP: 2-F:0.1 mg base/kg/day						
8935	4.24	119.1	10.7	5.6	124	35.0
8937	4.58	119.8	10.9	6.2	121	21.1
8934	4.05	118.1	11.1	5.0	122	75.2
8945	4.50	121.5	11.0	6.5	124	-- B
MEAN	4.34	119.6	10.9	5.8	123	43.8
SD	0.243	1.43	0.17	0.67	1.5	28.10
N	4	4	4	4	4	3
GROUP: 3-F:1.0 mg base/kg/day						
8928	4.22	112.2	11.4	5.0	125	27.6
8940	4.28	123.3	11.2	5.1	122	16.9
8931	4.50	120.5	11.2	7.2	114	32.9
8943	4.72	119.4	11.0	6.5	127	25.0
MEAN	4.43	118.9	11.2	6.0	122	25.6
SD	0.228	4.73	0.16	1.08	5.7	6.67
N	4	4	4	4	4	4
GROUP: 4-F:4.0 mg base/kg/day						
8941	4.50	117.9	11.2	6.5	115	-- B
8933	4.25	114.3	11.1	7.2	124	50.1
8936	4.86	118.4	11.1	5.8	108	-- B
8944	4.39	117.1	11.8	5.5	128	39.4
MEAN	4.50	116.9	11.3	6.3	119	44.8
SD	0.261	1.83	0.34	0.76	9.0	7.57
N	4	4	4	4	4	2

(--) - Data Unavailable

B - Below Linearity

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK -1

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	ALT IU/L	AST IU/L	TP g/dL	ALB g/dL	GLOB g/dL	A/G -	TBILI mg/dL	ALKP IU/L
GROUP: 1-F:0 mg base/kg/day								
8929	23	29	6.7	3.7	3.0	1.23	0.11	86
8942	33	38	6.1	3.7	2.4	1.54	0.15	130
8930	33	34	6.1	3.2	2.9	1.10	0.15	84
8938	28	26	5.9	3.1	2.8	1.11	0.13	98
MEAN	29	32	6.2	3.4	2.8	1.25	0.14	100
SD	4.8	5.3	0.35	0.32	0.26	0.205	0.019	21.3
N	4	4	4	4	4	4	4	4
GROUP: 2-F:0.1 mg base/kg/day								
8935	49	26	6.0	3.1	2.9	1.07	0.13	117
8937	25	29	5.9	3.3	2.6	1.27	0.14	85
8934	24	38	6.2	3.5	2.7	1.30	0.12	185
8945	31	33	6.2	3.5	2.7	1.30	0.15	114
MEAN	32	32	6.1	3.4	2.7	1.24	0.14	125
SD	11.6	5.2	0.15	0.19	0.13	0.111	0.013	42.4
N	4	4	4	4	4	4	4	4
GROUP: 3-F:1.0 mg base/kg/day								
8928	30	27	6.2	3.4	2.8	1.21	0.13	113
8940	37	47	6.4	3.6	2.8	1.29	0.14	106
8931	26	24	6.2	3.4	2.8	1.21	0.13	88
8943	47	41	6.2	3.5	2.7	1.30	0.14	186
MEAN	35	35	6.3	3.5	2.8	1.25	0.14	123
SD	9.2	11.0	0.10	0.10	0.05	0.049	0.006	43.1
N	4	4	4	4	4	4	4	4
GROUP: 4-F:4.0 mg base/kg/day								
8941	28	25	6.9	3.4	3.5	0.97	0.12	65
8933	19	35	6.0	3.2	2.8	1.14	0.15	148
8936	23	32	6.4	3.2	3.2	1.00	0.16	136
8944	35	32	6.9	3.7	3.2	1.16	0.17	165
MEAN	26	31	6.6	3.4	3.2	1.07	0.15	129
SD	6.9	4.2	0.44	0.24	0.29	0.096	0.022	44.0
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK -1

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	GGT IU/L	CHOL mg/dL	TRIG mg/dL	LDH IU/L	CK IU/L	BUN mg/dL	CREAT mg/dL	NA mEq/L
GROUP: 1-F:0 mg base/kg/day								
8929	5.5	177	63	30	168	13.8	0.65	145
8942	5.2	177	55	94	243	13.0	0.62	145
8930	4.9	151	44	53	182	13.2	0.68	144
8938	4.4	175	43	108	242	11.0	0.73	144
MEAN	5.0	170	51	71	209	12.8	0.67	145
SD	0.47	12.7	9.5	36.1	39.4	1.22	0.047	0.6
N	4	4	4	4	4	4	4	4

GROUP: 2-F:0.1 mg base/kg/day								
8935	3.0	197	52	89	211	15.0	0.65	146
8937	4.0	151	44	34	156	12.3	0.65	145
8934	5.4	128	30	50	271	9.9	0.59	145
8945	4.5	163	46	60	312	12.0	0.73	145
MEAN	4.2	160	43	58	238	12.3	0.66	145
SD	1.00	28.8	9.3	23.1	68.4	2.09	0.057	0.5
N	4	4	4	4	4	4	4	4

GROUP: 3-F:1.0 mg base/kg/day								
8928	2.8	166	49	27	233	11.0	0.68	146
8940	4.3	172	51	124	447	14.1	0.63	143
8931	3.2	169	43	31	107	12.0	0.70	146
8943	4.2	197	57	99	298	18.6	0.71	143
MEAN	3.6	176	50	70	271	13.9	0.68	145
SD	0.74	14.2	5.8	48.7	141.5	3.37	0.036	1.7
N	4	4	4	4	4	4	4	4

GROUP: 4-F:4.0 mg base/kg/day								
8941	6.6	245	60	34	138	13.5	0.62	146
8933	5.1	150	51	34	273	12.6	0.67	143
8936	2.0	184	59	49	254	13.8	0.71	144
8944	4.9	241	71	81	325	16.0	0.81	144
MEAN	4.7	205	60	50	248	14.0	0.70	144
SD	1.92	46.1	8.2	22.2	78.9	1.44	0.081	1.3
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK -1

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	K mEq/L	CL mEq/L	CA mg/dL	IP mg/dL	GLU mg/dL	HAPT mg/dL
GROUP: 1-F:0 mg base/kg/day						
8929	4.25	116.5	11.0	6.7	118	76.5
8942	4.33	110.3	10.5	6.1	112	28.1
8930	4.35	116.0	11.1	6.0	108	27.6
8938	4.04	109.6	10.7	5.8	114	-- B
MEAN	4.24	113.1	10.8	6.2	113	44.1
SD	0.142	3.65	0.28	0.39	4.2	28.09
N	4	4	4	4	4	3
GROUP: 2-F:0.1 mg base/kg/day						
8935	3.88	108.9	10.2	5.5	108	-- B
8937	4.66	113.3	10.5	6.0	120	-- B
8934	4.06	106.7	10.8	5.5	108	70.0
8945	4.58	117.6	11.0	6.8	115	-- B
MEAN	4.30	111.6	10.6	6.0	113	70.0
SD	0.384	4.84	0.35	0.61	5.9	NA
N	4	4	4	4	4	1
GROUP: 3-F:1.0 mg base/kg/day						
8928	4.04	109.2	10.4	6.0	120	43.7
8940	3.98	115.6	10.4	4.1	127	-- B
8931	4.72	116.5	10.7	5.9	130	23.4
8943	4.54	109.8	10.5	6.7	119	27.9
MEAN	4.32	112.8	10.5	5.7	124	31.7
SD	0.366	3.81	0.14	1.11	5.4	10.66
N	4	4	4	4	4	3
GROUP: 4-F:4.0 mg base/kg/day						
8941	4.11	111.3	11.2	6.6	126	33.1
8933	4.47	110.8	10.8	5.8	111	45.6
8936	4.73	109.0	10.7	6.4	105	-- B
8944	4.28	115.6	10.8	5.7	141	37.9
MEAN	4.40	111.7	10.9	6.1	121	38.9
SD	0.266	2.80	0.22	0.44	16.1	6.31
N	4	4	4	4	4	3

(--) - Data Unavailable
B - Below Linearity

NA - Not Applicable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK 4

STUDY IO: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal IO	ALT IU/L	AST IU/L	TP g/dL	ALB g/dL	GLOB g/dL	A/G -	TBILI mg/dL	ALKP IU/L
GROUP: 1-F:0 mg base/kg/day								
8929	27	34	6.3	3.5	2.8	1.25	0.15	77
8942	58	43	6.1	3.3	2.8	1.18	0.11	119
8930	30	30	6.1	3.3	2.8	1.18	0.13	81
8938	24	28	6.3	3.5	2.8	1.25	0.13	92
MEAN	35	34	6.2	3.4	2.8	1.22	0.13	92
SD	15.7	6.7	0.12	0.12	0.00	0.040	0.016	18.9
N	4	4	4	4	4	4	4	4
GROUP: 2-F:0.1 mg base/kg/day								
8935	50	24	6.2	3.2	3.0	1.07	0.12	114
8937	23	24	6.4	3.4	3.0	1.13	0.15	70
8934	21	35	6.1	3.2	2.9	1.10	0.11	202
8945	30	36	6.1	3.3	2.8	1.18	0.18	92
MEAN	31	30	6.2	3.3	2.9	1.12	0.14	120
SD	13.2	6.7	0.14	0.10	0.10	0.047	0.032	57.9
N	4	4	4	4	4	4	4	4
GROUP: 3-F:1.0 mg base/kg/day								
8928	33	33	6.2	3.4	2.8	1.21	0.14	79
8940	35	47	6.1	3.1	3.0	1.03	0.19	84
8931	29	30	6.3	3.5	2.8	1.25	0.21	67
8943	43	43	6.4	3.5	2.9	1.21	0.21	175
MEAN	35	38	6.3	3.4	2.9	1.18	0.19	101
SD	5.9	8.1	0.13	0.19	0.10	0.098	0.033	49.7
N	4	4	4	4	4	4	4	4
GROUP: 4-F:4.0 mg base/kg/day								
8941	25	23	6.6	3.4	3.2	1.06	0.19	64
8933	15	33	6.2	3.0	3.2	0.94	0.21	110
8936	28	36	6.4	3.1	3.3	0.94	0.22	112
8944	36	39	6.6	3.0	3.6	0.83	0.25	107
MEAN	26	33	6.5	3.1	3.3	0.94	0.22	98
SD	8.7	6.9	0.19	0.19	0.19	0.094	0.025	22.9
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK 4

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	GGT IU/L	CHOL mg/dL	TRIG mg/dL	LDH IU/L	CK IU/L	BUN mg/dL	CREAT mg/dL	NA mEq/L
GROUP: 1-F:0 mg base/kg/day								
8929	3.9	159	40	54	317	12.6	0.73	146
8942	0.0	184	51	119	242	14.4	0.54	146
8930	4.8	180	61	72	149	15.2	0.71	146
8938	5.0	183	51	103	158	14.0	0.81	146
MEAN	3.4	177	51	87	217	14.1	0.70	146
SD	2.33	11.8	8.6	29.4	79.0	1.09	0.114	0.0
N	4	4	4	4	4	4	4	4
GROUP: 2-F:0.1 mg base/kg/day								
8935	4.0	204	49	50	192	15.9	0.65	145
8937	3.5	165	37	26	87	14.5	0.72	146
8934	2.5	155	48	104	182	11.9	0.60	146
8945	3.5	142	40	62	327	13.2	0.76	143
MEAN	3.4	167	44	61	197	13.9	0.68	145
SD	0.63	26.7	5.9	32.6	98.7	1.72	0.071	1.4
N	4	4	4	4	4	4	4	4
GROUP: 3-F:1.0 mg base/kg/day								
8928	6.1	161	44	23	182	15.8	0.68	146
8940	3.7	160	57	79	350	16.3	0.71	145
8931	3.4	162	32	62	107	16.9	0.84	145
8943	1.5	210	68	98	229	19.0	0.69	144
MEAN	3.7	173	50	66	217	17.0	0.73	145
SD	1.89	24.5	15.6	31.9	101.9	1.41	0.074	0.8
N	4	4	4	4	4	4	4	4
GROUP: 4-F:4.0 mg base/kg/day								
8941	3.4	218	45	68	89	16.1	0.71	147
8933	3.3	149	44	69	149	16.6	0.77	146
8936	5.9	179	42	54	205	19.5	0.74	146
8944	3.6	213	66	137	219	18.5	0.82	144
MEAN	4.1	190	49	82	166	17.7	0.76	146
SD	1.24	32.2	11.2	37.3	59.3	1.60	0.047	1.3
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK 4

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	K mEq/L	CL mEq/L	CA mg/dL	IP mg/dL	GLU mg/dL	HAPT mg/dL
GROUP: 1-F:0 mg base/kg/day						
8929	4.43	119.7	11.1	5.5	99	-- B
8942	4.66	114.4	11.3	4.6	104	-- B
8930	4.70	118.2	11.0	5.3	102	37.1
8938	4.54	109.2	11.3	6.0	113	-- B
MEAN	4.58	115.4	11.2	5.4	105	37.1
SD	0.122	4.68	0.15	0.58	6.0	NA
N	4	4	4	4	4	1

GROUP: 2-F:0.1 mg base/kg/day						
8935	4.34	109.7	11.0	6.2	102	-- B
8937	4.43	109.6	11.6	6.2	113	53.6
8934	4.41	111.5	10.8	4.5	103	137.6
8945	4.37	111.1	10.9	5.9	106	-- B
MEAN	4.39	110.5	11.1	5.7	106	95.6
SD	0.040	0.97	0.36	0.81	5.0	59.40
N	4	4	4	4	4	2

GROUP: 3-F:1.0 mg base/kg/day						
8928	3.87	116.4	11.1	4.8	114	88.5
8940	4.60	109.2	10.5	5.4	114	16.5
8931	4.75	115.6	11.2	6.1	109	24.7
8943	4.63	116.0	10.9	4.6	110	29.4
MEAN	4.46	114.3	10.9	5.2	112	39.8
SD	0.400	3.42	0.31	0.68	2.6	32.92
N	4	4	4	4	4	4

GROUP: 4-F:4.0 mg base/kg/day						
8941	4.05	115.3	11.1	6.1	126	78.8
8933	4.50	109.9	10.5	6.0	102	164.8
8936	4.01	117.7	11.5	5.4	101	-- B
8944	4.61	117.0	11.2	6.0	123	174.5
MEAN	4.29	115.0	11.1	5.9	113	139.4
SD	0.307	3.53	0.42	0.32	13.3	52.68
N	4	4	4	4	4	3

(--) - Data Unavailable
B - Below Linearity

NA - Not Applicable

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK 13

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	ALT IU/L	AST IU/L	TP g/dL	ALB g/dL	GLOB g/dL	A/G -	TBILI mg/dL	ALKP IU/L
GROUP: 1-F:0 mg base/kg/day								
8929	25	25	6.4	3.4	3.0	1.13	0.14	52
8942	64	47	6.2	3.3	2.9	1.14	0.18	78
8930	24	29	6.5	3.6	2.9	1.24	0.15	62
8938	23	36	6.8	3.5	3.3	1.06	0.14	73
MEAN	34	34	6.5	3.5	3.0	1.14	0.15	66
SD	20.0	9.6	0.25	0.13	0.19	0.074	0.019	11.6
N	4	4	4	4	4	4	4	4

GROUP: 2-F:0.1 mg base/kg/day								
8935	59	25	6.6	3.3	3.3	1.00	0.14	102
8937	22	25	6.3	3.5	2.8	1.25	0.20	50
8934	22	41	6.2	3.3	2.9	1.14	0.20	116
8945	34	59	6.4	3.5	2.9	1.21	0.28	70
MEAN	34	38	6.4	3.4	3.0	1.15	0.21	85
SD	17.4	16.2	0.17	0.12	0.22	0.110	0.057	30.0
N	4	4	4	4	4	4	4	4

GROUP: 3-F:1.0 mg base/kg/day								
8928	33	27	6.1	3.3	2.8	1.18	0.12	65
8940	29	48	6.1	3.2	2.9	1.10	0.18	71
8931	28	29	6.0	3.4	2.6	1.31	0.17	52
8943	45	44	6.4	3.3	3.1	1.06	0.17	136
MEAN	34	37	6.2	3.3	2.9	1.16	0.16	81
SD	7.8	10.6	0.17	0.08	0.21	0.110	0.027	37.5
N	4	4	4	4	4	4	4	4

GROUP: 4-F:4.0 mg base/kg/day								
8941	27	26	6.5	3.3	3.2	1.03	0.09	60
8933	20	46	6.2	3.0	3.2	0.94	0.20	68
8936	26	34	6.5	3.3	3.2	1.03	0.19	77
8944	34	42	6.9	3.2	3.7	0.86	0.26	90
MEAN	27	37	6.5	3.2	3.3	0.97	0.19	74
SD	5.7	8.9	0.29	0.14	0.25	0.082	0.070	12.9
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK 13

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	GGT IU/L	CHOL mg/dL	TRIG mg/dL	LDH IU/L	CK IU/L	BUN mg/dL	CREAT mg/dL	NA mEq/L
GROUP: 1-F:0 mg base/kg/day								
8929	1.4	224	39	60	124	18.0	0.72	149
8942	4.5	170	40	48	211	19.7	0.69	145
8930	5.2	230	59	80	151	20.4	0.73	142
8938	0.9	251	143	205	271	25.2	0.78	143
MEAN	3.0	219	70	98	189	20.8	0.73	145
SD	2.16	34.5	49.4	72.4	65.5	3.09	0.037	3.1
N	4	4	4	4	4	4	4	4

GROUP: 2-F:0.1 mg base/kg/day								
8935	4.1	311	52	103	178	16.9	0.63	145
8937	0.0	153	38	75	121	18.7	0.75	146
8934	4.3	182	41	81	198	15.4	0.72	144
8945	4.6	193	47	102	1030	17.2	0.77	145
MEAN	3.3	210	45	90	382	17.1	0.72	145
SD	2.18	69.6	6.2	14.4	433.4	1.35	0.062	0.8
N	4	4	4	4	4	4	4	4

GROUP: 3-F:1.0 mg base/kg/day								
8928	0.0	181	42	57	97	13.8	0.79	144
8940	0.0	152	34	124	241	16.2	0.67	142
8931	4.9	167	52	56	94	18.6	0.85	146
8943	1.6	233	96	89	236	21.0	0.77	143
MEAN	1.6	183	56	82	167	17.4	0.77	144
SD	2.31	35.2	27.7	32.2	82.6	3.10	0.075	1.7
N	4	4	4	4	4	4	4	4

GROUP: 4-F:4.0 mg base/kg/day								
8941	4.4	270	95	42	94	18.4	0.70	144
8933	1.1	144	54	97	223	19.0	0.92	143
8936	4.4	244	53	59	133	22.4	0.77	144
8944	1.2	197	82	167	259	15.0	0.99	144
MEAN	2.8	214	71	91	177	18.7	0.85	144
SD	1.88	55.5	20.9	55.5	76.7	3.03	0.133	0.5
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK 13

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	K mEq/L	CL mEq/L	CA mg/dL	IP mg/dL	GLU mg/dL	HAPT mg/dL
GROUP: 1-F:0 mg base/kg/day						
8929	4.82	113.5	10.1	4.7	93	-- B
8942	4.03	112.5	9.9	4.8	110	41.1
8930	4.55	105.8	10.6	4.9	110	-- B
8938	4.71	114.2	10.4	4.5	116	-- B
MEAN	4.53	111.5	10.3	4.7	107	41.1
SD	0.350	3.86	0.31	0.17	9.9	NA
N	4	4	4	4	4	1
GROUP: 2-F:0.1 mg base/kg/day						
8935	4.07	108.3	10.0	5.1	104	81.0
8937	4.37	108.8	10.4	3.5	115	-- B
8934	3.82	113.3	10.0	3.8	118	66.0
8945	3.90	110.4	10.3	4.8	116	28.6
MEAN	4.04	110.2	10.2	4.3	113	58.5
SD	0.243	2.25	0.21	0.77	6.3	26.99
N	4	4	4	4	4	3
GROUP: 3-F:1.0 mg base/kg/day						
8928	4.00	107.9	10.5	3.9	107	50.1
8940	4.32	109.6	10.1	2.9	114	-- B
8931	4.74	107.3	10.4	4.3	112	-- B
8943	3.88	113.4	9.5	3.7	103	54.7
MEAN	4.24	109.6	10.1	3.7	109	52.4
SD	0.384	2.75	0.45	0.59	5.0	3.25
N	4	4	4	4	4	2
GROUP: 4-F:4.0 mg base/kg/day						
8941	4.31	104.9	10.4	5.0	108	112.1
8933	3.98	115.4	10.1	4.6	95	157.1
8936	4.63	107.2	10.4	4.5	108	55.3
8944	4.22	109.2	10.2	3.6	99	112.8
MEAN	4.29	109.2	10.3	4.4	103	109.3
SD	0.269	4.51	0.15	0.59	6.6	41.72
N	4	4	4	4	4	4

(--)- Data Unavailable
B - Below Linearity

NA - Not Applicable

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK 26

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	ALT IU/L	AST IU/L	TP g/dL	ALB g/dL	GLOB g/dL	A/G -	TBILI mg/dL	ALKP IU/L
GROUP: 1-F:0 mg base/kg/day								
8929	33	35	5.9	4.1	1.8	2.28	0.17	49
8942	42	41	6.3	4.3	2.0	2.15	0.20	83
8930	31	41	5.9	2.8	3.1	0.90	0.13	51
8938	24	30	6.0	3.3	2.7	1.22	0.13	68
MEAN	33	37	6.0	3.6	2.4	1.64	0.16	63
SD	7.4	5.3	0.19	0.70	0.61	0.682	0.034	16.0
N	4	4	4	4	4	4	4	4
GROUP: 2-F:0.1 mg base/kg/day								
8935	38	28	5.9	3.0	2.9	1.03	0.15	85
8937	19	21	6.0	3.3	2.7	1.22	0.19	36
8934	20	42	5.6	3.0	2.6	1.15	0.12	79
8945	32	37	5.8	3.2	2.6	1.23	0.17	55
MEAN	27	32	5.8	3.1	2.7	1.16	0.16	64
SD	9.3	9.3	0.17	0.15	0.14	0.092	0.030	22.6
N	4	4	4	4	4	4	4	4
GROUP: 3-F:1.0 mg base/kg/day								
8928	31	29	6.6	4.3	2.3	1.87	0.17	64
8940	29	53	6.1	3.9	2.2	1.77	0.19	56
8931	30	48	6.0	4.1	1.9	2.16	0.18	54
8943	49	27	6.0	3.3	2.7	1.22	0.15	108
MEAN	35	39	6.2	3.9	2.3	1.76	0.17	71
SD	9.5	13.2	0.29	0.43	0.33	0.393	0.017	25.4
N	4	4	4	4	4	4	4	4
GROUP: 4-F:4.0 mg base/kg/day								
8941	25	32	5.9	3.1	2.8	1.11	0.12	52
8933	20	51	6.3	3.7	2.6	1.42	0.18	86
8936	25	35	5.9	3.6	2.3	1.57	0.17	83
8944	34	47	6.6	2.9	3.7	0.78	0.22	70
MEAN	26	41	6.2	3.3	2.9	1.22	0.17	73
SD	5.8	9.2	0.34	0.39	0.60	0.350	0.041	15.5
N	4	4	4	4	4	4	4	4

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ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK 26

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	GGT IU/L	CHOL mg/dL	TRIG mg/dL	LDH IU/L	CK IU/L	BUN mg/dL	CREAT mg/dL	NA mEq/L
GROUP: 1-F:0 mg base/kg/day								
8929	2.0	147	42	58	123	14.1	0.74	146
8942	6.5	177	46	109	156	16.9	0.86	148
8930	4.3	137	37	83	276	12.1	0.76	144
8938	5.9	133	52	96	102	13.8	0.79	145
MEAN	4.7	149	44	87	164	14.2	0.79	146
SD	2.01	19.9	6.3	21.8	77.7	1.99	0.053	1.7
N	4	4	4	4	4	4	4	4
GROUP: 2-F:0.1 mg base/kg/day								
8935	0.0	148	48	187	124	14.2	0.62	145
8937	3.9	136	35	53	74	16.3	0.87	147
8934	4.1	106	31	45	100	11.1	0.70	146
8945	4.6	123	54	85	188	13.6	0.82	144
MEAN	3.2	128	42	93	122	13.8	0.75	146
SD	2.12	18.0	10.8	65.3	48.8	2.14	0.114	1.3
N	4	4	4	4	4	4	4	4
GROUP: 3-F:1.0 mg base/kg/day								
8928	4.4	184	54	36	115	24.1	0.81	146
8940	6.0	171	46	189	220	16.8	0.81	142
8931	5.3	150	64	92	138	16.4	0.86	145
8943	4.9	226	56	160	150	15.5	0.66	146
MEAN	5.2	183	55	119	156	18.2	0.79	145
SD	0.68	32.1	7.4	68.8	45.2	3.97	0.087	1.9
N	4	4	4	4	4	4	4	4
GROUP: 4-F:4.0 mg base/kg/day								
8941	4.4	155	65	61	106	15.4	0.78	146
8933	3.2	95	38	63	122	16.2	0.95	146
8936	3.8	156	44	51	113	18.6	0.77	146
8944	4.3	177	71	235	208	14.2	0.92	146
MEAN	3.9	146	55	103	137	16.1	0.86	146
SD	0.55	35.3	16.0	88.5	47.6	1.86	0.093	0.0
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK 26

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	K mEq/L	CL mEq/L	CA mg/dL	IP mg/dL	GLU mg/dL	HAPT mg/dL
GROUP: 1-F:0 mg base/kg/day						
8929	3.75	118.4	10.1	4.1	98	-- B
8942	4.46	121.8	10.5	4.0	89	93.9
8930	4.65	112.8	10.0	3.7	112	28.1
8938	4.38	112.9	10.2	4.4	98	-- B
MEAN	4.31	116.5	10.2	4.1	99	61.0
SD	0.390	4.41	0.22	0.29	9.5	46.53
N	4	4	4	4	4	2
GROUP: 2-F:0.1 mg base/kg/day						
8935	4.16	114.7	9.8	1.6	96	20.8
8937	4.29	117.1	10.4	4.2	88	23.6
8934	4.27	112.8	10.0	3.5	106	96.5
8945	4.64	113.9	10.0	4.3	94	30.6
MEAN	4.34	114.6	10.1	3.4	96	42.9
SD	0.208	1.82	0.25	1.25	7.5	35.99
N	4	4	4	4	4	4
GROUP: 3-F:1.0 mg base/kg/day						
8928	4.22	122.6	10.5	5.9	101	90.6
8940	4.46	119.5	9.9	3.4	106	-- B
8931	4.15	127.6	10.5	3.9	100	17.2
8943	4.38	114.7	10.1	4.1	94	72.2
MEAN	4.30	121.1	10.3	4.3	100	60.0
SD	0.142	5.42	0.30	1.09	4.9	38.19
N	4	4	4	4	4	3
GROUP: 4-F:4.0 mg base/kg/day						
8941	4.20	115.5	9.9	3.4	95	111.4
8933	4.16	121.0	10.5	4.1	105	179.9
8936	4.16	118.9	10.4	3.9	85	48.9
8944	4.73	112.5	9.8	2.8	96	56.2
MEAN	4.31	117.0	10.2	3.6	95	99.1
SD	0.279	3.75	0.35	0.58	8.2	60.66
N	4	4	4	4	4	4

(--)- Data Unavailable

B - Below Linearity

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK 52

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	ALT IU/L	AST IU/L	TP g/dL	ALB g/dL	GLOB g/dL	A/G -	TBILI mg/dL	ALKP IU/L
GROUP: 1-F:0 mg base/kg/day								
8929	32	21	5.5	3.2	2.3	1.39	0.13	42
8942	41	38	5.9	3.1	2.8	1.11	0.16	61
8930	27	32	5.5	3.0	2.5	1.20	0.23	39
8938	26	27	6.3	3.3	3.0	1.10	0.12	117
MEAN	32	30	5.8	3.2	2.7	1.20	0.16	65
SD	6.9	7.2	0.38	0.13	0.31	0.134	0.050	36.2
N	4	4	4	4	4	4	4	4

GROUP: 2-F:0.1 mg base/kg/day								
8935	54	32	6.4	3.2	3.2	1.00	0.14	111
8937	20	23	6.3	3.3	3.0	1.10	0.18	43
8934	22	36	6.3	3.4	2.9	1.17	0.19	88
8945	31	42	6.6	3.2	3.4	0.94	0.20	46
MEAN	32	33	6.4	3.3	3.1	1.05	0.18	72
SD	15.6	8.0	0.14	0.10	0.22	0.102	0.026	33.1
N	4	4	4	4	4	4	4	4

GROUP: 3-F:1.0 mg base/kg/day								
8928	30	28	6.3	3.1	3.2	0.97	0.15	40
8940	33	65	5.9	3.1	2.8	1.11	0.16	50
8931	30	41	5.6	3.1	2.5	1.24	0.13	48
8943	40	31	6.7	3.6	3.1	1.16	0.21	99
MEAN	33	41	6.1	3.2	2.9	1.12	0.16	59
SD	4.7	16.8	0.48	0.25	0.32	0.113	0.034	26.8
N	4	4	4	4	4	4	4	4

GROUP: 4-F:4.0 mg base/kg/day								
8941	32	27	6.3	3.2	3.1	1.03	0.12	68
8933	21	46	6.0	2.9	3.1	0.94	0.17	65
8936	34	44	5.9	2.9	3.0	0.97	0.12	75
8944	46	35	6.6	3.0	3.6	0.83	0.17	67
MEAN	33	38	6.2	3.0	3.2	0.94	0.15	69
SD	10.2	8.8	0.32	0.14	0.27	0.084	0.029	4.3
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK 52

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	GGT IU/L	CHOL mg/dL	TRIG mg/dL	LDH IU/L	CK IU/L	BUN mg/dL	CREAT mg/dL	NA mEq/L
GROUP: 1-F:0 mg base/kg/day								
8929	6.3	140	28	22	76	11.2	0.73	148
8942	8.4	178	36	98	168	14.9	0.70	150
8930	6.0	159	19	47	88	12.1	0.82	147
8938	7.6	178	53	77	123	13.9	0.87	148
MEAN	7.1	164	34	61	114	13.0	0.78	148
SD	1.12	18.2	14.4	33.4	41.3	1.68	0.079	1.3
N	4	4	4	4	4	4	4	4

GROUP: 2-F:0.1 mg base/kg/day								
8935	6.4	247	54	220	198	15.7	0.64	149
8937	6.8	205	37	80	77	13.7	0.69	148
8934	6.2	214	37	97	132	13.9	0.69	146
8945	6.2	228	73	147	476	13.8	0.78	147
MEAN	6.4	224	50	136	221	14.3	0.70	148
SD	0.28	18.3	17.2	62.8	177.2	0.95	0.058	1.3
N	4	4	4	4	4	4	4	4

GROUP: 3-F:1.0 mg base/kg/day								
8928	4.1	228	27	24	85	13.5	0.77	147
8940	4.9	144	38	110	488	15.0	0.85	146
8931	1.7	148	56	76	113	14.5	0.80	148
8943	5.4	307	84	69	134	19.9	0.97	145
MEAN	4.0	207	51	70	205	15.7	0.85	147
SD	1.64	77.2	24.9	35.4	189.7	2.85	0.088	1.3
N	4	4	4	4	4	4	4	4

GROUP: 4-F:4.0 mg base/kg/day								
8941	6.3	320	84	48	69	16.0	0.68	149
8933	4.7	113	30	61	208	13.7	0.91	149
8936	5.5	151	56	86	184	17.9	0.73	146
8944	5.1	314	70	138	149	18.2	0.86	147
MEAN	5.4	225	60	83	153	16.5	0.80	148
SD	0.68	108.0	23.0	39.8	60.7	2.08	0.108	1.5
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: WEEK 52

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	K mEq/L	CL mEq/L	CA mg/dL	IP mg/dL	GLU mg/dL	HAPT mg/dL
GROUP: 1-F:0 mg base/kg/day						
8929	4.41	112.0	9.8	3.9	90	16.5
8942	4.24	110.3	9.7	3.6	109	41.6
8930	4.31	110.2	9.6	2.8	109	16.5
8938	4.36	112.5	10.0	4.1	105	45.1
MEAN	4.33	111.3	9.8	3.6	103	29.9
SD	0.073	1.17	0.17	0.57	9.0	15.57
N	4	4	4	4	4	4
GROUP: 2-F:0.1 mg base/kg/day						
8935	4.48	105.5	10.0	4.1	95	107.1
8937	4.77	106.1	10.6	3.8	110	17.6
8934	4.23	105.4	9.9	2.5	104	117.0
8945	5.17	107.4	10.4	4.6	104	45.7
MEAN	4.66	106.1	10.2	3.8	103	71.9
SD	0.404	0.92	0.33	0.90	6.2	47.99
N	4	4	4	4	4	4
GROUP: 3-F:1.0 mg base/kg/day						
8928	4.05	105.2	10.2	3.9	103	84.5
8940	4.53	106.8	9.2	2.5	114	16.5
8931	4.62	112.3	9.3	3.0	103	16.5
8943	4.48	107.0	9.5	3.4	126	148.5
MEAN	4.42	107.8	9.6	3.2	112	66.5
SD	0.253	3.09	0.45	0.59	11.0	63.37
N	4	4	4	4	4	4
GROUP: 4-F:4.0 mg base/kg/day						
8941	4.47	106.8	9.7	4.7	99	138.7
8933	4.21	109.3	10.1	4.0	91	212.1
8936	4.53	112.9	9.9	3.6	90	75.9
8944	4.81	106.2	10.2	3.9	104	16.5
MEAN	4.51	108.8	10.0	4.1	96	110.8
SD	0.246	3.05	0.22	0.47	6.7	83.97
N	4	4	4	4	4	4

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APPENDIX G
Individual Hematology Data

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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Hematology Test Directory

STUDY: UIC-9

NO.	ABBR. UNITS	DESCRIPTION PRECISION	CALCULATED	OPERAND A	OPERAND B	---LOWER LIMIT---		---UPPER LIMIT---	
						MALE	FEMALE	MALE	FEMALE
1.	RBC 10 ⁶ /mm ³	Erythrocytes 0.00	NO			6.00	6.00	8.00	8.00
2.	HGB g/dL	Hemoglobin 0.0	NO			14.0	14.0	19.0	19.0
3.	HCT %	Hematocrit 0.0	NO			41.0	41.0	55.0	55.0
4.	MCV fL	Mean Corpuscular Volume 0.0	NO			65.0	65.0	73.0	73.0
5.	MCH pg	Mean Corpuscular Hemo. 0.0	NO			22.0	22.0	26.0	26.0
6.	MCHC g/dL	Mean Corpus. Hemo. Conc. 0.0	NO			33.0	33.0	37.0	37.0
7.	RETICS % RBCs	Reticulocytes 0.0	NO			0.0	0.0	0.8	0.8
8.	HB % RBCs	Heinz Bodies 0.0	NO			0.0	0.0	0.5	0.5
9.	% METHGB % HGBs	% Methemoglobin 0.0	NO			0.0	0.0	2.5	2.5
10.	PLT 10 ³ /mm ³	Platelets Integer	NO			200	200	500	500
11.	PT sec	Prothrombin Time 0.0	NO			6.0	6.0	9.0	9.0
12.	APTT sec	Act. Partial Thrombo. Time 0.0	NO			9.0	9.0	13.0	13.0
13.	WBC 10 ³ /mm ³	Leukocytes 0.0	NO			6.0	6.0	15.0	15.0

(END OF REPORT)

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK -3

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	RBC 10 ⁶ /mm ³	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RETICS % RBCs	HB % RBCs
GROUP: 1-M:0 mg base/kg/day								
8915	6.12	14.8	42.5	69.4	24.2	34.8	0.1	0.0
8911	6.38	15.1	44.3	69.4	23.7	34.1	0.1	0.0
8909	6.19	15.4	44.6	72.1	24.9	34.5	0.0	0.0
8922	6.38	14.9	42.2	66.1	23.4	35.3	0.4	0.0
MEAN	6.27	15.1	43.4	69.3	24.1	34.7	0.2	0.0
SD	0.133	0.26	1.22	2.46	0.66	0.51	0.17	0.00
N	4	4	4	4	4	4	4	4

GROUP: 2-M:0.1 mg base/kg/day								
8923	6.01	14.2	40.9	68.1	23.6	34.7	0.2	0.0
8907	7.39	16.7	48.6	65.8	22.6	34.4	0.1	0.0
8919	6.78	16.0	46.8	69.0	23.6	34.2	0.2	0.0
8924	6.34	14.9	43.0	67.8	23.5	34.7	0.0	0.0
MEAN	6.63	15.5	44.8	67.7	23.3	34.5	0.1	0.0
SD	0.597	1.12	3.51	1.35	0.49	0.24	0.10	0.00
N	4	4	4	4	4	4	4	4

GROUP: 3-M:1.0 mg base/kg/day								
8917	6.49	14.8	43.9	67.6	22.8	33.7	0.7	0.0
8910	6.45	15.4	45.7	70.9	23.9	33.7	0.1	0.0
8913	6.21	14.9	43.0	69.2	24.0	34.7	0.2	0.0
8914	7.18	17.1	50.0	69.6	23.8	34.2	0.1	0.0
MEAN	6.58	15.6	45.7	69.3	23.6	34.1	0.3	0.0
SD	0.417	1.07	3.11	1.36	0.56	0.48	0.29	0.00
N	4	4	4	4	4	4	4	4

GROUP: 4-M:4.0 mg base/kg/day								
8908	6.64	15.5	45.1	67.9	23.3	34.4	0.1	0.2
8926	5.79	14.1	40.8	70.5	24.4	34.6	0.7	0.0
8921	5.75	13.5	39.2	68.2	23.5	34.4	0.1	0.0
8918	6.02	14.6	42.1	69.9	24.3	34.7	0.1	0.0
MEAN	6.05	14.4	41.8	69.1	23.9	34.5	0.3	0.1
SD	0.411	0.85	2.50	1.27	0.56	0.15	0.30	0.10
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK -3

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	% METHGB % HGBs	PLT 10 ³ /mm ³	PT sec	APTT sec
GROUP: 1-M:0 mg base/kg/day				
8915	0.5	290	8.3	10.0
8911	0.7	230	8.4	9.6
8909	1.0	320	9.7	10.0
8922	0.6	320	8.7	10.2
MEAN	0.7	290	8.8	10.0
SD	0.22	42.4	0.64	0.25
N	4	4	4	4

GROUP: 2-M:0.1 mg base/kg/day				
8923	0.4	409	8.2	10.4
8907	0.7	367	8.4	12.0
8919	0.6	251	8.7	10.7
8924	0.2	320	8.2	11.2
MEAN	0.5	337	8.4	11.1
SD	0.22	67.7	0.24	0.70
N	4	4	4	4

GROUP: 3-M:1.0 mg base/kg/day				
8917	0.5	359	8.0	10.8
8910	0.5	306	8.5	10.5
8913	0.5	211	8.4	10.5
8914	0.4	274	8.9	10.3
MEAN	0.5	288	8.5	10.5
SD	0.05	61.9	0.37	0.21
N	4	4	4	4

GROUP: 4-M:4.0 mg base/kg/day				
8908	0.3	282	8.5	10.6
8926	0.5	271	8.4	10.7
8921	0.6	301	8.6	10.6
8918	0.5	404	8.6	10.5
MEAN	0.5	315	8.5	10.6
SD	0.13	60.9	0.10	0.08
N	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK -1

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	RBC 10 ⁶ /mm ³	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RETICS % RBCs	HB % RBCs
GROUP: 1-M:0 mg base/kg/day								
8915	6.05	14.5	42.1	69.6	24.0	34.4	0.3	0.1
8911	6.19	14.7	43.1	69.6	23.7	34.1	0.5	0.2
8909	5.72	14.2	41.0	71.7	24.8	34.6	0.0	0.0
8922	6.26	14.3	41.4	66.1	22.8	34.5	0.9	0.0
MEAN	6.06	14.4	41.9	69.3	23.8	34.4	0.4	0.1
SD	0.240	0.22	0.92	2.32	0.83	0.22	0.38	0.10
N	4	4	4	4	4	4	4	4
GROUP: 2-M:0.1 mg base/kg/day								
8923	5.65	13.4	38.5	68.1	23.7	34.8	0.1	0.0
8907	7.25	16.2	47.3	65.2	22.3	34.2	0.3	0.0
8919	6.43	15.0	44.4	69.1	23.3	33.8	0.1	0.0
8924	6.43	14.9	43.8	68.1	23.2	34.0	0.7	0.0
MEAN	6.44	14.9	43.5	67.6	23.1	34.2	0.3	0.0
SD	0.653	1.15	3.67	1.68	0.59	0.43	0.28	0.00
N	4	4	4	4	4	4	4	4
GROUP: 3-M:1.0 mg base/kg/day								
8917	5.92	13.6	39.7	67.1	23.0	34.3	0.4	0.0
8910	5.99	14.7	42.4	70.8	24.5	34.7	0.1	0.0
8913	5.83	13.5	40.2	69.0	23.2	33.6	0.4	0.0
8914	6.54	15.9	45.5	69.6	24.3	34.9	0.8	0.0
MEAN	6.07	14.4	42.0	69.1	23.8	34.4	0.4	0.0
SD	0.320	1.12	2.64	1.54	0.76	0.57	0.29	0.00
N	4	4	4	4	4	4	4	4
GROUP: 4-M:4.0 mg base/kg/day								
8908	6.11	13.9	40.9	66.9	22.7	34.0	0.1	0.0
8926	5.66	13.8	40.0	70.7	24.4	34.5	0.6	0.0
8921	5.54	13.1	38.2	69.0	23.6	34.3	0.1	0.0
8918	5.73	13.9	39.6	69.1	24.3	35.1	0.0	0.0
MEAN	5.76	13.7	39.7	68.9	23.8	34.5	0.2	0.0
SD	0.246	0.39	1.12	1.56	0.79	0.46	0.27	0.00
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK -1

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	% METHGB % HGBs	PLT 10 ³ /mm ³	PT sec	APTT sec
GROUP: 1-M:0 mg base/kg/day				
8915	0.5	276	8.5	9.6
8911	0.8	213	8.2	9.5
8909	0.7	274	10.0	9.9
8922	0.5	323	8.5	9.6
MEAN	0.6	272	8.8	9.7
SD	0.15	45.1	0.81	0.17
N	4	4	4	4

GROUP: 2-M:0.1 mg base/kg/day				
8923	0.5	297	8.2	11.4
8907	0.4	321	8.4	10.8
8919	0.8	284	9.0	9.9
8924	1.2	310	8.4	9.5
MEAN	0.7	303	8.5	10.4
SD	0.36	16.0	D.35	D.86
N	4	4	4	4

GROUP: 3-M:1.0 mg base/kg/day				
8917	0.6	297	8.4	10.4
8910	0.7	308	8.5	11.8
8913	0.4	277	8.3	10.3
8914	0.7	212	8.5	10.3
MEAN	0.6	274	8.4	10.7
SD	0.14	43.0	0.10	0.73
N	4	4	4	4

GROUP: 4-M:4.0 mg base/kg/day				
8908	0.8	261	8.6	9.9
8926	0.5	237	8.3	10.3
8921	0.7	233	8.3	10.0
8918	0.3	357	8.6	10.0
MEAN	0.6	272	8.5	10.1
SD	0.22	58.0	0.17	0.17
N	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK 4

STUDY IO: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	RBC 10 ⁶ /mm ³	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RETICS % RBCs	HB % RBCs
GROUP: 1-M:0 mg base/kg/day								
8915	5.99	14.4	41.3	68.9	24.0	34.9	0.0	0.0
8911	6.66	15.8	45.9	68.9	23.7	34.4	0.1	0.0
8909	6.04	14.9	43.0	71.2	24.7	34.7	0.0	0.0
8922	6.21	14.0	41.0	66.0	22.5	34.1	0.0	0.0
MEAN	6.22	14.8	42.8	68.8	23.7	34.5	0.0	0.0
SD	0.305	0.78	2.25	2.13	0.92	0.35	0.05	0.00
N	4	4	4	4	4	4	4	4
GROUP: 2-M:0.1 mg base/kg/day								
8923	5.76	13.5	39.0	67.7	23.4	34.6	0.1	0.0
8907	6.98	15.9	45.9	65.8	22.8	34.6	0.0	0.0
8919	6.58	15.5	45.1	68.5	23.6	34.4	0.0	0.1
8924	6.30	14.7	42.8	67.9	23.3	34.3	0.0	0.0
MEAN	6.41	14.9	43.2	67.5	23.3	34.5	0.0	0.0
SD	0.513	1.06	3.09	1.17	0.34	0.15	0.05	0.05
N	4	4	4	4	4	4	4	4
GROUP: 3-M:1.0 mg base/kg/day								
8917	6.09	13.9	40.7	66.8	22.8	34.2	0.3	0.0
8910	7.11	17.1	50.2	70.6	24.1	34.1	0.4	0.2
8913	6.19	14.6	42.8	69.1	23.6	34.1	0.3	0.0
8914	6.54	15.7	45.0	68.8	24.0	34.9	0.4	0.0
MEAN	6.48	15.3	44.7	68.8	23.6	34.3	0.4	0.1
SD	0.461	1.40	4.08	1.56	0.59	0.39	0.06	0.10
N	4	4	4	4	4	4	4	4
GROUP: 4-M:4.0 mg base/kg/day								
8908	5.99	14.0	40.9	68.3	23.4	34.2	0.1	0.0
8926	5.49	13.4	39.3	71.6	24.4	34.1	0.4	0.0
8921	5.43	12.4	36.8	67.8	22.8	33.7	0.0	0.0
8918	5.38	12.8	37.6	69.9	23.8	34.0	0.1	0.0
MEAN	5.57	13.2	38.7	69.4	23.6	34.0	0.2	0.0
SD	0.282	0.70	1.83	1.72	0.67	0.22	0.17	0.00
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK 4

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	% METHGB % HGBs	PLT 10 ³ /mm ³	PT sec	APTT sec
GROUP: 1-M:0 mg base/kg/day				
8915	0.5	222	8.9	10.6
8911	0.6	141	8.7	10.3
8909	0.8	265	10.3	10.7
8922	0.4	262	9.2	10.3
MEAN	0.6	223	9.3	10.5
SD	0.17	57.8	0.71	0.21
N	4	4	4	4

GROUP: 2-M:0.1 mg base/kg/day				
8923	0.7	288	8.5	10.8
8907	0.6	228	8.5	11.9
8919	0.8	275	9.1	10.4
8924	1.3	258	8.6	12.9
MEAN	0.9	262	8.7	11.5
SD	0.31	25.9	0.29	1.13
N	4	4	4	4

GROUP: 3-M:1.0 mg base/kg/day				
8917	1.5	202	8.6	10.7
8910	3.3	154	8.8	11.3
8913	7.0	124	8.5	10.5
8914	4.2	140	8.9	10.5
MEAN	4.0	155	8.7	10.8
SD	2.29	33.6	0.18	0.38
N	4	4	4	4

GROUP: 4-M:4.0 mg base/kg/day				
8908	12.7	71	8.6	10.7
8926	14.8	41	8.3	10.8
8921	6.5	44	8.4	11.1
8918	13.4	83	8.4	10.8
MEAN	11.9	60	8.4	10.9
SD	3.67	20.5	0.13	0.17
N	4	4	4	4

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ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK 13

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	RBC 10 ⁶ /mm ³	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RETICS % RBCs	HB % RBCs
GROUP: 1-M:0 mg base/kg/day								
8915	6.13	15.4	42.3	69.0	25.1	36.4	0.4	0.2
8911	6.72	16.6	46.6	69.3	24.7	35.6	1.2	0.0
8909	5.99	15.5	43.6	72.8	25.9	35.6	0.1	0.2
8922	6.58	15.4	43.8	66.6	23.4	35.2	0.9	0.0
MEAN	6.36	15.7	44.1	69.4	24.8	35.7	0.7	0.1
SD	0.350	0.59	1.81	2.55	1.04	0.50	0.49	0.12
N	4	4	4	4	4	4	4	4

GROUP: 2-M:0.1 mg base/kg/day								
8923	6.26	15.0	42.2	67.4	24.0	35.5	0.3	0.0
8907	7.08	16.9	46.6	65.8	23.9	36.3	0.4	0.4
8919	7.11	17.0	49.2	69.2	23.9	34.6	0.3	0.2
8924	6.92	17.0	47.4	68.5	24.6	35.9	0.5	0.1
MEAN	6.84	16.5	46.4	67.7	24.1	35.6	0.4	0.2
SD	0.397	0.98	2.97	1.48	0.34	0.73	0.10	0.17
N	4	4	4	4	4	4	4	4

GROUP: 3-M:1.0 mg base/kg/day								
8917	6.63	16.0	45.2	68.2	24.1	35.4	0.9	0.0
8910	6.76	17.1	47.7	70.6	25.3	35.8	0.2	0.1
8913	6.26	15.1	43.6	69.6	24.1	34.6	0.9	0.3
8914	6.76	17.0	47.1	69.7	25.1	36.1	1.9	0.1
MEAN	6.60	16.3	45.9	69.5	24.7	35.5	1.0	0.1
SD	0.236	0.94	1.87	0.99	0.64	0.65	0.70	0.13
N	4	4	4	4	4	4	4	4

GROUP: 4-M:4.0 mg base/kg/day								
8908	6.97	16.1	47.0	67.4	23.1	34.3	1.0	0.0
8926	6.11	14.9	42.3	69.2	24.4	35.2	1.4	0.0
8921	6.33	15.2	43.2	68.2	24.0	35.2	0.9	0.4
8918	5.80	14.1	40.1	69.1	24.3	35.2	0.9	0.1
MEAN	6.30	15.1	43.2	68.5	24.0	35.0	1.1	0.1
SD	0.495	0.83	2.88	0.85	0.59	0.45	0.24	0.19
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK 13

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	% METHGB % HGBs	PLT 10 ³ /mm ³	PT sec	APTT sec
GROUP: 1-M:0 mg base/kg/day				
8915	0.9	242	9.1	10.0
8911	0.6	165	8.5	10.3
8909	0.7	207	10.9	10.0
8922	1.1	226	9.4	9.6
MEAN	0.8	210	9.5	10.0
SD	0.22	33.2	1.02	0.29
N	4	4	4	4

GROUP: 2-M:0.1 mg base/kg/day				
8923	0.8	264	9.3	9.5
8907	0.8	237	8.9	11.2
8919	1.3	209	9.5	9.7
8924	0.8	291	9.1	10.0
MEAN	0.9	250	9.2	10.1
SD	0.25	35.2	0.26	0.76
N	4	4	4	4

GROUP: 3-M:1.0 mg base/kg/day				
8917	2.4	208	8.9	10.0
8910	3.0	200	9.2	10.6
8913	6.5	166	9.0	10.1
8914	3.8	96	9.4	9.6
MEAN	3.9	168	9.1	10.1
SD	1.81	51.0	0.22	0.41
N	4	4	4	4

GROUP: 4-M:4.0 mg base/kg/day				
8908	9.0	127	9.0	10.4
8926	13.2	87	8.6	10.1
8921	5.8	230	8.8	10.1
8918	11.0	155	9.2	9.8
MEAN	9.8	150	8.9	10.1
SD	3.14	60.3	0.26	0.24
N	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK 26

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	RBC 10 ⁶ /mm ³	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RETICS % RBCs	HB % RBCs
GROUP: 1-M:0 mg base/kg/day								
8915	5.79	14.9	40.1	69.3	25.7	37.2	0.3	0.0
8911	6.82	17.3	47.5	69.6	25.4	36.4	0.2	0.0
8909	5.81	15.4	42.1	72.5	26.5	36.6	0.2	0.1
8922	6.75	16.1	44.1	65.3	23.9	36.5	0.4	0.3
MEAN	6.29	15.9	43.5	69.2	25.4	36.7	0.3	0.1
SD	0.569	1.04	3.16	2.96	1.09	0.36	0.10	0.14
N	4	4	4	4	4	4	4	4
GROUP: 2-M:0.1 mg base/kg/day								
8923	6.20	15.4	41.9	67.6	24.8	36.8	0.2	0.9
8907	7.41	17.9	48.7	65.7	24.2	36.8	0.4	0.0
8919	6.70	16.4	45.8	68.4	24.5	35.8	0.1	0.3
8924	6.43	16.0	43.5	67.7	24.9	36.8	0.4	0.0
MEAN	6.69	16.4	45.0	67.3	24.6	36.6	0.3	0.3
SD	0.525	1.07	2.95	1.16	0.32	0.50	0.15	0.42
N	4	4	4	4	4	4	4	4
GROUP: 3-M:1.0 mg base/kg/day								
8917	6.13	15.3	41.6	67.9	25.0	36.8	0.3	0.2
8910	6.08	15.6	43.0	70.7	25.7	36.3	0.8	0.3
8913	5.84	14.3	39.2	67.1	24.5	36.5	0.6	0.2
8914	6.73	17.1	46.4	68.9	25.4	36.9	1.0	0.0
MEAN	6.20	15.6	42.6	68.7	25.2	36.6	0.7	0.2
SD	0.378	1.16	3.01	1.55	0.52	0.28	0.30	0.13
N	4	4	4	4	4	4	4	4
GROUP: 4-M:4.0 mg base/kg/day								
8908	6.44	15.5	44.0	68.3	24.1	35.2	1.2	0.1
8926	5.48	13.5	37.4	68.2	24.6	36.1	1.3	0.4
8921	5.51	13.4	37.3	67.7	24.3	35.9	0.3	0.0
8918	5.78	14.8	40.7	70.4	25.6	36.4	0.9	0.0
MEAN	5.80	14.3	39.9	68.7	24.7	35.9	0.9	0.1
SD	0.446	1.02	3.19	1.20	0.67	0.51	0.45	0.19
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK 26

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	% METHGB % HGBs	PLT 10 ³ /mm ³	PT sec	APTT sec
GROUP: 1-M:0 mg base/kg/day				
8915	1.0	202	8.5	10.3
8911	0.9	248	8.3	9.7
8909	0.7	249	9.8	10.3
8922	0.9	258	8.6	9.7
MEAN	0.9	239	8.8	10.0
SD	0.13	25.2	0.68	0.35
N	4	4	4	4

GROUP: 2-M:0.1 mg base/kg/day				
8923	1.0	266	8.9	9.8
8907	1.1	229	8.3	11.9
8919	0.7	215	8.8	10.9
8924	1.0	305	8.2	10.6
MEAN	1.0	254	8.6	10.8
SD	0.17	40.4	0.35	0.87
N	4	4	4	4

GROUP: 3-M:1.0 mg base/kg/day				
8917	2.5	160	8.2	10.5
8910	3.4	190	8.5	10.7
8913	6.2	191	8.4	10.1
8914	4.0	120	8.8	10.0
MEAN	4.0	165	8.5	10.3
SD	1.58	33.4	0.25	0.33
N	4	4	4	4

GROUP: 4-M:4.0 mg base/kg/day				
8908	11.1	139	8.5	10.4
8926	15.2	129	8.3	10.2
8921	4.8	281	8.3	9.8
8918	12.1	194	8.5	9.6
MEAN	10.8	186	8.4	10.0
SD	4.36	69.6	0.12	0.37
N	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK 52

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	RBC 10 ⁶ /mm ³	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RETICS % RBCs	HB % RBCs
GROUP: 1-M:0 mg base/kg/day								
8915	7.40	18.0	50.5	68.2	24.3	35.6	0.3	0.3
8911	7.52	18.4	51.8	68.9	24.5	35.5	0.8	0.1
8909	6.27	15.9	44.6	71.1	25.4	35.7	0.2	0.1
8922	7.68	17.8	50.3	65.5	23.2	35.4	0.7	1.7
MEAN	7.22	17.5	49.3	68.4	24.4	35.6	0.5	0.6
SD	0.642	1.11	3.20	2.31	0.90	0.13	0.29	0.77
N	4	4	4	4	4	4	4	4

GROUP: 2-M:0.1 mg base/kg/day								
8923	7.27	17.4	48.2	66.3	23.9	36.1	0.4	0.3
8907	8.20	19.1	53.4	65.1	23.3	35.8	1.0	1.5
8919	7.40	17.7	50.2	67.8	23.9	35.3	0.2	1.2
8924	7.23	17.2	48.2	66.7	23.8	35.7	0.2	2.3
MEAN	7.53	17.9	50.0	66.5	23.7	35.7	0.5	1.3
SD	0.456	0.86	2.45	1.11	0.29	0.33	0.38	0.83
N	4	4	4	4	4	4	4	4

GROUP: 3-M:1.0 mg base/kg/day								
8917	7.19	17.4	48.6	67.6	24.2	35.8	1.6	3.8
8910	7.58	18.8	52.1	68.7	24.8	36.1	0.4	1.2
8913	6.50	15.6	44.1	67.8	24.0	35.4	0.8	0.9
8914	6.95	17.4	48.2	69.4	25.0	36.1	0.8	0.7
MEAN	7.06	17.3	48.3	68.4	24.5	35.9	0.9	1.7
SD	0.452	1.31	3.27	0.83	0.48	0.33	0.50	1.45
N	4	4	4	4	4	4	4	4

GROUP: 4-M:4.0 mg base/kg/day								
8908	7.52	17.6	50.0	66.5	23.4	35.2	0.9	0.7
8926	6.94	16.5	46.8	67.4	23.8	35.3	1.2	4.8
8921	7.44	17.7	50.2	67.5	23.8	35.3	1.4	0.5
8918	5.91	14.5	41.3	69.9	24.5	35.1	0.8	1.7
MEAN	6.95	16.6	47.1	67.8	23.9	35.2	1.1	1.9
SD	0.741	1.49	4.15	1.45	0.46	0.10	0.28	1.99
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK 52

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

Animal ID	% METHGB % HGBs	PLT 10 ³ /mm ³	PT sec	APTT sec
GROUP: 1-M:0 mg base/kg/day				
8915	0.7	157	8.8	9.3
8911	0.6	168	8.4	9.0
8909	0.6	228	9.8	9.4
8922	0.7	197	8.7	9.4
MEAN	0.7	188	8.9	9.3
SD	0.06	31.8	0.61	0.19
N	4	4	4	4

GROUP: 2-M:0.1 mg base/kg/day				
8923	0.7	145	8.8	9.5
8907	0.8	209	8.3	11.0
8919	1.1	205	8.9	9.9
8924	1.5	309	8.4	11.1
MEAN	1.0	217	8.6	10.4
SD	0.36	68.0	0.29	0.80
N	4	4	4	4

GROUP: 3-M:1.0 mg base/kg/day				
8917	2.0	83	8.3	10.2
8910	3.3	214	8.3	10.9
8913	4.4	226	8.4	9.7
8914	4.1	122	9.0	9.4
MEAN	3.5	161	8.5	10.1
SD	1.07	69.9	0.34	0.66
N	4	4	4	4

GROUP: 4-M:4.0 mg base/kg/day				
8908	10.3	143	8.5	9.7
8926	11.9	134	8.3	9.9
8921	4.3	251	8.4	10.1
8918	9.0	198	8.4	9.8
MEAN	8.9	182	8.4	9.9
SD	3.27	54.3	0.08	0.17
N	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK -3

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	RBC 10 ⁶ /mm ³	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RETICS % RBCs	HB % RBCs
GROUP: 1-F:0 mg base/kg/day								
8929	6.94	16.5	47.8	68.9	23.8	34.5	0.1	0.0
8942	5.54	13.4	39.1	70.6	24.2	34.3	0.4	0.0
8930	6.49	15.2	43.9	67.6	23.4	34.6	0.0	0.0
8938	6.57	16.2	48.3	73.5	24.7	33.5	0.1	0.0
MEAN	6.39	15.3	44.8	70.2	24.0	34.2	0.2	0.0
SD	0.596	1.40	4.26	2.55	0.56	0.50	0.17	0.00
N	4	4	4	4	4	4	4	4
GROUP: 2-F:0.1 mg base/kg/day								
8935	6.12	15.1	44.9	73.4	24.7	33.6	0.4	0.0
8937	6.16	14.9	44.2	71.8	24.2	33.7	0.2	0.0
8934	6.26	14.9	43.5	69.5	23.8	34.3	0.6	0.0
8945	6.84	16.2	47.1	68.9	23.7	34.4	0.4	0.0
MEAN	6.35	15.3	44.9	70.9	24.1	34.0	0.4	0.0
SD	0.335	0.62	1.56	2.08	0.45	0.41	0.16	0.00
N	4	4	4	4	4	4	4	4
GROUP: 3-F:1.0 mg base/kg/day								
8928	6.47	15.7	45.6	70.5	24.3	34.4	0.0	0.0
8940	6.22	15.0	44.0	70.7	24.1	34.1	0.2	0.0
8931	7.19	16.8	49.3	68.6	23.4	34.1	0.1	0.0
8943	6.48	15.6	44.8	69.1	24.1	34.8	0.3	0.0
MEAN	6.59	15.8	45.9	69.7	24.0	34.4	0.2	0.0
SD	0.418	0.75	2.34	1.03	0.39	0.33	0.13	0.00
N	4	4	4	4	4	4	4	4
GROUP: 4-F:4.0 mg base/kg/day								
8941	6.49	16.0	47.2	72.7	24.7	33.9	0.1	0.0
8933	5.79	14.2	40.7	70.3	24.5	34.9	0.4	0.0
8936	6.88	16.5	49.1	71.4	24.0	33.6	0.1	0.0
8944	6.30	15.3	44.7	71.0	24.3	34.2	0.0	0.0
MEAN	6.37	15.5	45.4	71.4	24.4	34.2	0.2	0.0
SD	0.453	1.00	3.63	1.01	0.30	0.56	0.17	0.00
N	4	4	4	4	4	4	4	4

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ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK -3

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	% METHGB % HGBs	PLT 10 ³ /mm ³	PT sec	APTT sec
GROUP: 1-F:0 mg base/kg/day				
8929	0.7	277	9.1	10.3
8942	0.5	220	8.5	11.4
8930	0.5	335	8.7	10.3
8938	0.6	176	8.5	10.9
MEAN	0.6	252	8.7	10.7
SD	0.10	69.1	0.28	0.53
N	4	4	4	4

GROUP: 2-F:0.1 mg base/kg/day				
8935	1.2	311	8.4	12.3
8937	0.3	334	8.4	10.3
8934	0.6	223	8.6	11.8
8945	0.5	259	8.5	10.1
MEAN	0.7	282	8.5	11.1
SD	0.39	50.2	0.10	1.09
N	4	4	4	4

GROUP: 3-F:1.0 mg base/kg/day				
8928	0.5	299	8.5	10.2
8940	0.8	365	8.3	10.8
8931	0.6	281	8.8	11.1
8943	0.5	447	8.3	10.3
MEAN	0.6	348	8.5	10.6
SD	0.14	75.2	0.24	0.42
N	4	4	4	4

GROUP: 4-F:4.0 mg base/kg/day				
8941	0.6	275	8.7	11.0
8933	0.8	280	8.6	10.2
8936	0.6	223	8.9	11.4
8944	0.6	354	8.8	10.9
MEAN	0.7	283	8.8	10.9
SD	0.10	53.9	0.13	0.50
N	4	4	4	4

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ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK -1

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	RBC 10 ⁶ /mm ³	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RETICS % RBCs	HB % RBCs
GROUP: 1-F:0 mg base/kg/day								
8929	6.58	15.7	45.6	69.3	23.9	34.4	0.0	0.0
8942	5.83	14.2	40.9	70.2	24.4	34.7	0.5	0.0
8930	6.50	15.3	44.1	67.8	23.5	34.7	0.2	0.0
8938	6.12	15.1	45.2	73.9	24.7	33.4	0.3	0.0
MEAN	6.26	15.1	44.0	70.3	24.1	34.3	0.3	0.0
SD	0.349	0.63	2.13	2.60	0.53	0.62	0.21	0.00
N	4	4	4	4	4	4	4	4
GROUP: 2-F:0.1 mg base/kg/day								
8935	5.72	14.1	41.6	72.7	24.7	33.9	0.4	0.0
8937	5.69	14.1	40.9	71.9	24.8	34.5	0.2	0.2
8934	6.41	15.2	44.7	69.7	23.7	34.0	0.2	0.0
8945	6.58	15.8	45.7	69.5	24.0	34.6	0.1	0.0
MEAN	6.10	14.8	43.2	71.0	24.3	34.3	0.2	0.1
SD	0.462	0.84	2.33	1.59	0.54	0.35	0.13	0.10
N	4	4	4	4	4	4	4	4
GROUP: 3-F:1.0 mg base/kg/day								
8928	6.28	15.2	44.1	70.2	24.2	34.5	0.0	0.0
8940	5.98	14.8	42.4	70.9	24.7	34.9	0.2	0.0
8931	7.07	16.7	48.6	68.7	23.6	34.4	0.1	0.0
8943	6.12	14.8	42.2	69.0	24.2	35.1	0.2	0.2
MEAN	6.36	15.4	44.3	69.7	24.2	34.7	0.1	0.1
SD	0.487	0.90	2.97	1.03	0.45	0.33	0.10	0.10
N	4	4	4	4	4	4	4	4
GROUP: 4-F:4.0 mg base/kg/day								
8941	5.95	14.8	43.3	72.8	24.9	34.2	0.1	0.0
8933	6.11	14.9	43.1	70.5	24.4	34.6	0.0	0.0
8936	6.63	16.2	46.9	70.7	24.4	34.5	0.9	0.0
8944	6.14	15.3	43.6	71.0	24.9	35.1	0.1	0.0
MEAN	6.21	15.3	44.2	71.3	24.7	34.6	0.3	0.0
SD	0.294	0.64	1.80	1.05	0.29	0.37	0.42	0.00
N	4	4	4	4	4	4	4	4

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ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK -1

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	% METHGB % HGBs	PLT 10 ³ /mm ³	PT sec	APTT sec
GROUP: 1-F:0 mg base/kg/day				
8929	0.6	267	8.6	10.4
8942	0.4	290	9.0	10.6
8930	0.9	300	8.5	10.3
8938	0.6	207	8.4	10.6
MEAN	0.6	266	8.6	10.5
SD	0.21	41.7	0.26	0.15
N	4	4	4	4

GROUP: 2-F:0.1 mg base/kg/day				
8935	0.8	301	8.7	11.6
8937	0.6	343	8.6	9.7
8934	0.7	230	8.9	11.3
8945	0.6	232	8.7	10.1
MEAN	0.7	277	8.7	10.7
SD	0.10	55.3	0.13	0.92
N	4	4	4	4

GROUP: 3-F:1.0 mg base/kg/day				
8928	0.6	306	8.7	9.9
8940	0.5	378	8.5	10.6
8931	0.6	251	9.1	10.8
8943	0.7	485	8.4	10.3
MEAN	0.6	355	8.7	10.4
SD	0.08	101.1	0.31	0.39
N	4	4	4	4

GROUP: 4-F:4.0 mg base/kg/day				
8941	0.5	205	8.7	11.1
8933	0.5	300	9.0	10.2
8936	0.5	224	8.8	11.0
8944	0.7	400	8.9	11.2
MEAN	0.6	282	8.9	10.9
SD	0.10	88.6	0.13	0.46
N	4	4	4	4

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ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK 4

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	RBC 10 ⁶ /mm ³	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RETICS % RBCs	HB % RBCs
GROUP: 1-F:0 mg base/kg/day								
8929	6.63	15.7	45.3	68.3	23.7	34.7	0.1	0.0
8942	6.05	14.6	42.2	69.8	24.1	34.6	0.1	0.0
8930	6.22	14.7	42.4	68.2	23.6	34.7	0.0	0.0
8938	6.63	16.3	48.6	73.3	24.6	33.5	0.2	0.0
MEAN	6.38	15.3	44.6	69.9	24.0	34.4	0.1	0.0
SD	0.294	0.82	3.00	2.38	0.45	0.59	0.08	0.00
N	4	4	4	4	4	4	4	4

GROUP: 2-F:0.1 mg base/kg/day								
8935	6.22	15.3	45.0	72.3	24.6	34.0	0.4	0.2
8937	6.58	15.9	46.7	71.0	24.2	34.0	0.0	0.0
8934	6.95	16.2	47.7	68.6	23.3	34.0	0.2	0.0
8945	6.51	15.5	45.0	69.1	23.8	34.4	0.1	0.0
MEAN	6.57	15.7	46.1	70.3	24.0	34.1	0.2	0.1
SD	0.300	0.40	1.33	1.71	0.56	0.20	0.17	0.10
N	4	4	4	4	4	4	4	4

GROUP: 3-F:1.0 mg base/kg/day								
8928	5.83	14.1	41.2	70.7	24.2	34.2	0.5	0.0
8940	5.98	14.7	42.8	71.6	24.6	34.3	0.2	0.0
8931	6.70	16.1	46.2	69.0	24.0	34.8	0.0	0.1
8943	6.11	14.7	42.0	68.7	24.1	35.0	1.3	0.2
MEAN	6.16	14.9	43.1	70.0	24.2	34.6	0.5	0.1
SD	0.381	0.85	2.20	1.38	0.26	0.39	0.57	0.10
N	4	4	4	4	4	4	4	4

GROUP: 4-F:4.0 mg base/kg/day								
8941	5.72	14.2	41.7	72.9	24.8	34.1	0.2	0.0
8933	5.70	13.9	41.7	73.2	24.4	33.3	1.0	0.7
8936	6.33	15.1	44.4	70.1	23.9	34.0	0.5	0.0
8944	5.93	14.9	42.9	72.3	25.1	34.7	2.1	0.0
MEAN	5.92	14.5	42.7	72.1	24.6	34.0	1.0	0.2
SD	0.292	0.57	1.28	1.40	0.52	0.57	0.83	0.35
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK 4

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	% METHGB % HGBs	PLT 10 ³ /mm ³	PT sec	APTT sec
GROUP: 1-F:0 mg base/kg/day				
8929	0.5	213	9.6	10.5
8942	0.7	253	9.4	11.0
8930	0.9	329	8.8	10.5
8938	0.5	166	9.0	10.8
MEAN	0.7	240	9.2	10.7
SD	0.19	69.0	0.37	0.24
N	4	4	4	4

GROUP: 2-F:0.1 mg base/kg/day				
8935	0.8	267	9.0	11.9
8937	0.8	230	8.8	10.2
8934	0.7	201	8.7	12.6
8945	0.8	198	9.0	10.0
MEAN	0.8	224	8.9	11.2
SD	0.05	32.1	0.15	1.28
N	4	4	4	4

GROUP: 3-F:1.0 mg base/kg/day				
8928	4.9	124	8.8	10.4
8940	8.9	150	8.6	10.7
8931	4.2	139	9.3	10.8
8943	5.9	224	8.7	10.3
MEAN	6.0	159	8.9	10.6
SD	2.07	44.5	0.31	0.24
N	4	4	4	4

GROUP: 4-F:4.0 mg base/kg/day				
8941	10.2	86	9.0	10.4
8933	13.4	57	8.9	10.4
8936	8.6	76	9.0	11.2
8944	17.4	78	8.8	12.2
MEAN	12.4	74	8.9	11.1
SD	3.89	12.3	0.10	0.85
N	4	4	4	4

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ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK 13

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	RBC 10 ⁶ /mm ³	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RETICS % RBCs	HB % RBCs
GROUP: 1-F:0 mg base/kg/day								
8929	6.92	16.9	48.0	69.4	24.4	35.2	0.2	0.0
8942	6.14	15.4	43.2	70.4	25.1	35.6	0.2	0.0
8930	6.35	15.5	43.2	68.0	24.4	35.9	0.6	0.2
8938	7.58	19.5	56.3	74.3	25.7	34.6	0.8	0.0
MEAN	6.75	16.8	47.7	70.5	24.9	35.3	0.5	0.1
SD	0.645	1.91	6.18	2.70	0.63	0.56	0.30	0.10
N	4	4	4	4	4	4	4	4

GROUP: 2-F:0.1 mg base/kg/day								
8935	5.68	14.7	40.9	72.0	25.9	35.9	0.1	0.2
8937	7.26	18.2	51.4	70.8	25.1	35.4	0.5	0.1
8934	6.35	15.9	43.7	68.8	25.0	36.4	0.6	0.1
8945	6.94	17.4	48.2	69.5	25.1	36.1	0.8	0.1
MEAN	6.56	16.6	46.1	70.3	25.3	36.0	0.5	0.1
SD	0.696	1.56	4.67	1.42	0.42	0.42	0.29	0.05
N	4	4	4	4	4	4	4	4

GROUP: 3-F:1.0 mg base/kg/day								
8928	6.14	15.5	44.3	72.1	25.2	35.0	0.8	0.3
8940	6.09	15.2	42.2	69.3	25.0	36.0	0.9	0.0
8931	6.78	17.1	49.0	72.3	25.2	34.9	0.2	0.0
8943	6.55	16.2	44.8	68.4	24.7	36.2	0.7	0.5
MEAN	6.39	16.0	45.1	70.5	25.0	35.5	0.7	0.2
SD	0.332	0.84	2.85	1.97	0.24	0.67	0.31	0.24
N	4	4	4	4	4	4	4	4

GROUP: 4-F:4.0 mg base/kg/day								
8941	6.25	15.8	45.6	73.0	25.3	34.6	0.5	0.0
8933	5.83	15.0	42.3	72.6	25.7	35.5	1.1	0.0
8936	6.06	15.1	42.3	69.8	24.9	35.7	1.0	0.3
8944	6.92	17.5	48.9	70.7	25.3	35.8	1.6	0.6
MEAN	6.27	15.9	44.8	71.5	25.3	35.4	1.1	0.2
SD	0.469	1.16	3.16	1.53	0.33	0.55	0.45	0.29
N	4	4	4	4	4	4	4	4

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ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK 13

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	% METHGB % HGBs	PLT 10 ³ /mm ³	PT sec	APTT sec
GROUP: 1-F:0 mg base/kg/day				
8929	0.6	256	9.7	10.4
8942	0.7	217	9.7	10.2
8930	2.1	279	9.4	9.5
8938	1.4	198	9.2	10.7
MEAN	1.2	238	9.5	10.2
SD	0.70	36.7	0.24	0.51
N	4	4	4	4

GROUP: 2-F:0.1 mg base/kg/day				
8935	0.7	296	9.5	10.8
8937	1.2	264	10.4	8.5
8934	0.9	243	9.7	11.5
8945	0.9	236	9.4	9.4
MEAN	0.9	260	9.8	10.1
SD	0.21	26.9	0.45	1.35
N	4	4	4	4

GROUP: 3-F:1.0 mg base/kg/day				
8928	5.4	176	9.2	9.9
8940	6.6	222	9.0	10.5
8931	5.2	122	9.1	10.8
8943	4.7	314	8.9	10.6
MEAN	5.5	209	9.1	10.5
SD	0.81	81.3	0.13	0.39
N	4	4	4	4

GROUP: 4-F:4.0 mg base/kg/day				
8941	7.5	133	9.4	11.3
8933	16.2	120	9.3	9.9
8936	10.0	153	9.5	9.6
8944	16.3	305	9.5	11.1
MEAN	12.5	178	9.4	10.5
SD	4.45	85.9	0.10	0.85
N	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK 26

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	RBC 10 ⁶ /mm ³	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RETICS % RBCs	HB % RBCs
GROUP: 1-F:0 mg base/kg/day								
8929	7.05	17.8	48.6	68.9	25.2	36.6	0.1	0.1
8942	6.75	17.6	47.7	70.7	26.1	36.9	0.3	0.0
8930	7.26	18.0	48.6	66.9	24.8	37.0	0.4	0.0
8938	7.09	18.7	52.3	73.8	26.4	35.8	0.5	0.0
MEAN	7.04	18.0	49.3	70.1	25.6	36.6	0.3	0.0
SD	0.212	0.48	2.04	2.93	0.75	0.54	0.17	0.05
N	4	4	4	4	4	4	4	4

GROUP: 2-F:0.1 mg base/kg/day								
8935	5.83	15.6	42.4	72.7	26.8	36.8	0.7	0.0
8937	7.15	18.4	50.3	70.3	25.7	36.6	0.4	0.0
8934	6.93	17.3	47.3	68.3	25.0	36.6	0.2	0.4
8945	7.06	18.1	49.5	70.1	25.6	36.6	0.8	0.0
MEAN	6.74	17.4	47.4	70.4	25.8	36.7	0.5	0.1
SD	0.615	1.26	3.55	1.81	0.75	0.10	0.28	0.20
N	4	4	4	4	4	4	4	4

GROUP: 3-F:1.0 mg base/kg/day								
8928	6.13	16.0	44.0	71.8	26.1	36.4	0.5	0.4
8940	5.99	15.4	42.3	70.6	25.7	36.4	1.3	0.0
8931	6.66	16.8	46.0	69.1	25.2	36.5	0.3	0.0
8943	6.14	15.7	42.6	69.4	25.6	36.9	0.6	0.0
MEAN	6.23	16.0	43.7	70.2	25.7	36.6	0.7	0.1
SD	0.295	0.60	1.69	1.23	0.37	0.24	0.43	0.20
N	4	4	4	4	4	4	4	4

GROUP: 4-F:4.0 mg base/kg/day								
8941	7.07	18.4	51.0	72.1	26.0	36.1	1.0	0.0
8933	6.45	16.4	46.8	72.6	25.4	35.0	2.0	0.0
8936	6.04	15.4	42.2	69.9	25.5	36.5	0.7	0.0
8944	6.64	17.1	46.8	70.5	25.8	36.5	1.3	0.9
MEAN	6.55	16.8	46.7	71.3	25.7	36.0	1.3	0.2
SD	0.428	1.26	3.59	1.28	0.28	0.71	0.56	0.45
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK 26

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	% METHGB % HGBs	PLT 10 ³ /mm ³	PT sec	APTT sec
GROUP: 1-F:0 mg base/kg/day				
8929	0.9	230	9.3	10.3
8942	1.0	285	9.1	10.4
8930	0.9	265	8.5	10.4
8938	0.6	171	8.6	10.6
MEAN	0.9	238	8.9	10.4
SD	0.17	50.0	0.39	0.13
N	4	4	4	4

GROUP: 2-F:0.1 mg base/kg/day				
8935	1.0	284	8.5	11.0
8937	1.3	313	8.5	9.5
8934	0.9	256	8.9	11.6
8945	0.9	229	8.7	9.9
MEAN	1.0	271	8.7	10.5
SD	0.19	36.2	0.19	0.97
N	4	4	4	4

GROUP: 3-F:1.0 mg base/kg/day				
8928	4.3	296	8.6	10.4
8940	8.5	294	8.3	10.3
8931	4.0	149	8.8	10.6
8943	5.4	398	8.5	10.2
MEAN	5.6	284	8.6	10.4
SD	2.06	102.4	0.21	0.17
N	4	4	4	4

GROUP: 4-F:4.0 mg base/kg/day				
8941	8.7	144	8.9	12.1
8933	16.1	97	8.6	10.2
8936	7.1	191	8.9	10.3
8944	17.7	351	8.9	10.8
MEAN	12.4	196	8.8	10.9
SD	5.28	110.4	0.15	0.87
N	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK 52

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	RBC 10 ⁶ /mm ³	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RETICS % RBCs	HB % RBCs
GROUP: 1-F:0 mg base/kg/day								
8929	6.68	16.6	46.3	69.3	24.9	35.9	0.3	0.6
8942	7.37	18.2	51.0	69.2	24.7	35.7	0.2	0.5
8930	7.08	17.2	47.8	67.5	24.3	36.0	1.1	0.0
8938	7.43	18.7	54.5	73.4	25.2	34.3	0.2	1.1
MEAN	7.14	17.7	49.9	69.9	24.8	35.5	0.5	0.6
SD	0.343	0.95	3.64	2.51	0.38	0.79	0.44	0.45
N	4	4	4	4	4	4	4	4

GROUP: 2-F:0.1 mg base/kg/day								
8935	5.78	14.8	41.7	72.1	25.6	35.5	0.4	1.4
8937	6.59	16.5	46.3	70.3	25.0	35.6	0.1	1.1
8934	6.77	16.4	45.2	66.8	24.2	36.3	0.1	2.5
8945	7.58	18.7	52.0	68.6	24.7	36.0	0.2	0.3
MEAN	6.68	16.6	46.3	69.5	24.9	35.9	0.2	1.3
SD	0.739	1.60	4.28	2.27	0.59	0.37	0.14	0.91
N	4	4	4	4	4	4	4	4

GROUP: 3-F:1.0 mg base/kg/day								
8928	6.12	15.2	42.5	69.4	24.8	35.8	0.2	1.9
8940	6.75	17.0	47.9	71.0	25.2	35.5	0.8	0.4
8931	7.28	17.8	50.5	69.4	24.5	35.2	0.7	0.6
8943	6.00	14.7	41.5	69.2	24.5	35.4	0.6	2.2
MEAN	6.54	16.2	45.6	69.8	24.8	35.5	0.6	1.3
SD	0.594	1.47	4.31	0.84	0.33	0.25	0.26	0.91
N	4	4	4	4	4	4	4	4

GROUP: 4-F:4.0 mg base/kg/day								
8941	6.61	16.5	47.7	72.2	25.0	34.6	0.5	0.2
8933	6.11	15.3	44.5	72.8	25.0	34.4	1.7	0.7
8936	6.58	16.6	47.0	71.4	25.2	35.3	1.9	0.3
8944	4.66	15.4	33.9	72.7	33.0	45.4	1.4	0.7
MEAN	5.99	16.0	43.3	72.3	27.1	37.4	1.4	0.5
SD	0.916	0.70	6.40	0.64	3.97	5.33	0.62	0.26
N	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: WEEK 52

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

Animal ID	% METHGB % HGBs	PLT 10 ³ /mm ³	PT sec	APTT sec
GROUP: 1-F:0 mg base/kg/day				
8929	0.5	233	9.7	9.8
8942	1.4	246	9.2	10.0
8930	0.5	237	9.0	9.8
8938	0.6	151	8.5	10.5
MEAN	0.8	217	9.1	10.0
SD	0.44	44.2	0.50	0.33
N	4	4	4	4

GROUP: 2-F:0.1 mg base/kg/day				
8935	1.2	364	8.8	10.2
8937	0.9	334	8.4	9.5
8934	1.1	248	8.9	11.9
8945	0.8	276	8.8	9.7
MEAN	1.0	306	8.7	10.3
SD	0.18	52.9	0.22	1.09
N	4	4	4	4

GROUP: 3-F:1.0 mg base/kg/day				
8928	5.9	241	8.6	9.7
8940	8.5	315	8.4	9.9
8931	5.2	165	8.7	10.6
8943	8.4	366	8.4	9.6
MEAN	7.0	272	8.5	10.0
SD	1.70	87.7	0.15	0.45
N	4	4	4	4

GROUP: 4-F:4.0 mg base/kg/day				
8941	8.8	193	8.6	11.0
8933	15.6	95	8.6	9.9
8936	6.5	211	8.8	10.7
8944	17.5	243	9.0	10.3
MEAN	12.1	186	8.8	10.5
SD	5.28	63.8	0.19	0.48
N	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 1-M : 0 mg base/kg/day

SEX: MALE

Animal ID	WEEK -3	WEEK -1	WEEK 4	WEEK 13
8915	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight
8911	Poikilocytes,Slight; Anisocytosis,Slight; Howell-Jolly Bodies, Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight
8909	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight
8922	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 1-M : 0 mg base/kg/day

SEX: MALE

Animal ID	WEEK 26	WEEK 52
8915	Poikilocytes,Slight	Poikilocytes,Slight
8911	Poikilocytes,Slight	Poikilocytes,Slight
8909	Poikilocytes,Slight	Poikilocytes,Slight
8922	Poikilocytes,Slight; Howell-Jolly Bodies, Slight	Poikilocytes,Slight

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 2-M : 0.1 mg base/kg/day

SEX: MALE

Animal ID	WEEK -3	WEEK -1	WEEK 4	WEEK 13
8923	Poikilocytes,Slight; Anisocytosis,Slight	Polychromasia,Slight Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight
8907	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight
8919	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight
8924	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 2-M : 0.1 mg base/kg/day

SEX: MALE

Animal ID	WEEK 26	WEEK 52
8923	Poikilocytes,Slight	Poikilocytes,Slight
8907	Poikilocytes,Slight	Poikilocytes,Slight
8919	Poikilocytes,Slight	Poikilocytes,Slight
8924	Poikilocytes,Slight	Poikilocytes,Slight

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 3-M : 1.0 mg base/kg/day

SEX: MALE

Animal ID	WEEK -3	WEEK -1	WEEK 4	WEEK 13
8917	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight
8910	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight
8913	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Polychromasia,Slight Poikilocytes,Slight
8914	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 3-M : 1.0 mg base/kg/day

SEX: MALE

Animal ID	WEEK 26	WEEK 52
8917	Poikilocytes,Slight	Poikilocytes,Slight
8910	Poikilocytes,Slight	Poikilocytes,Slight
8913	Poikilocytes,Slight	Poikilocytes,Slight
8914	Poikilocytes,Slight	Pyknotic Cells, Slight;Howell-Jolly Bodies,Slight

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 4-M : 4.0 mg base/kg/day

SEX: MALE

Animal ID	WEEK -3	WEEK -1	WEEK 4	WEEK 13
8908	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight
8926	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight
8921	Poikilocytes,Slight; Anisocytosis,Slight; Howell-Jolly Bodies, Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Howell-Jolly Bodies, Slight	Poikilocytes,Slight
8918	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Howell-Jolly Bodies, Slight	Poikilocytes,Slight

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 4-M : 4.0 mg base/kg/day

SEX: MALE

Animal ID	WEEK 26	WEEK 52
8908	Poikilocytes,Slight	Poikilocytes,Slight
8926	Polychromasia,Slight Poikilocytes,Slight	Poikilocytes,Slight
8921	Poikilocytes,Slight	Poikilocytes,Slight
8918	Polychromasia,Slight Poikilocytes,Slight	Poikilocytes,Slight

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 1-F : 0 mg base/kg/day

SEX: FEMALE

Animal ID	WEEK -3	WEEK -1	WEEK 4	WEEK 13
8929	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight
8942	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight
8930	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight
8938	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 1-F : 0 mg base/kg/day

SEX: FEMALE

Animal ID	WEEK 26	WEEK 52
8929	Poikilocytes,Slight	Poikilocytes,Slight
8942	Poikilocytes,Slight	Poikilocytes,Slight
8930	Polychromasia,Slight Poikilocytes,Slight; Basophilic Stippling Slight	Poikilocytes,Slight
8938	Poikilocytes,Slight	Poikilocytes,Slight

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 2-F : 0.1 mg base/kg/day

SEX: FEMALE

Animal ID	WEEK -3	WEEK -1	WEEK 4	WEEK 13
8935	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight
8937	Poikilocytes,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight
8934	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight
8945	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 2-F : 0.1 mg base/kg/day

SEX: FEMALE

Animal ID	WEEK 26	WEEK 52
8935	Poikilocytes,Slight	Poikilocytes,Slight
8937	Poikilocytes,Slight	Poikilocytes,Slight
8934	Poikilocytes,Slight	Poikilocytes,Slight
8945	Poikilocytes,Slight	Poikilocytes,Slight; Howell-Jolly Bodies, Slight

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 3-F : 1.0 mg base/kg/day

SEX: FEMALE

Animal ID	WEEK -3	WEEK -1	WEEK 4	WEEK 13
8928	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight
8940	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Howell-Jolly Bodies, Slight	Howell-Jolly Bodies, Slight;Poikilocytes, Slight
8931	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight
8943	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 3-F : 1.0 mg base/kg/day

SEX: FEMALE

Animal ID	WEEK 26	WEEK 52
8928	Poikilocytes,Slight	Poikilocytes,Slight
8940	Poikilocytes,Slight	Poikilocytes,Slight
8931	Poikilocytes,Slight	Poikilocytes,Slight; Pyknotic Cells, Slight
8943	Poikilocytes,Slight	Poikilocytes,Slight

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 4-F : 4.0 mg base/kg/day

SEX: FEMALE

Animal ID	WEEK -3	WEEK -1	WEEK 4	WEEK 13
8941	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight
8933	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight
8936	Poikilocytes,Slight; Anisocytosis,Slight	Polychromasia,Slight Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Poikilocytes,Slight
8944	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight; Anisocytosis,Slight	Poikilocytes,Slight	Howell-Jolly Bodies, Slight;Poikilocytes, Slight

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

RBC MORPHOLOGY OBSERVATIONS

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 4-F : 4.0 mg base/kg/day

SEX: FEMALE

Animal ID	WEEK 26	WEEK 52
8941	Poikilocytes,Slight	Poikilocytes,Slight
8933	Poikilocytes,Slight	Poikilocytes,Slight; Platelets Low,Slight
8936	Poikilocytes,Slight	Poikilocytes,Slight
8944	Polychromasia,Slight Poikilocytes,Slight	Poikilocytes,Slight

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-9

STUDY NO: 219

GROUP: 1-M : 0 mg base/kg/day

SEX: MALE

Animal ID		WEEK -3		WEEK -1		WEEK 4		WEEK 13	
		CNT	ABS	CNT	ABS	CNT	ABS	CNT	ABS
8915	Nucleated Red Cells	0		0		0		0	
	M. Neutrophils	58	4.5	53	5.2	66	5.3	71	7.3
	I. Neutrophils	1	0.1	0	0.0	1	0.1	0	0.0
	Lymphocytes	28	2.2	37	3.6	26	2.1	24	2.5
	Monocytes	0	0.0	4	0.4	2	0.2	1	0.1
	Eosinophils	11	0.9	4	0.4	4	0.3	4	0.4
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	2	0.2	2	0.2	1	0.1	0	0.0
	WBC		7.8		9.8		8.1		10.3
8911	Nucleated Red Cells	0		0		0		0	
	M. Neutrophils	59	5.0	66	6.0	64	5.8	76	8.4
	I. Neutrophils	0	0.0	0	0.0	0	0.0	0	0.0
	Lymphocytes	31	2.6	27	2.5	28	2.5	20	2.2
	Monocytes	7	0.6	0	0.0	5	0.5	2	0.2
	Eosinophils	3	0.3	4	0.4	3	0.3	1	0.1
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	0	0.0	3	0.3	0	0.0	1	0.1
	WBC		8.5		9.1		9.0		11.0
8909	Nucleated Red Cells	0		0		0		0	
	M. Neutrophils	62	5.1	64	6.1	72	6.5	78	9.7
	I. Neutrophils	1	0.1	0	0.0	1	0.1	2	0.2
	Lymphocytes	31	2.5	27	2.6	22	2.0	13	1.6
	Monocytes	2	0.2	2	0.2	2	0.2	4	0.5
	Eosinophils	3	0.2	5	0.5	3	0.3	1	0.1
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	1	0.1	2	0.2	0	0.0	2	0.2
	WBC		8.2		9.5		9.0		12.4
8922	Nucleated Red Cells	0		0		1		0	
	M. Neutrophils	52	3.6	72	7.2	65	4.7	70	6.4
	I. Neutrophils	2	0.1	3	0.3	1	0.1	0	0.0
	Lymphocytes	34	2.4	13	1.3	27	1.9	24	2.2
	Monocytes	3	0.2	3	0.3	2	0.1	1	0.1
	Eosinophils	9	0.6	5	0.5	4	0.3	3	0.3
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	0	0.0	4	0.4	1	0.1	2	0.2
	WBC		7.0		10.0		7.2		9.1

WBC corrected for NRBC = or > 10

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 1-M : 0 mg base/kg/day

SEX: MALE

Animal ID		WEEK 26		WEEK 52	
		CNT	ABS	CNT	ABS
8915	Nucleated Red Cells	1		0	
	M. Neutrophils	69	6.1	60	5.2
	I. Neutrophils	0	0.0	0	0.0
	Lymphocytes	26	2.3	34	2.9
	Monocytes	0	0.0	1	0.1
	Eosinophils	4	0.4	5	0.4
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	1	0.1	0	0.0
	WBC		8.9		8.6
8911	Nucleated Red Cells	0		0	
	M. Neutrophils	64	6.5	67	6.6
	I. Neutrophils	0	0.0	0	0.0
	Lymphocytes	28	2.8	30	2.9
	Monocytes	2	0.2	1	0.1
	Eosinophils	5	0.5	2	0.2
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	1	0.1	0	0.0
	WBC		10.1		9.8
8909	Nucleated Red Cells	0		0	
	M. Neutrophils	75	9.0	78	7.4
	I. Neutrophils	1	0.1	0	0.0
	Lymphocytes	20	2.4	17	1.6
	Monocytes	1	0.1	3	0.3
	Eosinophils	3	0.4	2	0.2
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	0	0.0	0	0.0
	WBC		12.0		9.5
8922	Nucleated Red Cells	0		0	
	M. Neutrophils	80	10.3	79	9.0
	I. Neutrophils	2	0.3	0	0.0
	Lymphocytes	11	1.4	13	1.5
	Monocytes	1	0.1	2	0.2
	Eosinophils	4	0.5	6	0.7
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	2	0.3	0	0.0
	WBC		12.9		11.4

WBC corrected for NRBC = or > 10

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-9

STUDY NO: 219

GROUP: 2-M : 0.1 mg base/kg/day

SEX: MALE

Animal ID		WEEK -3		WEEK -1		WEEK 4		WEEK 13	
		CNT	ABS	CNT	ABS	CNT	ABS	CNT	ABS
8923	Nucleated Red Cells	0		0		1		0	
	M. Neutrophils	74	5.6	68	4.4	73	6.4	71	5.0
	I. Neutrophils	0	0.0	1	0.1	1	0.1	0	0.0
	Lymphocytes	23	1.7	27	1.7	18	1.6	22	1.6
	Monocytes	1	0.1	2	0.1	4	0.3	5	0.4
	Eosinophils	2	0.2	2	0.1	4	0.3	0	0.0
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	0	0.0	0	0.0	0	0.0	2	0.1
	WBC		7.5		6.4		8.7		7.1
8907	Nucleated Red Cells	0		0		0		0	
	M. Neutrophils	62	4.0	68	5.2	60	4.4	72	7.2
	I. Neutrophils	1	0.1	1	0.1	0	0.0	0	0.0
	Lymphocytes	33	2.1	25	1.9	35	2.6	21	2.1
	Monocytes	2	0.1	3	0.2	3	0.2	4	0.4
	Eosinophils	2	0.1	1	0.1	2	0.1	1	0.1
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	0	0.0	2	0.2	0	0.0	2	0.2
	WBC		6.4		7.6		7.3		10.0
8919	Nucleated Red Cells	0		1		0		0	
	M. Neutrophils	71	5.0	78	8.0	75	6.1	77	6.8
	I. Neutrophils	2	0.1	1	0.1	0	0.0	0	0.0
	Lymphocytes	19	1.3	19	1.9	16	1.3	21	1.8
	Monocytes	0	0.0	0	0.0	7	0.6	1	0.1
	Eosinophils	6	0.4	1	0.1	1	0.1	1	0.1
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	2	0.1	1	0.1	1	0.1	0	0.0
	WBC		7.0		10.2		8.1		8.8
8924	Nucleated Red Cells	0		0		0		0	
	M. Neutrophils	47	4.1	64	5.9	57	6.3	64	7.0
	I. Neutrophils	1	0.1	0	0.0	0	0.0	0	0.0
	Lymphocytes	46	4.0	26	2.4	37	4.1	30	3.3
	Monocytes	1	0.1	3	0.3	5	0.6	3	0.3
	Eosinophils	5	0.4	5	0.5	1	0.1	2	0.2
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	0	0.0	2	0.2	0	0.0	1	0.1
	WBC		8.7		9.2		11.0		11.0

WBC corrected for NRBC = or > 10

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 2-M : 0.1 mg base/kg/day

SEX: MALE

Animal ID		WEEK 26		WEEK 52	
		CNT	ABS	CNT	ABS
8923	Nucleated Red Cells	0		0	
	M. Neutrophils	77	5.5	64	4.2
	I. Neutrophils	0	0.0	0	0.0
	Lymphocytes	17	1.2	31	2.0
	Monocytes	1	0.1	2	0.1
	Eosinophils	4	0.3	3	0.2
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	1	0.1	0	0.0
	WBC		7.1		6.5
8907	Nucleated Red Cells	1		1	
	M. Neutrophils	81	7.8	60	4.7
	I. Neutrophils	1	0.1	1	0.1
	Lymphocytes	13	1.2	34	2.7
	Monocytes	1	0.1	1	0.1
	Eosinophils	3	0.3	4	0.3
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	1	0.1	0	0.0
	WBC		9.6		7.9
8919	Nucleated Red Cells	1		0	
	M. Neutrophils	84	7.6	74	5.4
	I. Neutrophils	0	0.0	0	0.0
	Lymphocytes	16	1.5	23	1.7
	Monocytes	0	0.0	1	0.1
	Eosinophils	0	0.0	2	0.1
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	0	0.0	0	0.0
	WBC		9.1		7.3
8924	Nucleated Red Cells	0		1	
	M. Neutrophils	93	27.5	80	12.2
	I. Neutrophils	0	0.0	0	0.0
	Lymphocytes	5	1.5	17	2.6
	Monocytes	1	0.3	3	0.5
	Eosinophils	1	0.3	0	0.0
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	0	0.0	0	0.0
	WBC		29.6		15.2

WBC corrected for NRBC = or > 10

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 3-M : 1.0 mg base/kg/day

SEX: MALE

Animal ID		WEEK -3		WEEK -1		WEEK 4		WEEK 13	
		CNT	ABS	CNT	ABS	CNT	ABS	CNT	ABS
8917	Nucleated Red Cells	0		0		0		0	
	M. Neutrophils	50	4.1	52	4.6	60	5.6	64	6.9
	I. Neutrophils	0	0.0	0	0.0	1	0.1	0	0.0
	Lymphocytes	45	3.6	41	3.6	35	3.3	30	3.2
	Monocytes	1	0.1	3	0.3	2	0.2	1	0.1
	Eosinophils	3	0.2	2	0.2	2	0.2	4	0.4
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	1	0.1	2	0.2	0	0.0	1	0.1
	WBC		8.1		8.9		9.3		10.8
8910	Nucleated Red Cells	0		0		0		0	
	M. Neutrophils	61	4.1	73	5.8	66	5.0	76	6.3
	I. Neutrophils	2	0.1	2	0.2	2	0.2	0	0.0
	Lymphocytes	28	1.9	21	1.7	26	2.0	19	1.6
	Monocytes	3	0.2	1	0.1	3	0.2	2	0.2
	Eosinophils	5	0.3	2	0.2	3	0.2	1	0.1
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	1	0.1	1	0.1	0	0.0	2	0.2
	WBC		6.8		7.9		7.5		8.3
8913	Nucleated Red Cells	0		1		0		0	
	M. Neutrophils	54	3.6	65	5.3	64	6.4	69	6.3
	I. Neutrophils	0	0.0	0	0.0	1	0.1	0	0.0
	Lymphocytes	37	2.4	30	2.4	26	2.6	24	2.2
	Monocytes	1	0.1	2	0.2	8	0.8	0	0.0
	Eosinophils	4	0.3	3	0.2	1	0.1	5	0.5
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	4	0.3	0	0.0	0	0.0	2	0.2
	WBC		6.6		8.1		10.0		9.1
8914	Nucleated Red Cells	0		0		0		0	
	M. Neutrophils	63	5.3	68	6.0	61	4.6	65	7.2
	I. Neutrophils	0	0.0	0	0.0	0	0.0	0	0.0
	Lymphocytes	30	2.5	26	2.3	22	1.7	25	2.8
	Monocytes	1	0.1	3	0.3	5	0.4	4	0.4
	Eosinophils	6	0.5	1	0.1	9	0.7	4	0.4
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	0	0.0	2	0.2	3	0.2	2	0.2
	WBC		8.4		8.8		7.6		11.1

WBC corrected for NRBC = or > 10

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 3-M : 1.0 mg base/kg/day

SEX: MALE

Animal ID		WEEK 26		WEEK 52	
		CNT	ABS	CNT	ABS
8917	Nucleated Red Cells	0		0	
	M. Neutrophils	53	5.9	50	5.7
	I. Neutrophils	0	0.0	2	0.2
	Lymphocytes	36	4.0	40	4.6
	Monocytes	1	0.1	4	0.5
	Eosinophils	4	0.4	4	0.5
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	6	0.7	0	0.0
WBC		11.2		11.4	
8910	Nucleated Red Cells	0		0	
	M. Neutrophils	74	6.7	70	6.7
	I. Neutrophils	1	0.1	0	0.0
	Lymphocytes	18	1.6	19	1.8
	Monocytes	4	0.4	9	0.9
	Eosinophils	3	0.3	2	0.2
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	0	0.0	0	0.0
WBC		9.0		9.5	
8913	Nucleated Red Cells	0		0	
	M. Neutrophils	54	3.6	61	5.4
	I. Neutrophils	0	0.0	0	0.0
	Lymphocytes	37	2.4	30	2.7
	Monocytes	1	0.1	2	0.2
	Eosinophils	7	0.5	7	0.6
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	1	0.1	0	0.0
WBC		6.6		8.9	
8914	Nucleated Red Cells	0		0	
	M. Neutrophils	67	7.2	67	7.1
	I. Neutrophils	0	0.0	0	0.0
	Lymphocytes	28	3.0	25	2.7
	Monocytes	0	0.0	4	0.4
	Eosinophils	3	0.3	4	0.4
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	2	0.2	0	0.0
WBC		10.8		10.6	

WBC corrected for NRBC = or > 10

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

WHITE DIFFERENTIAL DATA

STUDY IO: UIC-9
STUDY NO: 219

GROUP: 4-M : 4.0 mg base/kg/day

SEX: MALE

Animal IO		WEEK -3		WEEK -1		WEEK 4		WEEK 13	
		CNT	ABS	CNT	ABS	CNT	ABS	CNT	ABS
8908	Nucleated Red Cells	0		1		3		0	
	M. Neutrophils	49	4.9	74	7.4	65	8.0	79	10.0
	I. Neutrophils	2	0.2	2	0.2	1	0.1	0	0.0
	Lymphocytes	33	3.3	18	1.8	22	2.7	15	1.9
	Monocytes	4	0.4	5	0.5	8	1.0	1	0.1
	Eosinophils	12	1.2	1	0.1	4	0.5	4	0.5
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	0	0.0	0	0.0	0	0.0	1	0.1
WBC		10.1		10.0		12.3		12.6	
8926	Nucleated Red Cells	1		0		0		4	
	M. Neutrophils	60	4.7	61	5.2	71	7.0	80	12.6
	I. Neutrophils	0	0.0	1	0.1	0	0.0	0	0.0
	Lymphocytes	34	2.7	31	2.7	23	2.3	15	2.4
	Monocytes	5	0.4	4	0.3	2	0.2	5	0.8
	Eosinophils	1	0.1	2	0.2	3	0.3	0	0.0
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	0	0.0	1	0.1	1	0.1	0	0.0
WBC		7.9		8.6		9.9		15.7	
8921	Nucleated Red Cells	0		0		1		0	
	M. Neutrophils	46	1.8	64	4.4	59	3.8	79	9.2
	I. Neutrophils	1	0.0	0	0.0	0	0.0	0	0.0
	Lymphocytes	49	1.9	28	1.9	34	2.2	15	1.8
	Monocytes	1	0.0	5	0.3	4	0.3	4	0.5
	Eosinophils	2	0.1	1	0.1	2	0.1	1	0.1
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	1	0.0	2	0.1	1	0.1	1	0.1
WBC		3.9		6.9		6.5		11.7	
8918	Nucleated Red Cells	0		0		0		0	
	M. Neutrophils	61	5.1	73	6.1	71	6.4	84	11.1
	I. Neutrophils	1	0.1	1	0.1	2	0.2	0	0.0
	Lymphocytes	32	2.7	22	1.8	20	1.8	11	1.5
	Monocytes	2	0.2	2	0.2	3	0.3	3	0.4
	Eosinophils	4	0.3	2	0.2	3	0.3	2	0.3
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	0	0.0	0	0.0	1	0.1	0	0.0
WBC		8.3		8.3		9.0		13.2	

WBC corrected for NRBC = or > 10

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

WHITE DIFFERENTIAL DATA

STUDY IO: UIC-9
STUDY NO: 219

GROUP: 4-M : 4.0 mg base/kg/day

SEX: MALE

Animal IO		WEEK 26		WEEK 52	
		CNT	ABS	CNT	ABS
8908	Nucleated Red Cells	1		0	
	M. Neutrophils	81	12.1	72	10.6
	I. Neutrophils	0	0.0	1	0.1
	Lymphocytes	16	2.4	16	2.4
	Monocytes	0	0.0	6	0.9
	Eosinophils	3	0.4	5	0.7
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	0	0.0	0	0.0
	WBC		14.9		14.7
8926	Nucleated Red Cells	0		0	
	M. Neutrophils	80	10.0	72	7.1
	I. Neutrophils	3	0.4	0	0.0
	Lymphocytes	12	1.5	23	2.3
	Monocytes	5	0.6	2	0.2
	Eosinophils	0	0.0	3	0.3
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	0	0.0	0	0.0
	WBC		12.5		9.9
8921	Nucleated Red Cells	0		0	
	M. Neutrophils	89	8.3	84	9.5
	I. Neutrophils	0	0.0	0	0.0
	Lymphocytes	10	0.9	15	1.7
	Monocytes	1	0.1	1	0.1
	Eosinophils	0	0.0	0	0.0
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	0	0.0	0	0.0
	WBC		9.3		11.3
8918	Nucleated Red Cells	0		0	
	M. Neutrophils	89	11.2	78	13.3
	I. Neutrophils	0	0.0	0	0.0
	Lymphocytes	6	0.8	13	2.2
	Monocytes	2	0.3	8	1.4
	Eosinophils	3	0.4	1	0.2
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	0	0.0	0	0.0
	WBC		12.6		17.0

WBC corrected for NRBC = or > 10

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 1-F : 0 mg base/kg/day

SEX: FEMALE

Animal ID		WEEK -3		WEEK -1		WEEK 4		WEEK 13	
		CNT	ABS	CNT	ABS	CNT	ABS	CNT	ABS
8929	Nucleated Red Cells	0		0		0		0	
	M. Neutrophils	52	3.3	61	4.2	63	5.1	70	7.5
	I. Neutrophils	1	0.1	0	0.0	3	0.2	1	0.1
	Lymphocytes	43	2.7	25	1.7	27	2.2	22	2.4
	Monocytes	1	0.1	7	0.5	3	0.2	3	0.3
	Eosinophils	2	0.1	2	0.1	3	0.2	2	0.2
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	1	0.1	5	0.3	1	0.1	2	0.2
	WBC		6.3		6.9		8.1		10.7
8942	Nucleated Red Cells	0		0		0		0	
	M. Neutrophils	72	6.8	63	6.4	68	6.5	60	5.9
	I. Neutrophils	3	0.3	2	0.2	0	0.0	0	0.0
	Lymphocytes	16	1.5	29	3.0	27	2.6	27	2.7
	Monocytes	5	0.5	3	0.3	1	0.1	2	0.2
	Eosinophils	1	0.1	1	0.1	3	0.3	7	0.7
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	3	0.3	2	0.2	1	0.1	4	0.4
	WBC		9.4		10.2		9.5		9.9
8930	Nucleated Red Cells	0		0		0		0	
	M. Neutrophils	55	3.9	64	5.6	80	10.7	77	7.1
	I. Neutrophils	1	0.1	1	0.1	0	0.0	0	0.0
	Lymphocytes	38	2.7	28	2.5	14	1.9	21	1.9
	Monocytes	1	0.1	5	0.4	4	0.5	1	0.1
	Eosinophils	3	0.2	0	0.0	1	0.1	1	0.1
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	2	0.1	2	0.2	1	0.1	0	0.0
	WBC		7.0		8.8		13.4		9.2
8938	Nucleated Red Cells	0		0		0		0	
	M. Neutrophils	56	4.6	46	4.6	45	4.3	62	5.9
	I. Neutrophils	1	0.1	1	0.1	0	0.0	0	0.0
	Lymphocytes	38	3.1	43	4.3	45	4.3	34	3.2
	Monocytes	0	0.0	6	0.6	4	0.4	0	0.0
	Eosinophils	4	0.3	3	0.3	3	0.3	3	0.3
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	1	0.1	1	0.1	3	0.3	1	0.1
	WBC		8.2		10.0		9.6		9.5

WBC corrected for NRBC = or > 10

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 1-F : 0 mg base/kg/day

SEX: FEMALE

Animal ID		WEEK 26		WEEK 52	
		CNT	ABS	CNT	ABS
8929	Nucleated Red Cells	0		0	
	M. Neutrophils	74	4.4	57	3.4
	I. Neutrophils	1	0.1	1	0.1
	Lymphocytes	19	1.1	37	2.2
	Monocytes	3	0.2	1	0.1
	Eosinophils	1	0.1	4	0.2
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	2	0.1	0	0.0
	WBC		6.0		5.9
8942	Nucleated Red Cells	0		0	
	M. Neutrophils	57	5.0	75	8.9
	I. Neutrophils	0	0.0	0	0.0
	Lymphocytes	37	3.2	14	1.7
	Monocytes	1	0.1	6	0.7
	Eosinophils	3	0.3	5	0.6
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	2	0.2	0	0.0
	WBC		8.7		11.9
8930	Nucleated Red Cells	0		0	
	M. Neutrophils	62	5.6	62	4.7
	I. Neutrophils	0	0.0	0	0.0
	Lymphocytes	32	2.9	34	2.6
	Monocytes	0	0.0	0	0.0
	Eosinophils	4	0.4	4	0.3
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	2	0.2	0	0.0
	WBC		9.0		7.5
8938	Nucleated Red Cells	0		0	
	M. Neutrophils	55	3.7	60	5.0
	I. Neutrophils	0	0.0	1	0.1
	Lymphocytes	41	2.8	34	2.8
	Monocytes	1	0.1	2	0.2
	Eosinophils	1	0.1	3	0.2
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	2	0.1	0	0.0
	WBC		6.8		8.3

WBC corrected for NRBC = or > 10

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 2-F : 0.1 mg base/kg/day

SEX: FEMALE

Animal ID		WEEK -3		WEEK -1		WEEK 4		WEEK 13	
		CNT	ABS	CNT	ABS	CNT	ABS	CNT	ABS
8935	Nucleated Red Cells	0		0		0		0	
	M. Neutrophils	64	5.0	66	5.7	65	5.3	69	7.0
	I. Neutrophils	2	0.2	1	0.1	0	0.0	1	0.1
	Lymphocytes	28	2.2	26	2.3	29	2.4	24	2.4
	Monocytes	2	0.2	2	0.2	2	0.2	2	0.2
	Eosinophils	1	0.1	2	0.2	0	0.0	2	0.2
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	3	0.2	3	0.3	4	0.3	2	0.2
	WBC		7.8		8.7		8.2		10.2
8937	Nucleated Red Cells	0		2		0		0	
	M. Neutrophils	53	1.8	58	3.0	60	3.0	61	3.2
	I. Neutrophils	2	0.1	0	0.0	0	0.0	0	0.0
	Lymphocytes	37	1.3	37	1.9	34	1.7	34	1.8
	Monocytes	1	0.0	3	0.2	2	0.1	4	0.2
	Eosinophils	7	0.2	2	0.1	2	0.1	1	0.1
	Basophils	0	0.0	0	0.0	1	0.1	0	0.0
	Atypical Lymphocytes	0	0.0	0	0.0	1	0.1	0	0.0
	WBC		3.4		5.1		5.0		5.3
8934	Nucleated Red Cells	0		0		0		0	
	M. Neutrophils	65	7.3	69	8.3	69	11.0	73	9.2
	I. Neutrophils	2	0.2	1	0.1	2	0.3	0	0.0
	Lymphocytes	30	3.4	25	3.0	19	3.0	24	3.0
	Monocytes	1	0.1	3	0.4	7	1.1	2	0.3
	Eosinophils	1	0.1	2	0.2	3	0.5	1	0.1
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	1	0.1	0	0.0	0	0.0	0	0.0
	WBC		11.2		12.0		16.0		12.6
8945	Nucleated Red Cells	0		0		0		0	
	M. Neutrophils	67	5.1	51	4.4	67	5.0	80	8.0
	I. Neutrophils	0	0.0	0	0.0	0	0.0	0	0.0
	Lymphocytes	29	2.2	34	2.9	29	2.2	15	1.5
	Monocytes	0	0.0	7	0.6	0	0.0	1	0.1
	Eosinophils	4	0.3	6	0.5	3	0.2	4	0.4
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	0	0.0	2	0.2	1	0.1	0	0.0
	WBC		7.6		8.6		7.5		10.0

WBC corrected for NRBC = or > 10

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 2-F : 0.1 mg base/kg/day

SEX: FEMALE

Animal ID		WEEK 26		WEEK 52	
		CNT	ABS	CNT	ABS
8935	Nucleated Red Cells	0		0	
	M. Neutrophils	47	4.0	60	6.2
	I. Neutrophils	2	0.2	2	0.2
	Lymphocytes	39	3.4	33	3.4
	Monocytes	0	0.0	2	0.2
	Eosinophils	3	0.3	3	0.3
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	9	0.8	0	0.0
WBC		8.6		10.3	
8937	Nucleated Red Cells	0		0	
	M. Neutrophils	53	2.5	51	3.1
	I. Neutrophils	1	0.0	0	0.0
	Lymphocytes	42	2.0	43	2.6
	Monocytes	3	0.1	3	0.2
	Eosinophils	0	0.0	3	0.2
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	1	0.0	0	0.0
WBC		4.7		6.0	
8934	Nucleated Red Cells	0		0	
	M. Neutrophils	67	8.2	57	4.4
	I. Neutrophils	1	0.1	0	0.0
	Lymphocytes	26	3.2	39	3.0
	Monocytes	1	0.1	1	0.1
	Eosinophils	4	0.5	3	0.2
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	1	0.1	0	0.0
WBC		12.2		7.8	
8945	Nucleated Red Cells	0		0	
	M. Neutrophils	67	6.1	63	6.0
	I. Neutrophils	1	0.1	0	0.0
	Lymphocytes	24	2.2	34	3.2
	Monocytes	1	0.1	2	0.2
	Eosinophils	5	0.5	1	0.1
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	2	0.2	0	0.0
WBC		9.1		9.5	

WBC corrected for NRBC = or > 10

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

WHITE DIFFERENTIAL DATA

STUDY IO: UIC-9
STUDY NO: 219

GROUP: 3-F : 1.0 mg base/kg/day

SEX: FEMALE

Animal ID		WEEK -3		WEEK -1		WEEK 4		WEEK 13	
		CNT	ABS	CNT	ABS	CNT	ABS	CNT	ABS
8928	Nucleated Red Cells	0		0		0		0	
	M. Neutrophils	58	4.0	63	5.2	57	4.7	56	4.3
	I. Neutrophils	5	0.3	1	0.1	0	0.0	1	0.1
	Lymphocytes	33	2.3	28	2.3	34	2.8	30	2.3
	Monocytes	3	0.2	7	0.6	6	0.5	7	0.5
	Eosinophils	0	0.0	1	0.1	3	0.2	6	0.5
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	1	0.1	0	0.0	0	0.0	0	0.0
WBC		6.9		8.2		8.3		7.6	
8940	Nucleated Red Cells	0		0		0		0	
	M. Neutrophils	83	9.6	82	9.9	78	8.8	77	8.8
	I. Neutrophils	0	0.0	2	0.2	0	0.0	0	0.0
	Lymphocytes	10	1.2	10	1.2	13	1.5	13	1.5
	Monocytes	4	0.5	5	0.6	6	0.7	6	0.7
	Eosinophils	2	0.2	1	0.1	1	0.1	4	0.5
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	1	0.1	0	0.0	2	0.2	0	0.0
WBC		11.6		12.1		11.3		11.4	
8931	Nucleated Red Cells	0		0		0		0	
	M. Neutrophils	54	4.1	62	4.5	64	4.2	67	4.6
	I. Neutrophils	3	0.2	1	0.1	1	0.1	0	0.0
	Lymphocytes	36	2.7	30	2.2	24	1.6	23	1.6
	Monocytes	2	0.2	3	0.2	8	0.5	6	0.4
	Eosinophils	5	0.4	3	0.2	3	0.2	3	0.2
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	0	0.0	1	0.1	0	0.0	1	0.1
WBC		7.5		7.2		6.5		6.8	
8943	Nucleated Red Cells	0		0		0		0	
	M. Neutrophils	72	6.8	64	7.9	74	9.5	83	13.2
	I. Neutrophils	1	0.1	1	0.1	0	0.0	1	0.2
	Lymphocytes	21	2.0	30	3.7	15	1.9	13	2.1
	Monocytes	3	0.3	1	0.1	5	0.6	0	0.0
	Eosinophils	3	0.3	3	0.4	5	0.6	1	0.2
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	0	0.0	1	0.1	1	0.1	2	0.3
WBC		9.4		12.4		12.8		15.9	

WBC corrected for NRBC = or > 10

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 3-F : 1.0 mg base/kg/day

SEX: FEMALE

Animal ID		WEEK 26		WEEK 52	
		CNT	ABS	CNT	ABS
8928	Nucleated Red Cells	0		0	
	M. Neutrophils	68	6.1	54	4.5
	I. Neutrophils	0	0.0	0	0.0
	Lymphocytes	26	2.3	40	3.4
	Monocytes	3	0.3	3	0.3
	Eosinophils	2	0.2	3	0.3
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	1	0.1	0	0.0
WBC		8.9		8.4	
8940	Nucleated Red Cells	0		0	
	M. Neutrophils	82	9.7	74	10.3
	I. Neutrophils	1	0.1	1	0.1
	Lymphocytes	17	2.0	18	2.5
	Monocytes	0	0.0	5	0.7
	Eosinophils	0	0.0	2	0.3
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	0	0.0	0	0.0
WBC		11.8		13.9	
8931	Nucleated Red Cells	0		0	
	M. Neutrophils	73	6.1	65	5.3
	I. Neutrophils	0	0.0	0	0.0
	Lymphocytes	20	1.7	25	2.0
	Monocytes	5	0.4	6	0.5
	Eosinophils	2	0.2	4	0.3
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	0	0.0	0	0.0
WBC		8.4		8.1	
8943	Nucleated Red Cells	0		0	
	M. Neutrophils	77	9.5	78	12.7
	I. Neutrophils	1	0.1	0	0.0
	Lymphocytes	15	1.8	19	3.1
	Monocytes	2	0.2	3	0.5
	Eosinophils	4	0.5	0	0.0
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	1	0.1	0	0.0
WBC		12.3		16.3	

WBC corrected for NRBC = or > 10

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 4-F : 4.0 mg base/kg/day

SEX: FEMALE

Animal ID		WEEK -3		WEEK -1		WEEK 4		WEEK 13	
		CNT	ABS	CNT	ABS	CNT	ABS	CNT	ABS
8941	Nucleated Red Cells	0		1		0		0	
	M. Neutrophils	58	4.5	63	6.7	75	6.5	78	7.3
	I. Neutrophils	1	0.1	0	0.0	0	0.0	0	0.0
	Lymphocytes	36	2.8	32	3.4	22	1.9	17	1.6
	Monocytes	3	0.2	4	0.4	0	0.0	1	0.1
	Eosinophils	0	0.0	1	0.1	3	0.3	4	0.4
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	2	0.2	0	0.0	0	0.0	0	0.0
	WBC		7.7		10.7		8.7		9.3
8933	Nucleated Red Cells	0		0		0		0	
	M. Neutrophils	56	3.6	66	4.9	69	6.3	77	7.9
	I. Neutrophils	0	0.0	1	0.1	1	0.1	0	0.0
	Lymphocytes	40	2.6	29	2.1	24	2.2	20	2.0
	Monocytes	0	0.0	3	0.2	2	0.2	1	0.1
	Eosinophils	3	0.2	1	0.1	2	0.2	2	0.2
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	1	0.1	0	0.0	2	0.2	0	0.0
	WBC		6.4		7.4		9.2		10.2
8936	Nucleated Red Cells	0		0		0		0	
	M. Neutrophils	62	3.3	65	5.7	77	8.2	70	7.6
	I. Neutrophils	1	0.1	2	0.2	0	0.0	0	0.0
	Lymphocytes	36	1.9	25	2.2	17	1.8	22	2.4
	Monocytes	0	0.0	1	0.1	4	0.4	3	0.3
	Eosinophils	0	0.0	7	0.6	1	0.1	3	0.3
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	1	0.1	0	0.0	1	0.1	2	0.2
	WBC		5.4		8.8		10.6		10.9
8944	Nucleated Red Cells	0		0		0		0	
	M. Neutrophils	68	3.9	60	3.2	75	7.2	83	9.7
	I. Neutrophils	2	0.1	0	0.0	0	0.0	0	0.0
	Lymphocytes	26	1.5	28	1.5	21	2.0	14	1.6
	Monocytes	0	0.0	1	0.1	0	0.0	2	0.2
	Eosinophils	2	0.1	5	0.3	2	0.2	1	0.1
	Basophils	0	0.0	0	0.0	0	0.0	0	0.0
	Atypical Lymphocytes	2	0.1	6	0.3	2	0.2	0	0.0
	WBC		5.7		5.3		9.6		11.7

WBC corrected for NRBC = or > 10

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

WHITE DIFFERENTIAL DATA

STUDY ID: UIC-9
STUDY NO: 219

GROUP: 4-F : 4.0 mg base/kg/day

SEX: FEMALE

Animal ID		WEEK 26		WEEK 52	
		CNT	ABS	CNT	ABS
8941	Nucleated Red Cells	0		1	
	M. Neutrophils	77	8.1	66	6.7
	I. Neutrophils	0	0.0	2	0.2
	Lymphocytes	21	2.2	23	2.3
	Monocytes	1	0.1	5	0.5
	Eosinophils	1	0.1	4	0.4
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	0	0.0	0	0.0
WBC		10.5		10.2	
8933	Nucleated Red Cells	0		3	
	M. Neutrophils	76	10.7	80	13.6
	I. Neutrophils	1	0.1	1	0.2
	Lymphocytes	22	3.1	14	2.4
	Monocytes	0	0.0	2	0.3
	Eosinophils	1	0.1	3	0.5
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	0	0.0	0	0.0
WBC		14.1		17.0	
8936	Nucleated Red Cells	0		0	
	M. Neutrophils	85	13.9	81	12.6
	I. Neutrophils	0	0.0	0	0.0
	Lymphocytes	12	2.0	11	1.7
	Monocytes	0	0.0	3	0.5
	Eosinophils	3	0.5	5	0.8
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	0	0.0	0	0.0
WBC		16.3		15.6	
8944	Nucleated Red Cells	0		0	
	M. Neutrophils	76	8.5	67	6.2
	I. Neutrophils	0	0.0	4	0.4
	Lymphocytes	14	1.6	21	2.0
	Monocytes	0	0.0	3	0.3
	Eosinophils	10	1.1	5	0.5
	Basophils	0	0.0	0	0.0
	Atypical Lymphocytes	0	0.0	0	0.0
WBC		11.2		9.3	

WBC corrected for NRBC = or > 10

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APPENDIX H
Individual Urinalysis Data

URINALYSIS INFORMATION

DRAFT

A. Abbreviations

APP = Appearance	DY = Dark Yellow
SG = Specific Gravity	PY = Pale Yellow
PRO = Protein	LY = Light Yellow
GLU = Glucose	BR = Brown
KET = Ketones	AM = Amber
BILI = Bilirubin	> = Greater than
BL = Blood	FAT = Fatty
URO = Urobilinogen	WH = White
LEU = Leukocytes	BY = Bright Yellow
NIT = Nitrite	CL = Colorless
EPI = Epithelial	E = Erythrocyte
SQ = Squamous	FG = Fine Granular
TRANS = Transitional	CG = Course Granular
NA = Not Applicable	HY = Hyaline
TP = Triple Phosphate	GR = Granular
QNS = Quantity Not Sufficient	S = Starch
Y = Yellow	RC = Red Cell
	WC = Waxy

B. Qualitative Evaluation

Protein:	Negative Trace 1+ (30 mg/dl) 2+ (100 mg/dl) 3+ (500 mg/dl)	Bilirubin:	Negative 1+ (slight) 2+ (moderate) 3+ (marked)
Glucose:	Normal Trace (1/20 g/dl) 1+ (1/10 g/dl) 2+ (1/4 g/dl) 3+ (1/2 g/dl) 4+ (1 g/dl)	Blood:	Negative 5-10 Ery/ul 50 Ery/ul 250 Ery/ul
Ketones:	Negative 1+ (slight amount) 2+ (moderate) 3+ (large)	Leukocytes:	Negative Trace 1+ (moderate) 2+ (marked)
Urobilinogen:	Normal 1+ (1 mg/dl) 2+ (4 mg/dl) 3+ (8 mg/dl) 4+ (12 mg/dl)	Nitrite:	Negative Positive

C. Microscopic Examination: Five fields are examined.

Casts: av. #/10x field
RBC's: av. #/45x field
WBC's: av. #/45x field

Epithelial Cells - Squamous: av. #/45x field
- Transitional: av. #/45x field
- Renal: av. #/45x field

Crystals; Bacteria; Sperm; Mucus - 0 = Negative
1+ = Occasional
2+ = Seen in every field
3+ = Large amounts in every field
4+ = Full fields

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

Male Urinalysis Data (Week -1)

DOSE LEVEL (mg base/kg/day)	ANIMAL NO.	APP	SG	COLOR	NTT	LEU	pH	PROT	GLU g/dl	KET	URO	BILI	BLOOD Ery/ul
0	8922	CLEAR	1.058	Y	NEG	NEG	6	TRACE	NOR	NEG	NOR	NEG	NEG
	8915	CLOUDY	1.040	Y	NEG	2+	7	1+	NOR	NEG	NOR	NEG	3+
	8911	CLOUDY	1.046	Y	NEG	NEG	7	1+	NOR	NEG	NOR	NEG	1+
	8909	CLEAR	1.050	Y	NEG	NEG	6	TRACE	NOR	NEG	NOR	NEG	NEG
0.1	8923	CLEAR	1.058	Y	POS	2+	6	TRACE	NOR	NEG	NOR	NEG	NEG
	8907	CLEAR	1.058	Y	NEG	NEG	6	1+	NOR	NEG	NOR	NEG	NEG
	8919	HAZY	1.044	Y	NEG	2+	6	1+	NOR	NEG	NOR	NEG	1+
	8924	HAZY	1.035	Y	NEG	NEG	7	1+	NOR	NEG	NOR	NEG	NEG
1.0	8917	HAZY	1.066	Y	POS	2+	6	1+	NOR	NEG	NOR	NEG	NEG
	8910	HAZY	1.030	Y	POS	2+	6	TRACE	NOR	NEG	NOR	NEG	1+
	8913	HAZY	1.018	Y	NEG	1+	9	1+	NOR	NEG	NOR	1+	2+
	8914	HAZY	1.046	Y	NEG	TRACE	6	TRACE	NOR	NEG	NOR	NEG	1+
4.0	8918	HAZY	1.044	Y	POS	NEG	7	TRACE	NOR	NEG	NOR	NEG	NEG
	8908	CLOUDY	1.048	Y	NEG	NEG	6	1+	NOR	NEG	NOR	NEG	3+
	8926	CLEAR	1.002	PY	POS	1+	7	TRACE	NOR	NEG	NOR	NEG	NEG
	8921	HAZY	1.035	Y	NEG	NEG	8	1+	NOR	NEG	NOR	NEG	NEG

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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Male Urinalysis Data (Week -1)

DOSE LEVEL (mg/kg/day)	ANIMAL NO.	CASTS	RBC	WBC	EPITHELIAL CELLS			CRYSTALS	BACTERIA	SPERM	MUCUS	YEAST CELLS
					SQ	TRANS	RENAL					
0	8922	1 HY 1 FG	0	6	3	0	0	1+ TP	1+	0	0	0
	8915	3 HY	0	13	5	0	0	3+ TP	1+	1+	0	0
	8911	1 HY	0	0	1	0	0	1+ TP	1+	0	0	0
	8909	2 FG	0	0	0	0	0	0	1+	0	0	0
0.1	8923	6 HY	0	20	3	0	0	0	1+	0	0	0
	8907	4 HY	0	0	5	0	0	1+ TP	1+	1+	0	0
	8919	7 HY	0	35	4	0	0	0	1+	0	0	0
	8924	7 HY	0	0	1	0	0	1+ TP	1+	0	0	0
1.0	8917	3 FG	0	5	4	0	0	1+ TP	1+	1+	0	0
	8910	4 HY	1	6	2	0	0	0	1+	1+	0	0
	8913	7 HY	0	3	0	0	0	0	1+	0	0	0
	8914	5 HY	1	2	3	0	0	1+ TP	1+	1+	0	1+
4.0	8918	4 HY	0	0	1	0	0	0	1+	0	0	0
	8908	6 HY	5	0	5	0	0	1+ TP	2+	0	0	0
	8926	1 HY	0	0	1	0	0	0	2+	0	0	0
	8921	15 HY 3 FG	0	0	2	0	0	1+ TP	1+	1+	0	0

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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Male Urinalysis Data (Week 13)

DOSE LEVEL (mg/kg/day)	ANIMAL NO.	APP	SG	COLOR	NTT	LEU	pH	PROT	GLU g/dl	KET	URO	BILI	BLOOD Ery/ul
0	8909	HAZY	1.054	DY	NEG	NEG	6	TRACE	NOR	NEG	NOR	NEG	NEG
	8911	HAZY	1.084	AM	NEG	1+	6	TRACE	NOR	NEG	NOR	2+	NEG
	8915	HAZY	1.024	PY	POS	2+	6	NEG	NOR	NEG	NOR	NEG	2+
	8922	TURBID	1.036	PY	POS	2+	9	1+	NOR	NEG	NOR	NEG	3+
0.1	8907	CLOUDY	1.050	Y	NEG	NEG	6	TRACE	NOR	NEG	NOR	NEG	1+
	8919	CLEAR	1.054	DY	NEG	TRACE	7	TRACE	NOR	NEG	NOR	NEG	NEG
	8923	HAZY	1.058	Y	NEG	1+	6	TRACE	NOR	NEG	NOR	NEG	1+
	8924	CLEAR	1.056	DY	NEG	NEG	6	TRACE	NOR	NEG	NOR	2+	NEG
1.0	8910	HAZY	1.075	Y	NEG	2+	5	TRACE	NOR	NEG	NOR	NEG	1+
	8913	HAZY	1.042	LY	POS	1+	5	TRACE	NOR	NEG	NOR	NEG	NEG
	8914	CLOUDY	1.116	AM	POS	NEG	5	TRACE	NOR	NEG	NOR	NEG	1+
	8917	CLEAR	1.052	Y	NEG	NEG	5	TRACE	NOR	NEG	NOR	NEG	NEG
4.0	8908	CLOUDY	1.054	DY	POS	NEG	6	TRACE	NOR	NEG	NOR	2+	NEG
	8918	HAZY	1.066	Y	POS	TRACE	5	TRACE	NOR	NEG	NOR	NEG	NEG
	8921	CLEAR	1.052	DY	NEG	NEG	6	TRACE	NOR	NEG	NOR	NEG	NEG
	8926	TURBID	1.068	AM	NEG	TRACE	6	TRACE	NOR	NEG	NOR	2+	1+

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ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

Male Urinalysis Data (Week 13)

DOSE LEVEL (mg/kg/day)	ANIMAL NO.	CASTS	RBC	WBC	EPITHELIAL CELLS			CRYSTALS	BACTERIA	SPERM	MUCUS	YEAST CELLS
					SQ	TRANS	RENAL					
0	8909	4 FG 1 HY	0	10	6	1	0	1+ TP	1+	1+	0	0
	8911	7 HY	0	10	4	0	0	2+ TP	1+	1+	0	0
	8915	1 HY	0	2	0	0	0	0	2+	1+	0	0
	8922	1 FG 2 HY	4	0	0	0	0	1+ TP	3+	1+	0	0
0.1	8907	3 HY 1 FG	10	0	4	0	0	0	1+	1+	0	0
	8919	3 FG	0	5	2	0	0	1+ TP	1+	1+	0	0
	8923	1 HY	2	5	0	0	0	0	1+	1+	0	0
	8924	2 HY 2 FG	0	0	1	0	1	1+ TP	1+	1+	0	0
1.0	8910	4 HY	5	25	1	3	0	1+ TP	1+	1+	0	0
	8913	2 HY 1 FG	0	6	2	0	0	0	1+	0	0	0
	8914	7 HY	0	0	2	0	0	1+ TP	1+	1+	0	0
	8917	1 FG	0	0	2	0	0	0	1+	2+	0	0
4.0	8908	16 HY	0	0	2	0	0	1+ TP	1+	0	0	0
	8918	1 FG	0	0	0	0	0	0	2+	1+	0	0
	8921	1 FG	0	0	0	3	0	0	1+	2+	0	0
	8926	2 HY	0	4	4	0	0	1+ TP	1+	1+	0	0

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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Male Urinalysis Data (Week 26)

DOSE LEVEL (mg/kg/day)	ANIMAL NO.	APP	SG	COLOR	NIT	LEU	pH	PROT	GLU g/dl	KET	URO	BILI	BLOOD Ery/ul
0	8909	CLEAR	1.056	DY	NEG	NEG	6	TRACE	NOR	NEG	NOR	NEG	NEG
	8911	CLOUDY	1.081	AM	NEG	2+	9	1+	NOR	NEG	NOR	2+	NEG
	8915	CLEAR	1.050	DY	NEG	2+	6	TRACE	NOR	NEG	NOR	NEG	1+
	8922	TURBID	1.105	AM	NEG	2+	6	1+	NOR	NEG	NOR	2+	1+
0.1	8907	CLEAR	1.056	DY	NEG	NEG	6	TRACE	NOR	NEG	NOR	2+	NEG
	8919	CLOUDY	1.056	DY	NEG	2+	7	1+	NOR	NEG	NOR	1+	2+
	8923	HAZY	1.033	Y	POS	2+	6	TRACE	NOR	NEG	NOR	NEG	1+
	8924	CLOUDY	1.018	Y	POS	2+	7	TRACE	NOR	NEG	NOR	NEG	2+
1.0	8910	CLEAR	1.031	Y	POS	2+	6	TRACE	NOR	NEG	NOR	NEG	NEG
	8913	CLEAR	1.016	Y	POS	1+	6	TRACE	NOR	NEG	NOR	NEG	1+
	8914	CLOUDY	1.099	AM	POS	TRACE	6	TRACE	NOR	NEG	NOR	NEG	1+
	8917	CLOUDY	1.052	DY	NEG	NEG	7	1+	NOR	NEG	NOR	NEG	NEG
4.0	8908	HAZY	1.060	AM	NEG	NEG	6	TRACE	NOR	NEG	NOR	2+	2+
	8918	TURBID	1.062	DY	NEG	NEG	7	TRACE	NOR	NEG	NOR	NEG	NEG
	8921	CLOUDY	1.105	AM	POS	NEG	6	TRACE	NOR	NEG	NOR	NEG	NEG
	8926	HAZY	1.050	DY	NEG	2+	7	TRACE	NOR	NEG	NOR	NEG	1+

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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Male Urinalysis Data (Week 26)

DOSE LEVEL (mg/kg/day)	ANIMAL NO.	CASTS	RBC	WBC	EPITHELIAL CELLS SQ TRANS RENAL			CRYSTALS	BACTERIA	SPERM	MUCUS	YEAST CELLS
0	8909	3 HY	0	0	1	0	0	0	2+	1+	0	0
	8911	1 HY	0	12	4	0	0	1+ TP	1+	1+	0	0
	8915	4 HY	0	10	1	0	0	1+ TP	2+	1+	0	0
	8922	3 HY	5	35	3	0	0	1+ TP	1+	0	0	0
0.1	8907	1 FG	0	0	0	0	0	0	1+	1+	0	0
	8919	1 FG	35	120	7	2	0	2+ TP	2+	1+	0	0
	8923	0	6	10	1	0	0	1+ TP	2+	1+	0	0
	8924	0	0	0	0	0	0	1+ TP	1+	0	0	0
1.0	8910	2 HY	0	3	1	0	0	0	2+	1+	0	0
	8913	2 HY	0	2	0	0	0	0	1+	1+	0	0
	8914	0	0	0	0	0	0	0	1+	1+	0	0
	8917	1 FG	0	0	0	0	0	2+ TP	1+	1+	0	0
4.0	8908	4 HY	3	0	1	0	0	1+ TP	1+	0	0	0
	8918	2 HY	0	0	0	0	0	2+ TP	1+	1+	0	0
	8921	5 HY	0	0	3	0	0	1+ TP	1+	0	0	0
	8926	2 HY	5	10	2	0	0	1+ TP	2+	1+	0	0

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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Male Urinalysis Data (Week 52)

DOSE LEVEL (mg/kg/day)	ANIMAL NO.	APP	SG	COLOR	NIT	LEU	pH	PROT	GLU g/dl	KET	URO	BILI	BLOOD Ery/ul
0	8909	HAZY	1.064	Y	NEG	1+	6	TRACE	NOR	NEG	NOR	2+	1+
	8911	CLOUDY	1.136	DY	NEG	2+	7	1+	NOR	NEG	NOR	NEG	NEG
	8915	HAZY	1.054	Y	NEG	TRACE	6	TRACE	NOR	NEG	NOR	NEG	NEG
	8922	CLOUDY	1.042	Y	POS	2+	6	1+	NOR	NEG	NOR	NEG	1+
0.1	8907	CLEAR	1.015	LY	POS	2+	6	TRACE	NOR	NEG	NOR	NEG	NEG
	8919	CLEAR	1.038	Y	POS	1+	8	TRACE	NOR	NEG	NOR	NEG	1+
	8923	CLOUDY	1.066	Y	NEG	2+	6	TRACE	NOR	NEG	NOR	NEG	1+
	8924	HAZY	1.011	PY	POS	1+	6	TRACE	NOR	NEG	NOR	NEG	NEG
1.0	8910	HAZY	1.058	Y	NEG	TRACE	6	TRACE	NOR	NEG	NOR	NEG	NEG
	8913	CLEAR	1.023	Y	POS	NEG	6	TRACE	NOR	NEG	NOR	NEG	NEG
	8914	CLOUDY	1.060	DY	NEG	TRACE	6	NEG	NOR	NEG	NOR	NEG	2+
	8917	HAZY	1.019	LY	POS	NEG	6	TRACE	NOR	NEG	NOR	NEG	NEG
4.0	8908	CLOUDY	1.090	AM	NEG	2+	6	TRACE	NOR	NEG	NOR	NEG	2+
	8918	TURBID	1.064	DY	NEG	NEG	7	1+	NOR	NEG	NOR	NEG	1+
	8921	CLEAR	1.066	DY	NEG	NEG	9	TRACE	NOR	NEG	NOR	NEG	NEG
	8926	CLEAR	1.052	Y	NEG	NEG	6	TRACE	NOR	NEG	NOR	NEG	NEG

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

Male Urinalysis Data (Week 52)

DOSE LEVEL (mg/kg/day)	ANIMAL NO.	CASTS	RBC	WBC	EPITHELIAL CELLS SQ TRANS RENAL			CRYSTALS	BACTERIA	SPERM	MUCUS	YEAST CELLS
0	8909	1 HY	2	5	0	0	0	2+ TP	1+	1+	0	0
	8911	4 HY	0	0	2	0	0	1+ TP	1+	1+	0	0
	8915	7 HY	0	0	4	2	0	1+ TP	1+	0	0	0
	8922	3 HY 1 FG	4	15	3	0	0	1+ TP	1+	1+	0	0
0.1	8907	1 HY 1 FG	0	2	1	2	0	0	1+	1+	0	0
	8919	5 FG	3	5	2	0	0	0	1+	1+	0	0
	8923	6 HY 1 FG	1	3	0	0	0	1+ TP	1+	0	0	0
	8924	0	0	2	1	0	0	0	1+	1+	0	0
1.0	8910	5 HY	5	0	3	0	0	1+ TP	2+	0	0	0
	8913	1 HY	0	0	0	0	0	0	1+	0	0	0
	8914	0	7	0	0	0	0	1+ TP	1+	0	0	0
	8917	6 HY	0	0	2	1	0	0	1+	1+	0	0
4.0	8908	5 HY	5	0	1	0	0	1+ TP	1+	1+	0	0
	8918	3 HY 1 FG	3	0	0	0	0	3+ TP	1+	1+	0	0
	8921	3 FG	0	0	1	0	0	2+ TP	1+	1+	0	0
	8926	1 HY	0	0	1	0	0	1+ TP	1+	1+	0	0

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

Female Urinalysis Data (Week -1)

DOSE LEVEL (mg base/kg/day)	ANIMAL NO.	APP	SG	COLOR	NIT	LEU	pH	PROT	GLU g/dl	KET	URO	BILI	BLOOD Ery/ul
0	8929	HAZY	1.087	Y	POS	NEG	6	1+	NOR	NEG	NOR	NEG	2+
	8942	CLEAR	1.048	Y	POS	NEG	8	TRACE	NOR	NEG	NOR	NEG	NEG
	8930	HAZY	1.056	Y	NEG	2+	8	1+	NOR	NEG	NOR	NEG	NEG
	8938	CLEAR	1.017	PY	POS	TRACE	7	TRACE	NOR	NEG	NOR	NEG	NEG
0.1	8935	HAZY	1.056	Y	POS	2+	6	TRACE	NOR	NEG	NOR	NEG	NEG
	8937	HAZY	1.054	Y	NEG	NEG	8	TRACE	NOR	NEG	NOR	NEG	NEG
	8934	CLOUDY	1.054	Y	POS	NEG	7	TRACE	NOR	NEG	NOR	NEG	NEG
1.0	8945	CLEAR	1.048	Y	POS	2+	7	TRACE	NOR	NEG	NOR	NEG	NEG
	8928	CLOUDY	1.087	Y	NEG	NEG	6	1+	NOR	NEG	NOR	NEG	2+
	8940	CLEAR	1.044	Y	POS	NEG	6	TRACE	NOR	NEG	NOR	NEG	NEG
	8931	HAZY	1.046	Y	POS	NEG	5	NEG	NOR	NEG	NOR	NEG	NEG
4.0	8943	HAZY	1.058	LY	POS	NEG	6	TRACE	NOR	NEG	NOR	NEG	NEG
	8941	CLEAR	1.087	Y	POS	NEG	7	TRACE	NOR	NEG	NOR	NEG	NEG
	8933	CLEAR	1.027	Y	POS	NEG	7	TRACE	NOR	NEG	NOR	NEG	NEG
	8936	HAZY	1.056	Y	POS	NEG	6	1+	NOR	NEG	NOR	NEG	2+
	8944	HAZY	1.034	Y	NEG	NEG	6	1+	NOR	NEG	NOR	NEG	NEG

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

Female Urinalysis Data (Week -1)

DRAFT

DOSE LEVEL (mg base/kg/day)	ANIMAL NO.	CASTS	RBC	WBC	EPITHELIAL CELLS			CRYSTALS	BACTERIA	SPERM	MUCUS	YEAST CELLS
					SQ	TRANS	RENAL					
0	8929	4 HY 2 FG	0	0	1	1	0	1+ TP	1+	0	0	0
	8942	5 HY 1 FG	0	0	0	0	0	1+ TP	1+	0	0	0
	8930	4 HY	0	20	2	4	0	2+ TP	1+	0	0	0
	8938	2 FG	0	2	0	0	0	1+ TP	1+	0	0	0
0.1	8935	2 HY 1 FG	0	5	1	1	0	1+ TP	1+	0	0	0
	8937	1 FG	0	0	0	0	0	1+ TP	1+	0	0	0
	8934	7 HY	0	0	2	0	0	1+ TP	1+	0	0	0
	8945	2 HY 1 FG	0	10	0	0	0	1+ TP	1+	0	0	0
1.0	8928	3 FG	5	0	1	7	0	1+ TP	1+	0	0	0
	8940	2 HY	0	0	0	0	0	1+ TP	1+	0	0	0
	8931	9 HY 10 FG	0	10	2	2	0	1+ TP	1+	0	0	0
	8943	3 HY	3	0	1	0	0	1+ TP	1+	0	0	0
4.0	8941	3 HY 1 FG	0	0	1	0	0	1+ TP	1+	0	0	0
	8933	9 HY	0	9	4	2	0	1+ TP	1+	0	0	0
	8936	3 HY 25 FG	0	0	1	0	0	1+ TP	1+	0	0	0
	8944	4 HY	0	0	1	0	0	1+ TP	1+	0	0	0

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

Female Urinalysis Data (Week 13)

DOSE LEVEL (mg/kg/day)	ANIMAL NO.	APP	SG	COLOR	NIT	LEU	pH	PROT	GLU g/dl	KET	URO	BILI	BLOOD Ery/ul
0	8929	HAZY	1.210	Y	NEG	NEG	5	TRACE	NOR	NEG	NOR	NEG	NEG
	8930	CLEAR	1.066	Y	POS	NEG	7	TRACE	NOR	NEG	NOR	NEG	NEG
	8938	HAZY	1.034	Y	NEG	NEG	6	TRACE	NOR	NEG	NOR	NEG	NEG
	8942	HAZY	1.048	Y	NEG	NEG	8	TRACE	NOR	NEG	NOR	NEG	2+
0.1	8934	CLOUDY	1.052	Y	NEG	NEG	7	TRACE	NOR	NEG	NOR	NEG	NEG
	8935	HAZY	1.072	Y	POS	NEG	6	TRACE	NOR	NEG	NOR	NEG	2+
	8937	CLOUDY	1.096	Y	NEG	1+	9	TRACE	NOR	NEG	NOR	NEG	NEG
	8945	CLOUDY	1.054	Y	NEG	NEG	7	TRACE	NOR	NEG	NOR	NEG	2+
1.0	8928	HAZY	1.064	Y	NEG	NEG	6	TRACE	NOR	NEG	NOR	NEG	NEG
	8931	HAZY	1.076	DY	NEG	NEG	6	TRACE	NOR	NEG	NOR	NEG	NEG
	8940	CLOUDY	1.072	Y	NEG	NEG	7	TRACE	NOR	NEG	NOR	NEG	3+
	8943	CLOUDY	1.045	LY	POS	TRACE	6	TRACE	NOR	NEG	NOR	NEG	NEG
4.0	8933	HAZY	1.054	DY	POS	NEG	6	TRACE	NOR	NEG	NOR	NEG	NEG
	8936	CLOUDY	1.198	DY	NEG	NEG	6	TRACE	NOR	NEG	NOR	NEG	NEG
	8941	HAZY	1.108	Y	POS	NEG	5	TRACE	NOR	NEG	NOR	NEG	NEG
	8944	HAZY	1.096	Y	POS	NEG	6	TRACE	NOR	NEG	NOR	NEG	NEG

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

Female Urinalysis Data (Week 13)

DOSE LEVEL (mg/kg/day)	ANIMAL NO.	CASTS	RBC	WBC	EPITHELIAL CELLS SQ TRANS RENAL			CRYSTALS	BACTERIA	SPERM	MUCUS	YEAST CELLS
0	8929	3 HY	0	0	3	0	0	1+ TP	1+	0	0	0
	8930	0	0	10	0	0	0	1+ TP	1+	0	0	0
	8938	3 FG 1 HY	0	5	2	0	0	0	1+	0	0	0
	8942	2 HY	0	0	2	0	0	1+ TP	1+	0	0	0
0.1	8934	1 HY 1 FG	0	0	1	0	0	1+ TP	1+	0	0	0
	8935	3 HY	1	0	2	0	0	1+ TP	1+	0	0	1+
	8937	2 HY	0	5	0	0	0	1+ TP	1+	0	0	0
	8945	2 HY	5	15	6	1	0	1+ TP	1+	0	0	0
1.0	8928	1 FG	0	0	0	0	0	2+ TP	1+	0	0	0
	8931	0	0	35	3	1	0	0	1+	0	0	0
	8940	1 HY	0	0	0	0	3	1+ TP	1+	0	0	1+
	8943	0	0	7	0	1	0	0	1+	0	0	0
4.0	8933	1 FG	0	0	2	1	0	0	1+	0	0	0
	8936	3 FG	0	0	5	0	0	1+ TP	1+	0	0	0
	8941	0	0	0	0	0	0	0	1+	0	0	0
	8944	3 HY	0	0	0	0	0	1+ TP	1+	0	0	0

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

Female Urinalysis Data (Week 26)

DOSE LEVEL (mg/kg/day)	ANIMAL NO.	APP	SG	COLOR	NIT	LEU	pH	PROT	GLU g/dl	KET	URO	BILI	BLOOD Ery/ul
0	8929	CLEAR	1.0810	DY	POS	NEG	6	1+	NOR	NEG	NOR	NEG	2+
	8930	CLEAR	1.052	DY	NEG	NEG	6	TRACE	NOR	NEG	NOR	NEG	NEG
	8938	CLEAR	1.026	Y	POS	NEG	7	TRACE	NOR	NEG	NOR	NEG	NEG
	8942	CLEAR	1.078	DY	POS	NEG	7	1+	NOR	NEG	NOR	NEG	NEG
0.1	8934	CLOUDY	1.060	Y	NEG	NEG	7	TRACE	NOR	NEG	NOR	NEG	2+
	8935	CLOUDY	1.099	AM	NEG	NEG	9	2+	NOR	NEG	NOR	NEG	NEG
	8937	CLOUDY	1.128	AM	NEG	2+	6	1+	NOR	NEG	NOR	NEG	1+
	8945	CLEAR	1.064	DY	POS	2+	8	TRACE	NOR	NEG	NOR	NEG	NEG
1.0	8928	CLEAR	1.078	DY	NEG	NEG	6	1+	NOR	NEG	NOR	1+	2+
	8931	HAZY	1.087	AM	POS	TRACE	8	TRACE	NOR	NEG	NOR	NEG	1+
	8940	CLEAR	1.042	DY	POS	NEG	7	TRACE	NOR	NEG	NOR	NEG	NEG
	8943	HAZY	1.124	AM	POS	NEG	6	1+	NOR	NEG	NOR	NEG	NEG
4.0	8933	CLOUDY	1.046	DY	NEG	NEG	6	TRACE	NOR	NEG	NOR	NEG	NEG
	8936	CLEAR	1.093	DY	POS	NEG	6	TRACE	NOR	NEG	NOR	NEG	NEG
	8941	CLEAR	1.155	BR	POS	TRACE	6	1+	NOR	NEG	NOR	NEG	1+
	8944	CLOUDY	1.052	DY	NEG	NEG	6	TRACE	NOR	NEG	NOR	NEG	NEG

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

Female Urinalysis Data (Week 26)

DOSE LEVEL (mg/kg/day)	ANIMAL NO.	CASTS	RBC	WBC	EPITHELIAL CELLS			CRYSTALS	BACTERIA	SPERM	MUCUS	YEAST CELLS
					SQ	TRANS	RENAL					
0	8929	4 HY	5	0	1	0	0	1+ TP	1+	0	0	0
	8930	0	0	0	0	0	0	1+ TP	1+	0	0	0
	8938	0	0	0	0	0	0	1+ TP	1+	0	0	0
	8942	5 HY	0	0	4	0	0	2+ TP	1+	0	0	0
0.1	8934	3 HY 5 FG	12	0	1	0	0	2+ TP	2+	0	0	0
	8935	3 HY	0	0	3	1	2	1+ TP	1+	0	0	0
	8937	1 HY	0	12	2	2	0	1+ TP	1+	0	0	0
	8945	0	0	0	0	0	0	1+ TP	1+	0	0	0
1.0	8928	2 HY	0	0	1	0	0	2+ TP	1+	0	0	0
	8931	3 HY	0	0	2	0	1	2+ TP	1+	0	0	0
	8940	0	0	0	0	0	0	1+ TP	1+	0	0	0
	8943	5 HY	0	0	2	0	1	1+ TP	1+	0	0	0
4.0	8933	0	0	0	0	0	0	1+ TP	1+	0	0	0
	8936	0	0	0	0	0	0	1+ TP	1+	0	0	0
	8941	1 FG	0	0	0	0	0	1+ TP	1+	0	0	0
	8944	5 HY	0	0	1	0	0	0	1+	0	0	0

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

Female Urinalysis Data (Week 52)

DOSE LEVEL (mg/kg/day)	ANIMAL NO.	APP	SG	COLOR	NTT	LEU	pH	PROT	GLU g/dl	KET	URO	BILI	BLOOD Ery/ul
0	8929	CLOUDY	1.058	DY	NEG	NEG	6	TRACE	NOR	NEG	NOR	NEG	NEG
	8930	CLOUDY	1.044	DY	NEG	NEG	7	TRACE	NOR	NEG	NOR	NEG	NEG
	8938	CLEAR	1.058	Y	POS	2+	6	TRACE	NOR	NEG	NOR	NEG	3+
	8942	CLEAR	1.050	Y	POS	NEG	9	1+	NOR	NEG	NOR	NEG	1+
0.1	8934	HAZY	1.060	Y	POS	NEG	7	TRACE	NOR	NEG	NOR	NEG	NEG
	8935	HAZY	1.120	DY	POS	NEG	5	TRACE	NOR	NEG	NOR	NEG	NEG
	8937	CLEAR	1.068	Y	POS	NEG	7	TRACE	NOR	NEG	NOR	NEG	NEG
	8945	CLEAR	1.022	Y	NEG	NEG	6	TRACE	NOR	NEG	NOR	NEG	NEG
1.0	8928	CLOUDY	1.064	DY	NEG	NEG	6	TRACE	NOR	NEG	NOR	NEG	NEG
	8931	CLEAR	1.052	Y	POS	NEG	6	TRACE	NOR	NEG	NOR	NEG	2+
	8940	CLEAR	1.034	Y	POS	NEG	6	TRACE	NOR	NEG	NOR	NEG	NEG
	8943	CLEAR	1.070	AM	POS	NEG	6	TRACE	NOR	NEG	NOR	NEG	NEG
4.0	8933	HAZY	1.040	AM	POS	NEG	7	TRACE	NOR	NEG	1+	NEG	3+
	8936	CLEAR	1.026	Y	POS	TRACE	6	NEG	NOR	NEG	NOR	NEG	1+
	8941	TURBID	1.062	DY	POS	2+	8	3+	NOR	NEG	NOR	NEG	2+
	8944	HAZY	1.062	DY	NEG	NEG	6	TRACE	NOR	NEG	NOR	1+	NEG

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

Female Urinalysis Data (Week 52)

DOSE LEVEL (mg/kg/day)	ANIMAL NO.	CASTS	RBC	WBC	EPITHELIAL CELLS			CRYSTALS	BACTERIA	SPERM	MUCUS	YEAST CELLS
					SQ	TRANS	RENAL					
0	8929	1 HY	0	0	0	0	0	1+ TP	1+	0	0	0
	8930	0	0	0	2	0	0	4+ TP	1+	0	0	0
	8938	1 FG	7	10	4	0	0	2+ TP	1+	0	0	0
	8942	1 HY	0	0	0	0	0	1+ TP	1+	0	0	0
0.1	8934	22 HY 1 FG	0	0	3	0	0	1+ TP	1+	0	0	0
	8935	5 HY	0	0	8	3	0	1+ TP	1+	0	0	0
	8937	1 FG	0	0	1	0	0	1+ TP	1+	0	0	0
	8945	0	0	4	0	0	0	0	1+	0	0	0
1.0	8928	4 HY	0	0	1	0	0	1+ TP	1+	0	0	0
	8931	3 HY	0	0	1	0	0	0	1+	0	0	0
	8940	0	0	0	0	0	0	0	1+	0	0	0
	8943	0	0	0	8	0	0	1+ TP	1+	0	0	0
4.0	8933	1 HY	5	0	0	0	0	1+ TP	1+	0	0	0
	8936	9 HY	0	0	2	0	0	0	1+	0	0	0
	8941	0	0	0	1	0	0	1+ TP	1+	0	0	0
	8944	10 HY 1 FG	0	0	3	4	0	0	1+	0	0	0

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APPENDIX I
Individual Arterial Blood Gases

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL ANIMAL ARTERIAL BLOOD GASES DATA
PERIOD: WEEK 53

STUDY ID: UIC-9
STUDY NO: 219BG

SEX: MALE

Animal ID	PCO2 mmHg	PH -	HCO3- mmol/L	O2 SAT %	PO2 mmHg	TOTAL CO2 mmol/L
GROUP: 1-M:0 mg base/kg/day						
8909	47.6	7.327	25.2	83.3	52	26.6
8911	43.7	7.344	24.0	93.8	74	25.4
8915	44.1	7.327	23.3	82.4	50	24.7
8922	41.6	7.333	22.3	93.5	74	23.6
MEAN	44.3	7.333	23.7	88.3	63	25.1
SD	2.49	0.0080	1.22	6.25	13.3	1.26
N	4	4	4	4	4	4
GROUP: 2-M:0.1 mg base/kg/day						
8907	43.4	7.344	23.9	93.3	72	25.2
8919	40.4	7.307	20.4	91.0	67	21.6
8923	44.8	7.329	23.8	83.2	51	25.2
8924	46.3	7.328	24.5	84.1	53	26.0
MEAN	43.7	7.327	23.2	87.9	61	24.5
SD	2.51	0.0152	1.86	5.01	10.3	1.97
N	4	4	4	4	4	4
GROUP: 3-M:1.0 mg base/kg/day						
8910	46.0	7.327	24.3	71.9	41	25.8
8913	42.3	7.313	21.7	71.2	41	23.0
8914	43.8	7.314	22.5	90.1	64	23.8
8917	40.2	7.380	24.0	92.2	66	25.3
MEAN	43.1	7.333	23.1	81.4	53	24.5
SD	2.45	0.0316	1.23	11.35	13.9	1.30
N	4	4	4	4	4	4
GROUP: 4-M:4.0 mg base/kg/day						
8908	43.6	7.349	24.3	74.9	42	25.6
8918	36.6	7.409	23.4	92.7	65	24.5
8921	47.6	7.324	25.0	14.5	14	26.5
8926	43.7	7.371	25.6	84.5	51	26.9
MEAN	42.9	7.363	24.6	66.7	43	25.9
SD	4.58	0.0360	0.95	35.52	21.5	1.07
N	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL ANIMAL ARTERIAL BLOOD GASES DATA
PERIOD: WEEK 53

STUDY ID: UIC-9
STUDY NO: 2198G

SEX: FEMALE

Animal ID	PCO2 mmHg	PH -	HCO3- mmol/L	O2 SAT %	PO2 mmHg	TOTAL CO2 mmol/L
GROUP: 1-F:0 mg base/kg/day						
8929	52.9	7.274	24.8	73.0	44	26.4
8930	41.1	7.402	25.8	93.4	69	27.1
8938	39.2	7.362	22.4	96.1	85	23.7
8942	46.2	7.354	26.0	80.5	47	27.4
MEAN	44.9	7.348	24.8	85.8	61	26.2
SD	6.13	0.0536	1.65	10.89	19.4	1.69
N	4	4	4	4	4	4

GROUP: 2-F:0.1 mg base/kg/day						
8934	44.4	7.359	25.3	93.1	70	26.7
8935	44.4	7.322	23.2	83.4	52	24.6
8937	41.3	7.351	23.1	84.4	52	24.4
8945	46.7	7.337	25.3	84.6	53	26.7
MEAN	44.2	7.342	24.2	86.4	57	25.6
SD	2.22	0.0163	1.24	4.51	8.8	1.27
N	4	4	4	4	4	4

GROUP: 3-F:1.0 mg base/kg/day						
8928	53.6	7.293	26.2	39.0	25	27.9
8931	41.1	7.355	23.2	93.4	72	24.4
8940	44.7	7.354	25.1	86.4	55	26.5
8943	44.5	7.291	21.7	84.4	55	23.0
MEAN	46.0	7.323	24.1	75.8	52	25.5
SD	5.35	0.0361	2.00	24.83	19.6	2.18
N	4	4	4	4	4	4

GROUP: 4-F:4.0 mg base/kg/day						
8933	50.8	7.243	22.1	72.0	45	23.7
8936	38.6	7.361	22.1	90.4	61	23.3
8941	42.5	7.330	22.6	92.7	71	23.9
8944	39.9	7.343	21.9	80.9	48	23.1
MEAN	43.0	7.319	22.2	84.0	56	23.5
SD	5.48	0.0524	0.30	9.49	12.0	0.37
N	4	4	4	4	4	4

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APPENDIX J
Cardiology Report

ROBERT L. HAMLIN, DVM, PHD, DACVIM
1520 GRENOBLE RD.
COLUMBUS, OHIO 43221
614-486-7542
FAX: 614-486-7545

DRAFT

September 29, 1997

Dr. Barry S. Levine
Director, Toxicology Research Laboratory
University of Illinois
1940 West Taylor Street
Chicago, Illinois 60612-7353

RE: 32 ECGs from Study No. 219, week 51 and Final Report.

Dear Dr. Levine,

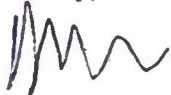
In week 51, two males (nos. 8908 and 8921) and two females (nos. 8933 and 8936) receiving 4 mg base/kg/day and one female receiving 1 mg base/kg/day (no. 8928) had T-wave changes in which the T-waves became biphasic (+/-). These changes appear to represent a drug-effect. Biphasic T-waves were not seen in weeks 12 and 25. Enhanced Ta-waves were seen in two low dose animals. These observations were probably within normal limits and do not represent a drug-effect.

Changes in T-waves indicate alterations in repolarization due, most likely, to alterations in conductance over specific ionic channels, most likely potassium channels. These changes are rather subtle, and I doubt that they represent significant toxicologic effects.

When comparing ECGs for all recording periods, although there are alterations in orientation of QRS vector and in configuration of ST-T, the changes do not appear to be systematic. That is, they occur just as prevalently in dogs receiving vehicle or low dose as with high dose.

There were no drug-effects on heart rate, P-wave duration, or PR, QRS, or QT intervals. Increased P-wave duration for females receiving 4 mg base/kg/day in weeks 12, 25, and 51 was also seen in the baseline period (week-3).

Sincerely,



Robert L. Hamlin, DVM, PhD, DACVIM (Cardiology/Internal Medicine)

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

Electrocardiogram Diagnosis of Males

Dose (mg base/kg/day)	Animal Number	Week -3	Week 12	Week 25	Week 51
0	8922	WNL	WNL	WNL	WNL
	8915	WNL	WNL	WNL	WNL
	8911	WNL	WNL	WNL	WNL
	8909	WNL	WNL	WNL	WNL
0.1	8923	WNL	WNL	WNL	PWNL (LTW)
	8907	WNL	WNL	WNL	WNL
	8919	WNL	WNL	WNL	WNL
	8924	WNL	WNL	WNL	WNL
1.0	8917	WNL	WNL	WNL	WNL
	8910	WNL	WNL*	WNL	WNL (RAD)
	8913	WNL	WNL	WNL	WNL
	8914	WNL	WNL	WNL	WNL
4.0	8918	WNL	WNL	WNL	WNL
	8908	WNL	WNL	WNL	±TW
	8926	WNL	WNL	WNL	WNL
	8921	WNL	WNL	WNL	±TW

*Panting artifact

WNL = Within normal limits
PWNL = Probably within normal limits

LTW = Large Ta Waves
±TW = +/- T waves: possible drug effect
RAD = Right axis deviation

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

Electrocardiogram Diagnosis of Females

Dose (mg base/kg/day)	Animal Number	Week -3	Week 12	Week 25	Week 51
0	8929	WNL	WNL	WNL	WNL
	8942	WNL	WNL	WNL	WNL
	8930	WNL	WNL	WNL	WNL
	8938	WNL	WNL	WNL	WNL
0.1	8935	WNL	WNL	WNL	WNL
	8937	WNL	WNL	WNL	WNL
	8934	WNL	WNL	WNL	WNL
	8945	WNL	WNL	WNL	PWNL (LTW)
1.0	8928	WNL	WNL	WNL	±TW
	8940	WNL	WNL	WNL	WNL
	8931	WNL	WNL	WNL	WNL
	8943	WNL	WNL	WNL	WNL
4.0	8941	WNL	WNL	WNL	WNL
	8933	WNL	WNL	WNL	±TW
	8936	WNL	WNL	WNL	±TW
	8944	WNL	WNL*	WNL	WNL

*Electrical alternans; could be due to ventilation, pericardial effusion or autonomic imbalance.

WNL = Within normal limits
PWNL = Probably within normal limits

LTW = Large Ta Waves
±TW = +/- T waves: possible drug effect
RAD = Right axis deviation

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY REPORT
TEST: Heart Rate

STUDY ID: 219ECG
STUDY NO: 219ECG
ABBR: HR

SEX: MALE

UNITS: bpm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Week 12	Week 25	Week 51
Group: 1-M : 0 mg base/kg/day				
MEAN	134	137	133	134
SD	11.0	33.4	13.1	15.5
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	113	110	119	127
SD	18.7	17.5	12.9	21.4
N	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day				
MEAN	132	127	100	125
SD	13.9	24.2	24.6	11.5
N	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day				
MEAN	106	119	105	120
SD	26.6	39.6	26.1	22.1
N	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY REPORT
TEST: P Wave Duration

STUDY ID: 219ECG
STUDY NO: 219ECG
ABBR: P

SEX: MALE

UNITS: ms

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Week 12	Week 25	Week 51
Group: 1-M : 0 mg base/kg/day				
MEAN	40	41	40	44
SD	1.8	3.3	4.8	2.2
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	39	40	40	40
SD	1.7	3.8	2.4	2.1
N	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day				
MEAN	44	45	45	44
SD	2.9	4.1	1.3	4.5
N	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day				
MEAN	42	43	43	41
SD	2.5	2.2	2.2	3.5
N	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY REPORT
TEST: PR Interval

STUDY ID: 219ECG
STUDY NO: 219ECG
ABBR: PR

SEX: MALE

UNITS: ms

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Week 12	Week 25	Week 51
Group: 1-M : 0 mg base/kg/day				
MEAN	104	99	101	103
SD	4.4	6.7	10.7	6.4
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	94	94	92	94
SD	5.6	4.1	11.7	9.0
N	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day				
MEAN	105	106	99	101
SD	7.1	5.5	9.3	5.3
N	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day				
MEAN	102	95	96	100
SD	14.5	11.9	10.4	16.8
N	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY REPORT
TEST: QRS Interval

STUDY ID: 219ECG
STUDY NO: 219ECG
ABBR: QRS

SEX: MALE

UNITS: ms

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Week 12	Week 25	Week 51
Group: 1-M : 0 mg base/kg/day				
MEAN	40	41	41	44
SD	1.9	2.2	1.4	2.5
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	39	41	39	40
SD	2.9	2.5	0.6	0.0
N	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day				
MEAN	39	42	42	43
SD	1.5	2.5	2.8	3.3
N	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day				
MEAN	39	39	40	40
SD	0.8	1.5	1.3	1.9
N	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY REPORT
TEST: QT Interval

STUDY ID: 219ECG
STUDY NO: 219ECG
ABBR: QT

SEX: MALE

UNITS: ms

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Week 12	Week 25	Week 51
Group: 1-M : 0 mg base/kg/day				
MEAN	193	173	178	176
SD	10.2	13.6	27.7	7.9
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	202	183	172	171
SD	1.5	19.9	14.2	8.9
N	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day				
MEAN	195	188	193	187
SD	5.6	12.8	15.2	21.8
N	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day				
MEAN	211	176	197	174
SD	20.0	19.7	17.4	7.0
N	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY REPORT
TEST: Heart Rate

STUDY ID: 219ECG
STUDY NO: 219ECG
ABBR: HR

SEX: FEMALE

UNITS: bpm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Week 12	Week 25	Week 51
Group: 1-F : 0 mg base/kg/day				
MEAN	117	117	105	108
SD	27.9	14.1	21.2	24.6
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	136	141	153*	133
SD	1.5	10.0	14.3	28.1
N	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day				
MEAN	124	107	115	116
SD	11.8	9.1	7.5	12.8
N	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day				
MEAN	128	123	128	142
SD	17.9	28.8	27.9	32.5
N	4	4	4	4

*-Significant Difference from Control P < .05

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY REPORT
TEST: P Wave Duration

STUDY ID: 219ECG
STUDY NO: 219ECG
ABBR: P

SEX: FEMALE

UNITS: ms

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Week 12	Week 25	Week 51
Group: 1-F : 0 mg base/kg/day				
MEAN	35	40	39	40
SD	2.8	2.9	2.1	3.3
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	39	41	42	47*
SD	3.2	3.8	2.4	1.9
N	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day				
MEAN	40	40	41	42
SD	3.1	2.6	2.9	2.2
N	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day				
MEAN	43*	48*	46*	48*
SD	1.9	4.2	3.4	2.8
N	4	4	4	4

*-Significant Difference from Control P < .05

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY REPORT
TEST: PR Interval

STUDY ID: 219ECG
STUDY NO: 219ECG
ABBR: PR

SEX: FEMALE

UNITS: ms

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Week 12	Week 25	Week 51
Group: 1-F : 0 mg base/kg/day				
MEAN	99	103	98	107
SD	8.3	8.3	4.0	4.4
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	102	98	97	106
SD	5.6	8.1	2.0	8.6
N	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day				
MEAN	102	96	97	101
SD	9.8	9.5	5.0	8.3
N	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day				
MEAN	109	112	104	103
SD	13.1	10.3	15.3	3.7
N	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY REPORT
TEST: QRS Interval

STUDY ID: 219ECG
STUDY NO: 219ECG
ABBR: QRS

SEX: FEMALE

UNITS: ms

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Week 12	Week 25	Week 51
Group: 1-F : 0 mg base/kg/day				
MEAN	38	41	41	40
SD	2.4	5.3	3.4	1.7
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	38	40	39	42
SD	2.1	1.3	1.7	3.6
N	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day				
MEAN	42	40	42	42
SD	1.4	1.3	1.3	1.0
N	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day				
MEAN	42	42	42	44
SD	3.8	2.2	2.6	3.3
N	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY REPORT
TEST: QT Interval

STUDY ID: 219ECG
STUDY NO: 219ECG
ABBR: QT

SEX: FEMALE

UNITS: ms

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	Week -3	Week 12	Week 25	Week 51
Group: 1-F : 0 mg base/kg/day				
MEAN	191	181	179	181
SD	10.8	11.5	9.7	15.1
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	177	175	164	178
SD	14.5	17.6	5.6	13.9
N	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day				
MEAN	190	191	192	180
SD	12.8	12.1	9.1	5.5
N	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day				
MEAN	194	191	188	183
SD	7.1	9.1	15.1	12.1
N	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL ANIMAL REPORT BY GROUP
TEST: Heart Rate

STUDY ID: 219ECG
STUDY NO: 219ECG
ABBR: HR

SEX: MALE

UNITS: bpm

Animal ID	Week -3	Week 12	Week 25	Week 51
GROUP: 1-M:0 mg base/kg/day				
8922	137	148	151	140
8915	118	127	129	111
8911	141	175	131	140
8909	141	96	120	145
MEAN	134	137	133	134
SD	11.0	33.4	13.1	15.5
N	4	4	4	4

GROUP: 2-M:0.1 mg base/kg/day				
8923	126	133	116	112
8907	111	113	137	138
8919	87	99	106	107
8924	127	94	118	152
MEAN	113	110	119	127
SD	18.7	17.5	12.9	21.4
N	4	4	4	4

GROUP: 3-M:1.0 mg base/kg/day				
8917	152	95	72	130
8910	127	134	99	108
8913	129	126	132	133
8914	120	153	97	129
MEAN	132	127	100	125
SD	13.9	24.2	24.6	11.5
N	4	4	4	4

GROUP: 4-M:4.0 mg base/kg/day				
8918	88	121	97	104
8908	81	62	72	98
8926	138	150	118	139
8921	118	141	132	139
MEAN	106	119	105	120
SD	26.6	39.6	26.1	22.1
N	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL ANIMAL REPORT BY GROUP
TEST: Heart Rate

STUDY ID: 219ECG
STUDY NO: 219ECG
ABBR: HR

SEX: FEMALE

UNITS: bpm

Animal ID	Week -3	Week 12	Week 25	Week 51
GROUP: 1-F:0 mg base/kg/day				
8929	80	117	87	93
8942	146	136	118	125
8930	128	109	128	132
8938	115	104	87	81
MEAN	117	117	105	108
SD	27.9	14.1	21.2	24.6
N	4	4	4	4

GROUP: 2-F:0.1 mg base/kg/day				
8935	137	152	172	171
8937	137	130	156	106
8934	137	147	141	135
8945	134	136	143	119
MEAN	136	141	153	133
SD	1.5	10.0	14.3	28.1
N	4	4	4	4

GROUP: 3-F:1.0 mg base/kg/day				
8928	125	106	105	105
8940	131	103	123	131
8931	107	120	115	106
8943	133	99	117	123
MEAN	124	107	115	116
SD	11.8	9.1	7.5	12.8
N	4	4	4	4

GROUP: 4-F:4.0 mg base/kg/day				
8941	101	102	101	131
8933	136	128	157	170
8936	136	99	107	101
8944	138	161	146	166
MEAN	128	123	128	142
SD	17.9	28.8	27.9	32.5
N	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL ANIMAL REPORT BY GROUP
TEST: P Wave Duration

STUDY ID: 219ECG
STUDY NO: 219ECG
ABBR: P

SEX: MALE

UNITS: ms

Animal ID	Week -3	Week 12	Week 25	Week 51
GROUP: 1-M:0 mg base/kg/day				
8922	39	39	33	41
8915	38	45	43	45
8911	41	43	41	46
8909	42	38	43	45
MEAN	40	41	40	44
SD	1.8	3.3	4.8	2.2
N	4	4	4	4

GROUP: 2-M:0.1 mg base/kg/day				
8923	39	43	43	42
8907	38	43	38	42
8919	37	37	41	38
8924	41	36	38	39
MEAN	39	40	40	40
SD	1.7	3.8	2.4	2.1
N	4	4	4	4

GROUP: 3-M:1.0 mg base/kg/day				
8917	46	44	44	43
8910	40	44	43	41
8913	46	50	46	50
8914	43	40	45	40
MEAN	44	45	45	44
SD	2.9	4.1	1.3	4.5
N	4	4	4	4

GROUP: 4-M:4.0 mg base/kg/day				
8918	39	40	43	37
8908	45	43	44	45
8926	42	44	45	40
8921	43	45	40	43
MEAN	42	43	43	41
SD	2.5	2.2	2.2	3.5
N	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL ANIMAL REPORT BY GROUP
TEST: P Wave Duration

STUDY ID: 219ECG
STUDY NO: 219ECG
ABBR: P

SEX: FEMALE

UNITS: ms

Animal ID	Week -3	Week 12	Week 25	Week 51
GROUP: 1-F:0 mg base/kg/day				
8929	36	36	39	38
8942	33	40	39	37
8930	38	43	42	42
8938	32	41	37	44
MEAN	35	40	39	40
SD	2.8	2.9	2.1	3.3
N	4	4	4	4

GROUP: 2-F:0.1 mg base/kg/day				
8935	37	42	45	48
8937	36	36	40	48
8934	40	45	40	46
8945	43	42	43	44
MEAN	39	41	42	47
SD	3.2	3.8	2.4	1.9
N	4	4	4	4

GROUP: 3-F:1.0 mg base/kg/day				
8928	37	40	43	44
8940	38	41	43	43
8931	44	42	40	41
8943	39	36	37	39
MEAN	40	40	41	42
SD	3.1	2.6	2.9	2.2
N	4	4	4	4

GROUP: 4-F:4.0 mg base/kg/day				
8941	41	45	43	45
8933	41	43	45	47
8936	43	50	46	50
8944	45	52	51	51
MEAN	43	48	46	48
SD	1.9	4.2	3.4	2.8
N	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL ANIMAL REPORT BY GROUP
TEST: PR Interval

STUDY ID: 219ECG
STUDY NO: 219ECG
ABBR: PR

SEX: MALE

UNITS: ms

Animal ID	Week -3	Week 12	Week 25	Week 51
GROUP: 1-M:0 mg base/kg/day				
8922	100	100	93	107
8915	101	93	91	94
8911	107	95	110	102
8909	109	108	111	108
MEAN	104	99	101	103
SD	4.4	6.7	10.7	6.4
N	4	4	4	4

GROUP: 2-M:0.1 mg base/kg/day				
8923	97	96	109	107
8907	100	98	83	92
8919	89	90	88	86
8924	89	90	87	92
MEAN	94	94	92	94
SD	5.6	4.1	11.7	9.0
N	4	4	4	4

GROUP: 3-M:1.0 mg base/kg/day				
8917	107	109	104	97
8910	113	112	95	106
8913	96	100	88	95
8914	103	103	109	104
MEAN	105	106	99	101
SD	7.1	5.5	9.3	5.3
N	4	4	4	4

GROUP: 4-M:4.0 mg base/kg/day				
8918	118	110	108	115
8908	110	98	102	114
8926	89	83	87	85
8921	90	88	88	86
MEAN	102	95	96	100
SD	14.5	11.9	10.4	16.8
N	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL ANIMAL REPORT BY GROUP
TEST: PR Interval

STUDY ID: 219ECG
STUDY NO: 219ECG
ABBR: PR

SEX: FEMALE

UNITS: ms

Animal ID	Week -3	Week 12	Week 25	Week 51
GROUP: 1-F:0 mg base/kg/day				
8929	105	101	96	110
8942	90	93	93	100
8930	107	113	102	108
8938	94	105	100	108
MEAN	99	103	98	107
SD	8.3	8.3	4.0	4.4
N	4	4	4	4

GROUP: 2-F:0.1 mg base/kg/day				
8935	100	102	94	95
8937	110	106	98	116
8934	98	88	98	107
8945	99	94	98	105
MEAN	102	98	97	106
SD	5.6	8.1	2.0	8.6
N	4	4	4	4

GROUP: 3-F:1.0 mg base/kg/day				
8928	87	83	90	92
8940	105	100	101	107
8931	109	105	100	109
8943	105	94	98	96
MEAN	102	96	97	101
SD	9.8	9.5	5.0	8.3
N	4	4	4	4

GROUP: 4-F:4.0 mg base/kg/day				
8941	93	100	93	99
8933	109	118	100	104
8936	109	108	95	100
8944	125	123	126	107
MEAN	109	112	104	103
SD	13.1	10.3	15.3	3.7
N	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL ANIMAL REPORT BY GROUP
TEST: QRS Interval

STUDY ID: 219ECG
STUDY NO: 219ECG
ABBR: QRS

SEX: MALE

UNITS: ms

Animal ID	Week -3	Week 12	Week 25	Week 51
GROUP: 1-M:0 mg base/kg/day				
8922	39	44	42	43
8915	39	40	39	43
8911	43	39	42	47
8909	40	40	41	41
MEAN	40	41	41	44
SD	1.9	2.2	1.4	2.5
N	4	4	4	4

GROUP: 2-M:0.1 mg base/kg/day				
8923	35	38	38	40
8907	42	40	39	40
8919	39	44	39	40
8924	39	40	38	40
MEAN	39	41	39	40
SD	2.9	2.5	0.6	0.0
N	4	4	4	4

GROUP: 3-M:1.0 mg base/kg/day				
8917	41	43	44	47
8910	38	43	41	44
8913	38	38	39	39
8914	40	43	45	43
MEAN	39	42	42	43
SD	1.5	2.5	2.8	3.3
N	4	4	4	4

GROUP: 4-M:4.0 mg base/kg/day				
8918	38	38	39	39
8908	39	41	40	43
8926	40	40	42	40
8921	39	38	40	39
MEAN	39	39	40	40
SD	0.8	1.5	1.3	1.9
N	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL ANIMAL REPORT BY GROUP
TEST: QRS Interval

STUDY ID: 219ECG
STUDY NO: 219ECG
ABBR: QRS

SEX: FEMALE

UNITS: ms

Animal ID	Week -3	Week 12	Week 25	Week 51
GROUP: 1-F:0 mg base/kg/day				
8929	38	38	40	39
8942	35	36	38	38
8930	38	41	41	40
8938	41	48	46	42
MEAN	38	41	41	40
SD	2.4	5.3	3.4	1.7
N	4	4	4	4

GROUP: 2-F:0.1 mg base/kg/day				
8935	36	39	37	37
8937	41	41	41	45
8934	38	38	39	41
8945	38	40	40	44
MEAN	38	40	39	42
SD	2.1	1.3	1.7	3.6
N	4	4	4	4

GROUP: 3-F:1.0 mg base/kg/day				
8928	43	42	43	42
8940	40	40	40	42
8931	42	39	42	40
8943	43	40	42	42
MEAN	42	40	42	42
SD	1.4	1.3	1.3	1.0
N	4	4	4	4

GROUP: 4-F:4.0 mg base/kg/day				
8941	38	41	39	41
8933	41	40	41	41
8936	43	43	43	44
8944	47	45	45	48
MEAN	42	42	42	44
SD	3.8	2.2	2.6	3.3
N	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL ANIMAL REPORT BY GROUP
TEST: QT Interval

STUDY ID: 219ECG
STUDY NO: 219ECG
ABBR: QT

SEX: MALE

UNITS: ms

Animal ID	Week -3	Week 12	Week 25	Week 51
GROUP: 1-M:0 mg base/kg/day				
8922	192	175	165	175
8915	180	172	167	184
8911	194	155	160	178
8909	205	188	219	165
MEAN	193	173	178	176
SD	10.2	13.6	27.7	7.9
N	4	4	4	4

GROUP: 2-M:0.1 mg base/kg/day				
8923	203	176	162	160
8907	200	160	158	167
8919	201	189	181	179
8924	203	207	187	177
MEAN	202	183	172	171
SD	1.5	19.9	14.2	8.9
N	4	4	4	4

GROUP: 3-M:1.0 mg base/kg/day				
8917	189	181	176	173
8910	202	199	193	211
8913	197	198	191	164
8914	193	173	213	198
MEAN	195	188	193	187
SD	5.6	12.8	15.2	21.8
N	4	4	4	4

GROUP: 4-M:4.0 mg base/kg/day				
8918	230	160	174	176
8908	212	200	210	178
8926	183	185	211	163
8921	218	160	193	177
MEAN	211	176	197	174
SD	20.0	19.7	17.4	7.0
N	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

INDIVIDUAL ANIMAL REPORT BY GROUP
TEST: QT Interval

STUDY ID: 219ECG
STUDY NO: 219ECG
ABBR: QT

SEX: FEMALE

UNITS: ms

Animal ID	Week -3	Week 12	Week 25	Week 51
GROUP: 1-F:0 mg base/kg/day				
8929	202	165	169	172
8942	193	187	174	170
8930	192	179	191	180
8938	176	191	183	203
MEAN	191	181	179	181
SD	10.8	11.5	9.7	15.1
N	4	4	4	4

GROUP: 2-F:0.1 mg base/kg/day				
8935	180	190	168	174
8937	183	159	170	176
8934	189	191	160	197
8945	156	161	159	164
MEAN	177	175	164	178
SD	14.5	17.6	5.6	13.9
N	4	4	4	4

GROUP: 3-F:1.0 mg base/kg/day				
8928	189	190	200	179
8940	172	195	179	184
8931	198	204	194	185
8943	200	175	195	173
MEAN	190	191	192	180
SD	12.8	12.1	9.1	5.5
N	4	4	4	4

GROUP: 4-F:4.0 mg base/kg/day				
8941	186	200	194	186
8933	202	182	171	167
8936	190	184	206	196
8944	197	197	182	181
MEAN	194	191	188	183
SD	7.1	9.1	15.1	12.1
N	4	4	4	4

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APPENDIX K
Ophthalmology Report

ANIMAL EYE ASSOCIATES

2845 SOUTH HARLEM • BERWYN, ILLINOIS 60402 • (708)749-4200
372 SOUTH MILWAUKEE AVE. • WHEELING, ILLINOIS 60090 • (708) 215-3933

DRAFT

SAMUEL J. VAINISI, DVM
Diplomate American College
of Veterinary Ophthalmologists

GRETCHEN M. SCHMIDT, DVM
Diplomate American College
of Veterinary Ophthalmologists

September 29, 1997

OPHTHALMIC REPORT

UIC/TRL Study No. 219

ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS

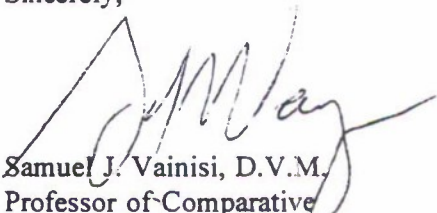
During Week -2 (July 9, 1996), a sufficient number of beagle dogs were given ophthalmic examinations by indirect ophthalmoscopy to result in sixteen males and sixteen females which were within normal limits.

During Week 12 (October 9, 1996), all thirty-two animals used in this study were re-examined. All dogs were within normal limits.

During Week 25 (January 7, 1997), all thirty-two animals used in this study were re-examined. All dogs were within normal limits.

During Week 51 (July 08, 1997), all thirty-two animals used in this study were re-examined. All dogs were within normal limits.

Sincerely,



Samuel J. Vainisi, D.V.M.
Professor of Comparative
Ophthalmology, Univ. of IL at Chicago

Diplomate, American College of
Veterinary Ophthalmologists

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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Ophthalmic Examinations (Males)

Dose (mg base/kg/day)	Animal Number	Week -2		Week 12		Week 25		Week 51	
		R.E.	L.E.	R.E.	L.E.	R.E.	L.E.	R.E.	L.E.
0	8909	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
	8911	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
	8915	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
	8922	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
0.1	8907	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
	8919	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
	8923	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
	8924	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
1.0	8910	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
	8913	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
	8914	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
	8917	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
4.0	8908	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
	8918	WNL	WNL (MF)	WNL	WNL	WNL	WNL	WNL	WNL
	8921	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
	8926	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL

R.E. = Right Eye
L.E. = Left Eye
WNL = Within Normal Limits
MF = Myelinated Fibers Around Optic Nerve

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

Ophthalmic Examinations (Females)

Dose (mg base/kg/day)	Animal Number	Week -2		Week 12		Week 25		Week 51	
		R.E.	L.E.	R.E.	L.E.	R.E.	L.E.	R.E.	L.E.
0	8929	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
	8930	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
	8938	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
	8942	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
0.1	8934	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
	8935	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
	8937	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
	8945	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
1.0	8928	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
	8931	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
	8940	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
	8943	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
4.0	8933	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
	8936	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
	8941	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL
	8944	WNL	WNL	WNL	WNL	WNL	WNL	WNL	WNL

R.E. = Right Eye
L.E. = Left Eye
WNL = Within Normal Limits
MF = Myelinated Fibers Around Optic Nerve

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APPENDIX L
Individual Organ Weights

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ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 219
STUDY NO: 219
SEX: MALE

GROUP: 1-M - 0 mg base/kg/day
ALL FATES DAYS: 365-366 ALL BALANCES

ANIMAL ID:	8909	8911	8915	8922
BALANCE NO.:	2191	2191	2191	2191
BODY WEIGHT (KG)	14.2	14.2	12.9	12.5
Adrenal Glands (G)	1.08	1.61	1.27	1.51
% BRAIN WEIGHT	1.46	2.12	1.51	1.85
Brain (G)	74.03	75.77	83.87	81.48
Heart (G)	98.24	102.63	101.64	97.53
% BRAIN WEIGHT	132.70	135.45	121.19	119.70
Kidneys (G)	66.06	75.38	60.14	60.73
% BRAIN WEIGHT	89.23	99.48	71.71	74.53
Liver (G)	327.65	332.39	282.84	281.70
% BRAIN WEIGHT	442.59	438.68	337.24	345.73
Lungs (G)	105.90	101.37	97.10	99.58
% BRAIN WEIGHT	143.05	133.79	115.77	122.21
Pituitary (G)	0.08	0.06	0.10	0.15
% BRAIN WEIGHT	0.11	0.08	0.12	0.18
Spleen (G)	38.68	50.48	45.59	34.07
% BRAIN WEIGHT	52.25	66.62	54.36	41.81
Testes + Epididymides (G)	26.03	23.94	17.38	21.65
% BRAIN WEIGHT	35.16	31.60	20.72	26.57
Thyroid + Parathyroids (G)	0.95	1.17	0.68	0.82
% BRAIN WEIGHT	1.28	1.54	0.81	1.01

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ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 219
STUDY NO: 219
SEX: MALE

GROUP: 2-M - 0.1 mg base/kg/day
ALL FATES DAYS: 365-366 ALL BALANCES

ANIMAL ID:	8907	8919	8923	8924
BALANCE NO.:	2191	2191	2191	2191
BODY WEIGHT (KG)	13.0	12.3	12.1	14.9
Adrenal Glands (G)	1.58	1.46	1.45	1.25
% BRAIN WEIGHT	1.95	1.57	1.85	1.49
Brain (G)	81.00	92.85	78.40	84.03
Heart (G)	101.73	98.69	115.85	108.14
% BRAIN WEIGHT	125.59	106.29	147.77	128.69
Kidneys (G)	59.49	63.42	58.19	82.11
% BRAIN WEIGHT	73.44	68.30	74.22	97.72
Liver (G)	286.21	279.22	338.33	342.05
% BRAIN WEIGHT	353.34	300.72	431.54	407.06
Lungs (G)	93.42	99.89	92.00	114.77
% BRAIN WEIGHT	115.33	107.58	117.35	136.58
Pituitary (G)	0.07	0.10	0.05	0.09
% BRAIN WEIGHT	0.09	0.11	0.06	0.11
Spleen (G)	33.18	41.60	33.64	38.50
% BRAIN WEIGHT	40.96	44.80	42.91	45.82
Testes + Epididymides (G)	23.09	18.91	20.76	24.22
% BRAIN WEIGHT	28.51	20.37	26.48	28.82
Thyroid + Parathyroids (G)	0.93	0.67	1.06	1.49
% BRAIN WEIGHT	1.15	0.72	1.35	1.77

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 219
STUDY NO: 219
SEX: MALE

GROUP: 3-M - 1.0 mg base/kg/day
ALL FATES DAYS: 365-366 ALL BALANCES

ANIMAL ID: BALANCE NO.:	8910 2191	8913 2191	8914 2191	8917 2191
BODY WEIGHT (KG)	11.6	11.3	13.1	12.7
Adrenal Glands (G)	2.03	1.37	1.40	1.70
% BRAIN WEIGHT	2.48	1.68	1.66	1.93
Brain (G)	82.02	81.78	84.25	88.16
Heart (G)	100.78	112.37	118.37	118.89
% BRAIN WEIGHT	122.87	137.40	140.50	134.86
Kidneys (G)	49.95	54.49	61.28	67.50
% BRAIN WEIGHT	60.90	66.63	72.74	76.56
Liver (G)	362.02	357.23	361.76	354.91
% BRAIN WEIGHT	441.38	436.82	429.39	402.57
Lungs (G)	126.65	131.91	168.01	123.29
% BRAIN WEIGHT	154.41	161.30	199.42	139.85
Pituitary (G)	0.06	0.05	0.11	0.09
% BRAIN WEIGHT	0.07	0.06	0.13	0.10
Spleen (G)	47.29	39.15	53.79	61.74
% BRAIN WEIGHT	57.66	47.87	63.84	70.03
Testes + Epididymides (G)	17.51	14.90	21.86	14.61
% BRAIN WEIGHT	21.35	18.22	25.95	16.57
Thyroid + Parathyroids (G)	0.86	1.03	1.00	0.81
% BRAIN WEIGHT	1.05	1.26	1.19	0.92

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 219
STUDY NO: 219
SEX: MALE

GROUP: 4-M - 4.0 mg base/kg/day
ALL FATES DAYS: 365-366 ALL BALANCES

ANIMAL ID: BALANCE NO.:	8908 2191	8918 2191	8921 2191	8926 2191
BODY WEIGHT (KG)	11.7	11.5	13.1	12.0
Adrenal Glands (G)	1.19	1.35	1.55	2.06
% BRAIN WEIGHT	1.32	1.79	1.92	2.20
Brain (G)	90.34	75.35	80.53	93.69
Heart (G)	112.87	103.13	124.29	130.62
% BRAIN WEIGHT	124.94	136.87	154.34	139.42
Kidneys (G)	59.80	60.63	57.89	78.36
% BRAIN WEIGHT	66.19	80.46	71.89	83.64
Liver (G)	373.32	384.14	478.60	488.97
% BRAIN WEIGHT	413.24	509.81	594.31	521.90
Lungs (G)	287.02	232.30	304.46	227.88
% BRAIN WEIGHT	317.71	308.29	378.07	243.23
Pituitary (G)	0.08	0.10	0.09	0.10
% BRAIN WEIGHT	0.09	0.13	0.11	0.11
Spleen (G)	67.40	57.67	59.09	61.96
% BRAIN WEIGHT	74.61	76.54	73.38	66.13
Testes + Epididymides (G)	19.10	16.49	20.51	20.65
% BRAIN WEIGHT	21.14	21.88	25.47	22.04
Thyroid + Parathyroids (G)	1.13	1.23	1.18	0.83
% BRAIN WEIGHT	1.25	1.63	1.46	0.88

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INDIVIDUAL ORGAN WEIGHTS

STUDY: 219
STUDY NO: 219
SEX: FEMALE

GROUP: 1-F - 0 mg base/kg/day
ALL FATES DAYS: 365-366 ALL BALANCES

ANIMAL ID: BALANCE NO.:	8929 2191	8930 2191	8938 2191	8942 2191
BODY WEIGHT (KG)	7.9	11.6	13.2	10.1
Adrenal Glands (G)	1.42	1.58	1.46	1.21
% BRAIN WEIGHT	1.84	1.91	2.02	1.71
Brain (G)	77.26	82.86	72.08	70.58
Heart (G)	83.29	90.47	96.79	72.46
% BRAIN WEIGHT	107.80	109.18	134.28	102.66
Kidneys (G)	37.61	49.58	45.04	40.60
% BRAIN WEIGHT	48.68	59.84	62.49	57.52
Liver (G)	194.72	263.78	362.45	271.68
% BRAIN WEIGHT	252.03	318.34	502.84	384.92
Lungs (G)	75.95	93.77	100.47	72.64
% BRAIN WEIGHT	98.30	113.17	139.39	102.92
Ovaries (G)	1.15	1.36	1.17	2.35
% BRAIN WEIGHT	1.49	1.64	1.62	3.33
Pituitary (G)	0.16	0.08	0.10	0.15
% BRAIN WEIGHT	0.21	0.10	0.14	0.21
Spleen (G)	28.54	36.44	61.10	29.61
% BRAIN WEIGHT	36.94	43.98	84.77	41.95
Thyroid + Parathyroids (G)	0.76	0.89	0.83	0.81
% BRAIN WEIGHT	0.98	1.07	1.15	1.15

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 219
STUDY NO: 219
SEX: FEMALE

GROUP: 2-F - 0.1 mg base/kg/day
ALL FATES DAYS: 365-366 ALL BALANCES

ANIMAL ID: BALANCE NO.:	8934 2191	8935 2191	8937 2191	8945 2191
BODY WEIGHT (KG)	12.2	13.1	11.3	16.5
Adrenal Glands (G)	1.34	1.34	1.49	2.47
% BRAIN WEIGHT	1.83	2.06	2.06	2.84
Brain (G)	73.29	64.95	72.35	87.01
Heart (G)	84.69	71.97	86.69	111.09
% BRAIN WEIGHT	115.55	110.81	119.82	127.68
Kidneys (G)	50.30	41.78	39.99	56.21
% BRAIN WEIGHT	68.63	64.33	55.27	64.60
Liver (G)	318.00	356.15	226.94	429.45
% BRAIN WEIGHT	433.89	548.34	313.67	493.56
Lungs (G)	78.71	78.76	81.01	99.98
% BRAIN WEIGHT	107.40	121.26	111.97	114.91
Ovaries (G)	1.42	1.15	0.82	2.12
% BRAIN WEIGHT	1.94	1.77	1.13	2.44
Pituitary (G)	0.05	0.13	0.08	0.12
% BRAIN WEIGHT	0.07	0.20	0.11	0.14
Spleen (G)	33.46	32.63	34.58	58.47
% BRAIN WEIGHT	45.65	50.24	47.80	67.20
Thyroid + Parathyroids (G)	1.10	1.00	0.96	1.18
% BRAIN WEIGHT	1.50	1.54	1.33	1.36

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ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 219
STUDY NO: 219
SEX: FEMALE

GROUP: 3-F - 1.0 mg base/kg/day
ALL FATES DAYS: 365-366 ALL BALANCES

ANIMAL ID:	8928	8931	8940	8943
BALANCE NO.:	2191	2191	2191	2191
BODY WEIGHT (KG)	9.2	9.9	9.5	14.2
Adrenal Glands (G)	1.40	1.70	1.53	1.78
% BRAIN WEIGHT	1.63	2.25	2.18	2.06
Brain (G)	85.68	75.39	70.27	86.26
Heart (G)	62.57	88.25	80.76	94.30
% BRAIN WEIGHT	73.03	117.06	114.93	109.32
Kidneys (G)	37.97	40.47	41.82	51.30
% BRAIN WEIGHT	44.32	53.68	59.51	59.47
Liver (G)	300.60	262.09	269.42	524.83
% BRAIN WEIGHT	350.84	347.64	383.41	608.43
Lungs (G)	84.72	91.81	124.25	113.14
% BRAIN WEIGHT	98.88	121.78	176.82	131.16
Ovaries (G)	1.64	0.60	1.06	1.67
% BRAIN WEIGHT	1.91	0.80	1.51	1.94
Pituitary (G)	0.09	0.09	0.07	0.07
% BRAIN WEIGHT	0.10	0.12	0.10	0.08
Spleen (G)	45.76	45.35	34.58	43.35
% BRAIN WEIGHT	53.41	60.15	49.21	50.26
Thyroid + Parathyroids (G)	0.53	0.90	0.69	1.34
% BRAIN WEIGHT	0.62	1.19	0.98	1.55

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ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 219
STUDY NO: 219
SEX: FEMALE

GROUP: 4-F - 4.0 mg base/kg/day
ALL FATES DAYS: 365-366 ALL BALANCES

ANIMAL ID:	8933	8936	8941	8944
BALANCE NO.:	2191	2191	2191	2191
BODY WEIGHT (KG)	10.3	10.7	9.7	11.7
Adrenal Glands (G)	1.37	1.70	1.25	1.16
% BRAIN WEIGHT	1.90	2.01	1.69	1.72
Brain (G)	72.26	84.57	73.77	67.56
Heart (G)	89.19	97.30	68.94	80.53
% BRAIN WEIGHT	123.43	115.05	93.45	119.20
Kidneys (G)	41.80	50.62	40.64	50.57
% BRAIN WEIGHT	57.85	59.86	55.09	74.85
Liver (G)	351.51	387.26	398.03	409.46
% BRAIN WEIGHT	486.45	457.92	539.56	606.07
Lungs (G)	178.31	255.10	142.35	128.08
% BRAIN WEIGHT	246.76	301.64	192.96	189.58
Ovaries (G)	1.28	1.34	1.27	1.37
% BRAIN WEIGHT	1.77	1.58	1.72	2.03
Pituitary (G)	0.08	0.14	0.04	0.14
% BRAIN WEIGHT	0.11	0.16	0.05	0.21
Spleen (G)	99.06	290.64	68.49	78.13
% BRAIN WEIGHT	137.09	343.67	92.84	115.64
Thyroid + Parathyroids (G)	0.75	0.91	0.72	1.10
% BRAIN WEIGHT	1.04	1.08	0.98	1.63

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APPENDIX M
Pathology Report

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DRAFT PATHOLOGY REPORT FOR
ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
UIC/TRL STUDY NUMBER 219

PREPARED
BY
PATHOLOGY ASSOCIATES INTERNATIONAL
2201 WEST CAMPBELL PARK DRIVE, SUITE 327
CHICAGO, IL 60612

FOR
TOXICOLOGY RESEARCH LABORATORY (M/C 868)
DEPARTMENT OF PHARMACOLOGY
UNIVERSITY OF ILLINOIS AT CHICAGO
COLLEGE OF MEDICINE
1940 WEST TAYLOR STREET
CHICAGO, IL 60612-7353

OCTOBER 22, 1997

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Draft Pathology Report
Toxicology Research Laboratory
Study Number 219

SECTION I
PATHOLOGY NARRATIVE

DRAFT PATHOLOGY REPORT

ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS

INTRODUCTION

This pathology report, submitted by Pathology Associates International (PAI) to Toxicology Research Laboratory, University of Illinois at Chicago (UIC/TRL), represents the histopathology findings for the study designated as "One Year Oral Toxicity Study of WR238605 Succinate in Dogs", UIC/TRL Study Number 219. This study was conducted to determine specific target organ toxicity, dose-response relationships, and a no observed adverse effect level of WR238605 succinate in Beagle dogs following one year of daily oral administration.

EXPERIMENTAL DESIGN AND METHODS

Three groups (low, mid, and high), each composed of 4 male and 4 female Beagle dogs were given the test article orally once daily in a gelatin capsule for at least 52 weeks. The dose levels administered were 0.1, 1.0, and 4.0 mg base/kg/day for animals in low, mid, and high dose groups, respectively. Also, one group (control), composed of 4 male and 4 female Beagle dogs was given the vehicle (1% Methylcellulose/0.2% Tween 80) orally in a gelatin capsule once daily for at least 52 weeks. The experimental design is summarized in Table I (Summary of Experimental Design).

All animals were sacrificed and necropsied in random order in Week 53. Animals were anesthetized with sodium pentobarbital and sacrificed by exsanguination. All necropsies were performed according to UIC/TRL Standard Operating Procedures and were conducted by PAI personnel. Tissues required by the protocol (see Table II, Protocol-Required Tissues) were examined and placed in 10% neutral buffered formalin, with the exception of eyes and optic nerve which were fixed in 3% glutaraldehyde, and testes with epididymides which were collected in Bouin's fixative. Bone marrow smears were prepared from the rib of each animal at necropsy. The bone marrow smears were fixed in methanol, stained with a Wrights-Giemsa stain, and evaluated microscopically to determine the myeloid:erythroid (M:E) ratio.

Tissues required for histopathologic evaluation were trimmed and processed, and slides were prepared in accordance with PAI Standard Operating Procedures. These tissues were evaluated by light microscopy and the results were tabulated. One tissue (thoracic spinal cord) was inadvertently not collected at necropsy for one low dose female (animal number 8934) and therefore was unavailable for evaluation. This protocol deviation did not affect the integrity of the study since spinal cord was not a target tissue. Also, thymus from one control male (animal

number 8922) was not verifiable at trim and was missing in the section. This protocol deviation did not affect the integrity of the study since thymus was not a target tissue.

Treatment-related lesions are summarized in Table III, Summary of Treatment-Related Lesions. Microscopic findings for all groups are summarized in the Project Summary tables (Section II). The mean group severity scores are found in the Severity Summary tables (Section III). Where applicable, all tissue changes received a severity grade based upon the following scale: 1 = minimal, 2 = mild, 3 = moderate, and 4 = marked. Mean group severity scores (SEV) for each change were determined by dividing the sum of the severity scores by the number of tissues examined. Microscopic findings in the protocol-required tissues for individual animals are presented in the Tabulated Animal Data tables (Section IV). The correlation of the necropsy findings and histopathology findings are reported in the Correlation of Gross and Microscopic (Micro) Findings (Section V). The codes used as entries in these tables are explained in the Report Codes Table. The results of the bone marrow evaluation are presented in the Bone Marrow Evaluation Report (Section VII).

RESULTS AND DISCUSSION

The Results and Discussion section is divided into four parts: Necropsy Findings, Diagnostic Terms, Histopathology Findings, and Bone Marrow Evaluation Findings. The Necropsy Findings portion describes lesions seen at necropsy or trimming that were test article-related. The Diagnostic Terms portion lists and clarifies diagnostic terminology that may be unclear. Terms listed in the Diagnostic Terms portion of this section include, but are not limited to, those that were considered to be test article-related. The Histopathology Findings portion of this section reports the results and provides discussion of the histopathologic evaluation of the tissues. The Bone Marrow Evaluation Findings portion of this section reports the results of bone marrow smear evaluations.

Necropsy Findings

Enlarged lung, multiple yellow foci in lung, enlarged bronchial lymph node, and altered pigmentation of mediastinal lymph node were interpreted as treatment-related necropsy findings. These findings were primarily found in male and female dogs given 1.0 or 4.0 mg base/kg/day of WR238605. Enlarged lung was observed in 3 of 4 high dose males and 2 of 4 high dose females and was usually correlated with accumulation of alveolar macrophages. Yellow foci were observed in lung from 4 of 4 high dose males, 1 of 4 mid dose males, 3 of 4 high dose females, and 2 of 4 mid dose females and was usually correlated with chronic interstitial inflammation. Enlarged bronchial lymph node was observed in 2 of 4 high dose males, 1 of 4 mid dose males, 2 of 4 high dose females, and 1 of 4 mid dose females and was usually correlated with accumulation of pigmented macrophages. Pigmentation in mediastinal lymph node was observed in 1 of 4 low dose males, 2 of 4 high dose males, and 2 of 4 high dose females and was usually correlated with hemorrhage and/or accumulation of pigmented macrophages.

All other gross lesions were interpreted as incidental findings. Gross observations are listed in the Correlation of Gross and Microscopic (Micro) Findings report in Section V. Microscopic findings were correlated with gross lesions when possible.

Diagnostic Terms

The morphologic characteristics of observations and lesions which require comment are presented in subsequent paragraphs to aid in the interpretation of the data.

Lung

Chronic interstitial inflammation was characterized by the presence of an increased number of alveolar macrophages in alveolar lumina and thickened alveolar walls which stained more basophilic than normal in the affected region. Foamy macrophage accumulation was diagnosed when luminal macrophages were very large with copious foamy cytoplasm. Hemorrhage was characterized by the presence of free erythrocytes and fibrin in the lumen of alveoli in the affected region. Lymphocyte accumulation was characterized by focal accumulation of mature lymphocytes around or adjacent to small arteries or major bronchi. Foamy macrophage accumulation and chronic interstitial inflammation were generally present in the same regions. Chronic interstitial inflammation was interpreted as the end result of macrophage accumulation, because it tended to develop in the more extensive lesions. Hemorrhage consisting of erythrocytes in alveolar lumen in the absence of fibrin deposits and associated edema was interpreted as an agonal event.

Liver

Kupffer cell pigmentation was characterized by the presence of enlarged Kupffer cells due to accumulation of brown granular material in their cytoplasm. Subacute centrilobular inflammation was characterized by the presence of lymphocytes and neutrophils surrounding central veins.

Kidney

Pigmentation in renal cortex was characterized by the presence of brown granular pigment in the cytoplasm of some renal tubular epithelial cells. The pattern of pigmented cell distribution was most consistent with specific accumulation in proximal convoluted tubules. Pigmentation of cortical epithelial cells was considered to be a morphologic indicator of chronic hemoglobin resorptive activity in the kidney.

Spleen

Pigmentation was characterized by the presence of focal groups of macrophages that contained dark brown granular material in their cytoplasm. Some pigment is normally present in splenic macrophages. Therefore, it was only diagnosed when present in sufficient quantity to be readily recognized at 40x magnification. Congestion was characterized by increased prominence of red pulp regions due to pooling of erythrocytes in splenic sinusoids.

Bone Marrow, Rib

Bone marrow hyperplasia was diagnosed when blood precursor cells were increased at the expense of lipid cells.

Gallbladder

Pigmentation of submucosal macrophages was characterized by the presence of macrophages in the submucosa that contained brown granular pigment in their cytoplasm.

Tonsil

Macrophage pigmentation was characterized by the presence of macrophages that contained brown granular pigment in their cytoplasm. Pigmented macrophages in tonsil occurred in the interstitium between lymphoid follicles.

Lymph Node

Macrophage pigmentation in lymph node was characterized by the presence of macrophages with brown granular pigment in their cytoplasm. When the number of macrophages was notably increased, they were diagnosed as an accumulation. Pigmented macrophages were found in sinusoidal areas of lymph node. Hemorrhage in lymph node was characterized by the presence of erythrocytes in sinusoidal areas of lymph node.

The remainder of the diagnoses used in this study were considered to be self-explanatory and were not discussed in this section.

Histopathology Findings

The incidence and severity of treatment-related histopathology findings are summarized in Table III, Summary of Treatment-Related Lesions. These findings are further discussed by organ in this section of the narrative report.

Lung

Accumulation of foamy macrophages and chronic interstitial inflammation were observed in all high and mid dose males and females. Treatment-related lesions were not observed in control and low dose males and females. Accumulation of foamy macrophages and chronic interstitial inflammation were interpreted as primary treatment-related effects.

The pathogenesis of these lung lesions cannot be stated with certainty. However, one possible mechanism could be a primary lesion (not evident from light microscopy) to endothelium and/or type I alveolar cells that would result in hemorrhage. The hemorrhages observed in this study were not associated with the treatment-related lung lesions and were interpreted as probable agonal events. Dose levels of WR238605 that would induce hemorrhage that exceeds the capacity for phagocytosis by macrophages and result in significant fibrin and extracellular protein accumulation in alveoli would probably not be compatible with 1 year survival. However, the presence of foamy macrophages in lung and

bone marrow hyperplasia are interpreted as indicators that a chronic low-grade hemorrhage has occurred. The presence of erythrocytes and blood protein could result in attraction of macrophages to the alveolar lumen. Macrophages may develop copious foamy cytoplasm as they attempt to digest the lipid membrane component of erythrocytes. Macrophages may release enzymes into the alveolar lumen resulting in an interstitial inflammatory response. Other potential causes of hemorrhage include high arterial blood pressure, lack of thrombocytes, or lack of one or more clotting factors.

Liver

Kupffer cell pigmentation was observed in all males and females in the high dose group [4 of 4 (SEV = 2.50) for males and 4 of 4 (SEV = 2.00) for females], in all females [4 of 4 (SEV = 2.00)] and 3 of 4 males (SEV = 0.75) in the mid dose group, and in 2 of 4 females (SEV = 0.50) in the low dose group. The severity grade of Kupffer cell pigmentation was minimal for both females (animal numbers 8937 and 8945) in the low dose group. Kupffer cell pigmentation was interpreted as a treatment-related effect that is consistent with in-vivo hemolysis. The minimal Kupffer cell pigmentation observed in the low dose group was not considered to be a clinically adverse effect.

Subacute centrilobular inflammation was only observed in males and females in the high dose group. Subacute centrilobular inflammation was interpreted as a possible result of hypoxia due to clinically significant reduced pulmonary function and/or anemia.

Kidney

Pigmentation of renal cortex epithelium was more frequent (4 of 4 animals) and severe (SEV = 2.50) in the high dose males relative to the other dose groups. Pigmentation was also present in the mid dose males [2 of 4 (SEV = 0.50)], high dose females [2 of 4 (SEV = 0.75)], and low dose females [1 of 4 (SEV = 0.25)]. The low dose female (animal number 8937) with pigmentation of renal cortex epithelium also had pigmentation of Kupffer cells in liver indicating a probable systemic source of the pigment. These data indicate a relatively good dose-response relationship for renal cortex pigmentation in males and a more variable response in females. The response variability in females may be due to reproductive cycle effects on the hematopoietic system. The renal tubule pigmentation in the low dose female was not interpreted as an adverse effect of the test article because of the lack of a good dose-response relationship in females and the reasonable possibility of other causes (any transient hemorrhagic event) producing this lesion. Pigmentation of renal cortex epithelium was interpreted as a treatment-related effect that is consistent with in-vivo hemolysis.

Spleen

Pigmentation was observed in the high dose [4 of 4 (SEV = 2.50)], mid dose [3 of 4 (SEV = 1.25)], low dose [1 of 4 (SEV = 0.25)], and control [2 of 4 (SEV = 1.00)] males; and in the high dose [4 of 4 (SEV = 2.00)], mid dose [4 of 4 (SEV = 2.00)], low dose [2 of 4 (SEV = 0.50)], and control [1 of 4 (SEV = 0.25)] females. The incidence and/or severity in the high and mid dose groups (male and female) were sufficiently increased to attribute the effect to

test article treatment. Pigmentation in spleen was interpreted as a treatment-related effect that is consistent with in-vivo hemolysis.

Bone Marrow

Bone marrow hyperplasia was observed in both males and females in the high and mid dose groups, but was not present in the low dose and control groups. The incidence and severity of bone marrow hyperplasia in the mid and high dose groups indicated a dose-dependent relationship to treatment. Bone marrow hyperplasia was interpreted as a treatment-related secondary biological response to the chronic pulmonary lesions and/or anemia.

Gallbladder

Pigmentation of macrophages only occurred in males and females in the high dose group. Macrophage pigmentation was interpreted as a treatment-related finding that is consistent with in-vivo hemolysis.

Tonsil

Pigmentation of macrophages occurred in males and females in the high and mid dose groups, but was not present in the low dose and control groups. Macrophage pigmentation was interpreted as a treatment-related effect that is consistent with in-vivo hemolysis.

Lymph Node

The most severe accumulation of pigmented macrophages occurred in bronchial lymph nodes (examined as gross lesions) from males and females in the high and mid dose groups. Pigmentation of macrophages occurred in mandibular lymph node from males and females in all dose groups, but the severity was increased in the high dose males [4 of 4 (SEV = 2.50)] and females [4 of 4 (SEV = 1.75)]. Pigmentation of macrophages in mesenteric lymph node occurred in males and females in the high and mid dose groups, but was not present in the low dose and control groups. Mandibular and mesenteric lymph node macrophage pigmentation were interpreted as treatment-related effects that may be secondary to either subclinical (no lesions detected) gastrointestinal hemorrhage or in-vivo hemolysis. Accumulation of pigmented macrophages in mediastinal lymph nodes (examined as gross lesions) occurred in males and females in the high dose group. Accumulation of pigmented macrophages in bronchial and mediastinal lymph nodes was interpreted as a treatment-related effect that was secondary to pulmonary lesions. Hemorrhage was observed in bronchial lymph node in one high dose male, and in one mid and high dose female. Hemorrhage was observed in mediastinal lymph node in low and high dose males, and in high dose females.

Bone Marrow Evaluation Findings

The bone marrow evaluation findings are presented with supporting data in Section VII of this report. There were no treatment-related changes in the M:E ratio of the bone marrow of male and female dogs.

CONCLUSIONS

Under the conditions of this study, daily oral administration of WR238605 succinate to Beagle dogs for at least 52 weeks at doses of 1.0 and 4.0 mg base/kg/day resulted in primary histopathologic lesions in lung (foamy macrophage accumulation and chronic interstitial inflammation). A variety of secondary morphologic changes were also observed in some animals with primary lung lesions, including pigmentation of Kupffer cells in liver, subacute centrilobular inflammation in liver, pigmentation of renal cortex epithelium, pigmentation in spleen, hyperplasia of bone marrow, pigmentation of submucosal macrophages in gallbladder, pigmentation of macrophages in tonsil, pigmentation of macrophages in mandibular lymph node, pigmentation of macrophages in mesenteric lymph node, hemorrhage in bronchial and mediastinal lymph nodes, and accumulation of pigmented macrophages in bronchial and mediastinal lymph node. Many of the secondary morphologic changes are consistent with in-vivo hemolysis. Treatment-related effects on bone marrow M:E ratios were not seen. The no adverse effect level for WR238605 succinate in this study was 0.1 mg base/kg/day.

Robert L. Morrissey, DVM, Ph.D.
Diplomate, ACVP

Date

TABLE I

SUMMARY OF EXPERIMENTAL DESIGN

<u>Group Number</u>	<u>Group</u>	<u>Dose Level (mg base/kg/day)</u>	<u>Concentration (mg base/ml)</u>	<u>Number of Males</u>	<u>Number of Females</u>
1	Control	0	0	4	4
2	Low	0.1	0.625	4	4
3	Mid	1.0	6.25	4	4
4	High	4.0	25.0	4	4

TABLE II

PROTOCOL-REQUIRED TISSUES

Adrenal glands	Pituitary gland
Aorta (thoracic)	Prostate
Brain (fore, mid, and hind)	Rib with costochondral junction
Cecum	Rib with marrow
Colon	Salivary gland (mandibular)
Diaphragm	Sciatic nerve
Duodenum	Skeletal muscle
Esophagus	Skin
Eyes with optic nerve	Spinal cord (thoracic)
Gallbladder	Spleen
Heart	Stomach
Ileum	Testes with epididymides
Jejunum	Thymus
Kidneys	Thyroid gland with parathyroids
Liver	Tongue
Lungs/Bronchi	Tonsil
Lymph node (mandibular and mesenteric)	Trachea
Mammary gland	Ureter
Ovaries	Urinary bladder
Pancreas	Uterus
	Gross lesions

TABLE III
SUMMARY OF TREATMENT-RELATED LESIONS

ORGAN - lesion	Sex	Dose Group (Dose Level)			
		Control (0 mg base/kg/day)	Low (0.1 mg base/kg/day)	Mid (1.0 mg base/kg/day)	High (4.0 mg base/kg/day)
LUNG					
- Inflammation, chronic, interstitium	M	0/4	0/4	4/4 (1.25)*	4/4 (2.75)
	F	0/4	0/4	4/4 (1.25)	4/4 (2.25)
- Accumulation, foamy macrophage	M	0/4	0/4	4/4 (2.00)	4/4 (3.00)
	F	0/4	0/4	4/4 (1.50)	4/4 (2.75)
LIVER					
- Pigmentation, Kupffer cell	M	0/4	0/4	3/4 (0.75)	4/4 (2.50)
	F	0/4	2/4 (0.50)	4/4 (2.00)	4/4 (2.00)
- Inflammation, subacute, centrilobular	M	0/4	0/4	0/4	3/4 (0.75)
	F	0/4	0/4	0/4	2/4 (0.50)
KIDNEY					
- Pigmentation, epithelium, cortex	M	0/4	0/4	2/4 (0.50)	4/4 (2.50)
	F	0/4	1/4 (0.25)	0/4	2/4 (0.75)
SPLEEN					
- Pigmentation	M	2/4 (1.00)	1/4 (0.25)	3/4 (1.25)	4/4 (2.50)
	F	1/4 (0.25)	2/4 (0.50)	4/4 (2.00)	4/4 (2.00)
BONE MARROW, RIB					
- Hyperplasia	M	0/4	0/4	1/4 (0.25)	3/4 (1.25)
	F	0/4	0/4	1/4 (0.25)	4/4 (1.75)
GALLBLADDER					
- Pigmentation, macrophage, submucosa	M	0/4	0/4	0/4	2/4 (1.00)
	F	0/4	0/4	0/4	1/4 (0.25)
TONSIL					
- Pigmentation, macrophage	M	0/4	0/4	3/4 (0.75)	4/4 (2.50)
	F	0/4	0/4	1/4 (0.75)	4/4 (3.00)
LYMPH NODE, MANDIBULAR					
- Pigmentation, macrophage	M	4/4 (1.00)	2/4 (0.50)	4/4 (1.00)	4/4 (2.50)
	F	2/4 (0.50)	2/4 (0.75)	4/4 (1.00)	4/4 (1.75)
LYMPH NODE, MESENTERIC					
- Pigmentation, macrophage	M	0/4	0/4	3/4 (0.75)	4/4 (2.00)
	F	0/4	0/4	4/4 (1.25)	4/4 (1.75)

* Incidence (mean group severity score)

TABLE III
 SUMMARY OF TREATMENT-RELATED LESIONS CONTINUED

ORGAN - lesion	Sex	Dose Group (Dose Level)			
		Control (0 mg base/kg/day)	Low (0.1 mg base/kg/day)	Mid (1.0 mg base/kg/day)	High (4.0 mg base/kg/day)
LYMPH NODE, BRONCHIAL					
- Accumulation, pigmented macrophage	M	-	-	2/2 (2.50)*	4/4 (3.00)
	F	-	-	1/1 (3.00)	4/4 (3.00)
- Hemorrhage	M	-	-	-	1/4 (0.50)
	F	-	-	1/1 (1.00)	1/4 (0.25)
LYMPH NODE, MEDIASTINAL					
- Accumulation, pigmented macrophage	M	-	0/1	-	2/2 (2.00)
	F	-	-	-	2/2 (2.00)
- Hemorrhage	M	-	1/1 (2.00)	-	2/2 (2.00)
	F	-	-	-	2/2 (2.50)

* Incidence (mean group severity score)

- Not examined

DRAFT

PATHOLOGY ASSOCIATES INTERNATIONAL
ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

Report Codes Table

A. Codes applying to organs

N	Tissues within normal histological limits
A	Autolysis precluding adequate evaluation
U	Tissues unavailable/unsuitable for complete evaluation

B. Codes applying to microscopic diagnoses

1	minimal
2	mild
3	moderate
4	marked
P	Present
-	No data entered

DRAFT

Draft Pathology Report
Toxicology Research Laboratory
Study Number 219

SECTION II
PROJECT SUMMARY

PATHOLOGY ASSOCIATES INTERNATIONAL
ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

PROJECT SUMMARY

STUDY ID : STUDY NUMBER 219

STUDY NUMBER: SN219

FATE: ALL

SEX: MALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:		Control	Low	Mid	High
		(1)	(2)	(3)	(4)
NUMBER OF ANIMALS:		4	4	4	4
		# %	# %	# %	# %
BRAIN, FORE	# EX	4	4	4	4
Gliosis, focal		1 25.0	0 0.0	0 0.0	0 0.0
BRAIN, MID	# EX	4	4	4	4
SPINAL CORD, THORACIC	# EX	4	4	4	4
Hemorrhage		2 50.0	0 0.0	1 25.0	1 25.0
BRAIN, HIND	# EX	4	4	4	4
HEART	# EX	4	4	4	4
Angiectasis, focal, valve		0 0.0	1 25.0	0 0.0	0 0.0
BLOOD VESSEL, AORTA	# EX	4	4	4	4
TRACHEA	# EX	4	4	4	4
Inflammation, chronic		1 25.0	1 25.0	2 50.0	0 0.0
ESOPHAGUS	# EX	4	4	4	4
LUNG	# EX	4	4	4	4
Accumulation, lymphocyte, perivascular		2 50.0	2 50.0	3 75.0	2 50.0
Inflammation, chronic, interstitium		0 0.0	0 0.0	4 100.0	4 100.0
Accumulation, foamy macrophages		0 0.0	0 0.0	4 100.0	4 100.0
Hemorrhage		0 0.0	0 0.0	0 0.0	1 25.0
KIDNEY	# EX	4	4	4	4
Mineralization, medulla		4 100.0	4 100.0	4 100.0	4 100.0
Pigmentation, epithelium, cortex		0 0.0	0 0.0	2 50.0	4 100.0
Inflammation, subacute, medulla		0 0.0	1 25.0	0 0.0	0 0.0

Incidence Calculated by No. of Tissues Scored

(1) - 0 mg base/kg/day

(2) - 0.1 mg base/kg/day

(3) - 1.0 mg base/kg/day

(4) - 4.0 mg base/kg/day

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GROUP:		Control	Low	Mid	High
		(1)	(2)	(3)	(4)
NUMBER OF ANIMALS:		4	4	4	4
SPLEEN	# EX	4	4	4	4
Pigmentation		2 50.0	1 25.0	3 75.0	4 100.0
Congestion		0 0.0	0 0.0	1 25.0	0 0.0
Siderotic plaque		0 0.0	2 50.0	1 25.0	1 25.0
PANCREAS	# EX	4	4	4	4
Inflammation, chronic, duct		1 25.0	0 0.0	1 25.0	1 25.0
INTESTINE SMALL, DUODENUM	# EX	4	4	4	4
Abscess, crypt		0 0.0	0 0.0	0 0.0	1 25.0
LIVER	# EX	4	4	4	4
Inflammation, chronic		4 100.0	4 100.0	4 100.0	4 100.0
Pigmentation, Kupffer cell		0 0.0	0 0.0	3 75.0	4 100.0
Inflammation, subacute, centrilobular		0 0.0	0 0.0	0 0.0	3 75.0
GALLBLADDER	# EX	4	4	4	4
Accumulation, lymphocyte		3 75.0	2 50.0	3 75.0	3 75.0
Pigmentation, macrophage, submucosa		0 0.0	0 0.0	0 0.0	2 50.0
ADRENAL GLAND	# EX	4	4	4	4
Congestion		0 0.0	1 25.0	0 0.0	1 25.0
SALIVARY GLAND	# EX	4	4	4	4
Inflammation, chronic		2 50.0	1 25.0	2 50.0	0 0.0
LYMPH NODE, MANDIBULAR	# EX	4	4	4	4
Pigmentation, macrophage		4 100.0	2 50.0	4 100.0	4 100.0
INTESTINE SMALL, JEJUNUM	# EX	4	4	4	4
Congestion		2 50.0	2 50.0	3 75.0	2 50.0
Congestion, Peyer's patch		0 0.0	0 0.0	0 0.0	1 25.0

Incidence Calculated by No. of Tissues Scored

(3) - 1.0 mg base/kg/day

(1) - 0 mg base/kg/day

(4) - 4.0 mg base/kg/day

(2) - 0.1 mg base/kg/day

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INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:		Control	Low	Mid	High
		(1)	(2)	(3)	(4)
NUMBER OF ANIMALS:		4	4	4	4
		# %	# %	# %	# %
INTESTINE LARGE, COLON	# EX	4	4	4	4
TONSIL	# EX	4	4	4	4
Bacterial colony		1 25.0	1 25.0	1 25.0	1 25.0
Inflammation, acute, lumen		2 50.0	1 25.0	2 50.0	4 100.0
Pigmentation, macrophage		0 0.0	0 0.0	3 75.0	4 100.0
INTESTINE SMALL, ILEUM	# EX	4	4	4	4
Congestion, mucosa		2 50.0	0 0.0	1 25.0	0 0.0
Congestion, Peyer's patch		2 50.0	1 25.0	2 50.0	1 25.0
LYMPH NODE, MESENTERIC	# EX	4	4	4	4
Hemorrhage		3 75.0	2 50.0	2 50.0	2 50.0
Pigmentation, macrophage		0 0.0	0 0.0	3 75.0	4 100.0
TONGUE	# EX	4	4	4	4
DIAPHRAGM	# EX	4	4	4	4
THYMUS	# EX	3	4	4	4
Cyst		1 33.0	0 0.0	0 0.0	0 0.0
Atrophy		1 33.0	1 25.0	0 0.0	2 50.0
URINARY BLADDER	# EX	4	4	4	4
SKELETAL MUSCLE	# EX	4	4	4	4
SKIN	# EX	4	4	4	4
MAMMARY GLAND	# EX	4	4	4	4

Incidence Calculated by No. of Tissues Scored
(1) - 0 mg base/kg/day
(2) - 0.1 mg base/kg/day

(3) - 1.0 mg base/kg/day
(4) - 4.0 mg base/kg/day

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GROUP:		Control		Low		Mid		High	
		(1)		(2)		(3)		(4)	
NUMBER OF ANIMALS:		4		4		4		4	
		#	%	#	%	#	%	#	%
THYROID GLAND	# EX	4		4		4		4	
PARATHYROID GLAND	# EX	4		4		4		4	
PITUITARY GLAND	# EX	4		4		4		4	
Cyst		2	50.0	2	50.0	1	25.0	3	75.0
INTESTINE LARGE, CECUM	# EX	4		4		4		4	
Congestion, Peyer's patch		1	25.0	0	0.0	1	25.0	0	0.0
STOMACH	# EX	4		4		4		4	
Accumulation, lymphocyte		3	75.0	4	100.0	4	100.0	4	100.0
TESTES	# EX	4		4		4		4	
EPIDIDYMIS	# EX	4		4		4		4	
Inflammation, chronic		0	0.0	0	0.0	0	0.0	1	25.0
PERIPHERAL NERVE, SCIATIC	# EX	4		4		4		4	
URETER	# EX	4		4		4		4	
EYE	# EX	4		4		4		4	
OPTIC NERVE	# EX	4		4		4		4	
PROSTATE	# EX	4		4		4		4	
Inflammation, chronic		2	50.0	0	0.0	3	75.0	0	0.0
Inflammation, chronic, active		0	0.0	0	0.0	0	0.0	1	25.0
Atrophy, focal, epithelium		0	0.0	0	0.0	3	75.0	1	25.0

Incidence Calculated by No. of Tissues Scored (3) - 1.0 mg base/kg/day
 (1) - 0 mg base/kg/day (4) - 4.0 mg base/kg/day
 (2) - 0.1 mg base/kg/day

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INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:		Control	Low	Mid	High
		(1)	(2)	(3)	(4)
NUMBER OF ANIMALS:		4	4	4	4
		# %	# %	# %	# %
BONE, RIB	# EX	4	4	4	4
BONE MARROW, RIB	# EX	4	4	4	4
Hyperplasia		0 0.0	0 0.0	1 25.0	3 75.0
LYMPH NODE, MEDIASTINAL	# EX	0	1	0	2
Accumulation, pigmented macrophages		0 0.0	0 0.0	0 0.0	2 100.0
Hemorrhage		0 0.0	1 100.0	0 0.0	2 100.0
LYMPH NODE, BRONCHIAL	# EX	0	0	2	4
Accumulation, pigmented macrophage		0 0.0	0 0.0	2 100.0	4 100.0
Hemorrhage		0 0.0	0 0.0	0 0.0	1 25.0

Incidence Calculated by No. of Tissues Scored (3) - 1.0 mg base/kg/day
 (1) - 0 mg base/kg/day (4) - 4.0 mg base/kg/day
 (2) - 0.1 mg base/kg/day

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

PROJECT SUMMARY

STUDY ID : STUDY NUMBER 219
 FATE: ALL

STUDY NUMBER: SN219

SEX: FEMALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:		Control		Low		Mid		High	
		(1)		(2)		(3)		(4)	
NUMBER OF ANIMALS:		4		4		4		4	
	# EX	#	%	#	%	#	%	#	%
BRAIN, FORE	# EX	4		4		4		4	
BRAIN, MID	# EX	4		4		4		4	
Inflammation, chronic, focal		1	25.0	0	0.0	0	0.0	0	0.0
SPINAL CORD, THORACIC	# EX	4		3		4		4	
Hemorrhage		2	50.0	1	33.0	1	25.0	1	25.0
Mineralization, focal		1	25.0	0	0.0	0	0.0	0	0.0
BRAIN, HIND	# EX	4		4		4		4	
HEART	# EX	4		4		4		4	
BLOOD VESSEL, AORTA	# EX	4		4		4		4	
TRACHEA	# EX	4		4		4		4	
Inflammation, chronic		1	25.0	1	25.0	1	25.0	1	25.0
ESOPHAGUS	# EX	4		4		4		4	
Inflammation, chronic		0	0.0	1	25.0	0	0.0	0	0.0
LUNG	# EX	4		4		4		4	
Accumulation, lymphocyte, perivascular		2	50.0	3	75.0	3	75.0	3	75.0
Inflammation, chronic, interstitium		0	0.0	0	0.0	4	100.0	4	100.0
Accumulation, foamy macrophages		0	0.0	0	0.0	4	100.0	4	100.0
Hemorrhage		1	25.0	1	25.0	1	25.0	1	25.0
KIDNEY	# EX	4		4		4		4	
Mineralization, medulla		4	100.0	4	100.0	4	100.0	4	100.0
Pigmentation, epithelium, cortex		0	0.0	1	25.0	0	0.0	2	50.0
Inflammation, chronic, interstitium		1	25.0	1	25.0	1	25.0	0	0.0
Nephropathy		2	50.0	0	0.0	0	0.0	3	75.0

Incidence Calculated by No. of Tissues Scored (3) - 1.0 mg base/kg/day
 (1) - 0 mg base/kg/day (4) - 4.0 mg base/kg/day
 (2) - 0.1 mg base/kg/day

PATHOLOGY ASSOCIATES INTERNATIONAL
ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

PROJECT SUMMARY

STUDY ID : STUDY NUMBER 219

STUDY NUMBER: SN219

FATE: ALL

SEX: FEMALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:		Control	Low	Mid	High
		(1)	(2)	(3)	(4)
NUMBER OF ANIMALS:		4	4	4	4
		# %	# %	# %	# %
SPLEEN	# EX	4	4	4	4
Pigmentation		1 25.0	2 50.0	4 100.0	4 100.0
Congestion		1 25.0	0 0.0	0 0.0	1 25.0
Siderotic plaque		1 25.0	1 25.0	0 0.0	0 0.0
Mineralization, serosa		0 0.0	0 0.0	0 0.0	1 25.0
PANCREAS	# EX	4	4	4	4
Inflammation, chronic, duct		1 25.0	1 25.0	1 25.0	1 25.0
INTESTINE SMALL, DUODENUM	# EX	4	4	4	4
Abscess, crypt		2 50.0	2 50.0	0 0.0	2 50.0
LIVER	# EX	4	4	4	4
Inflammation, chronic		4 100.0	4 100.0	4 100.0	4 100.0
Pigmentation, Kupffer cell		0 0.0	2 50.0	4 100.0	4 100.0
Inflammation, subacute, centrilobular		0 0.0	0 0.0	0 0.0	2 50.0
GALLBLADDER	# EX	4	4	4	4
Accumulation, lymphocyte		3 75.0	3 75.0	2 50.0	2 50.0
Pigmentation, macrophage, submucosa		0 0.0	0 0.0	0 0.0	1 25.0
Ectopic pancreas		0 0.0	0 0.0	0 0.0	1 25.0
ADRENAL GLAND	# EX	4	4	4	4
Congestion		1 25.0	0 0.0	0 0.0	0 0.0
Vacuolation, cortex		2 50.0	1 25.0	1 25.0	0 0.0
SALIVARY GLAND	# EX	4	4	4	4
Inflammation, chronic		2 50.0	1 25.0	1 25.0	2 50.0
LYMPH NODE, MANDIBULAR	# EX	4	4	4	4
Pigmentation, macrophage		2 50.0	2 50.0	4 100.0	4 100.0
Hemorrhage		1 25.0	0 0.0	1 25.0	0 0.0

Incidence Calculated by No. of Tissues Scored

(1) - 0 mg base/kg/day

(2) - 0.1 mg base/kg/day

(3) - 1.0 mg base/kg/day

(4) - 4.0 mg base/kg/day

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

PROJECT SUMMARY

STUDY ID : STUDY NUMBER 219

STUDY NUMBER: SN219

FATE: ALL

SEX: FEMALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:		Control	Low	Mid	High
		(1)	(2)	(3)	(4)
NUMBER OF ANIMALS:		4	4	4	4
		# %	# %	# %	# %
INTESTINE SMALL, JEJUNUM	# EX	4	4	4	4
Congestion		1 25.0	2 50.0	1 25.0	1 25.0
INTESTINE LARGE, COLON	# EX	4	4	4	4
TONSIL	# EX	4	4	4	4
Bacterial colony		1 25.0	2 50.0	0 0.0	1 25.0
Inflammation, acute, lumen		3 75.0	3 75.0	2 50.0	3 75.0
Pigmentation, macrophage		0 0.0	0 0.0	1 25.0	4 100.0
INTESTINE SMALL, ILEUM	# EX	4	4	4	4
Congestion, Peyer's patch		0 0.0	0 0.0	0 0.0	1 25.0
LYMPH NODE, MESENTERIC	# EX	4	4	4	4
Hemorrhage		4 100.0	4 100.0	4 100.0	2 50.0
Pigmentation, macrophage		0 0.0	0 0.0	4 100.0	4 100.0
TONGUE	# EX	4	4	4	4
DIAPHRAGM	# EX	4	4	4	4
THYMUS	# EX	4	4	4	4
Atrophy		1 25.0	1 25.0	1 25.0	1 25.0
URINARY BLADDER	# EX	4	4	4	4
SKELETAL MUSCLE	# EX	4	4	4	4
Fat infiltration		0 0.0	2 50.0	0 0.0	0 0.0
SKIN	# EX	4	4	4	4

Incidence Calculated by No. of Tissues Scored

(1) - 0 mg base/kg/day

(2) - 0.1 mg base/kg/day

(3) - 1.0 mg base/kg/day

(4) - 4.0 mg base/kg/day

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

 PROJECT SUMMARY

STUDY ID : STUDY NUMBER 219

STUDY NUMBER: SN219

FATE: ALL

SEX: FEMALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:	Control		Low		Mid		High	
	(1)		(2)		(3)		(4)	
NUMBER OF ANIMALS:	4		4		4		4	
	#	%	#	%	#	%	#	%
MAMMARY GLAND	#	EX	4		4		4	
Lactation	1	25.0	2	50.0	2	50.0	0	0.0
THYROID GLAND	#	EX	4		4		4	
Inflammation, chronic	1	25.0	1	25.0	0	0.0	0	0.0
Fatty infiltration	0	0.0	0	0.0	1	25.0	0	0.0
PARATHYROID GLAND	#	EX	4		4		4	
Cyst	0	0.0	2	50.0	0	0.0	0	0.0
PITUITARY GLAND	#	EX	4		4		4	
Cyst	0	0.0	2	50.0	0	0.0	1	25.0
INTESTINE LARGE, CECUM	#	EX	4		4		4	
STOMACH	#	EX	4		4		4	
Accumulation, lymphocyte	4	100.0	4	100.0	4	100.0	3	75.0
OVARY	#	EX	4		4		4	
Mineralization, oocyte	1	25.0	0	0.0	0	0.0	0	0.0
UTERUS	#	EX	4		4		4	
Oilatation	1	25.0	0	0.0	1	25.0	0	0.0
PERIPHERAL NERVE, SCIATIC	#	EX	4		4		4	
Inflammation, chronic, perivascular	0	0.0	1	25.0	0	0.0	0	0.0
URETER	#	EX	4		4		4	
EYE	#	EX	4		4		4	
Inflammation, chronic, retina	0	0.0	0	0.0	0	0.0	1	25.0

 Incidence Calculated by No. of Tissues Scored

(1) - 0 mg base/kg/day

(2) - 0.1 mg base/kg/day

(3) - 1.0 mg base/kg/day

(4) - 4.0 mg base/kg/day

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

PROJECT SUMMARY

STUDY ID : STUDY NUMBER 219
 FATE: ALL

STUDY NUMBER: SN219

SEX: FEMALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

GROUP:	Control (1)	Low (2)	Mid (3)	High (4)
NUMBER OF ANIMALS:	4	4	4	4
	# %	# %	# %	# %
OPTIC NERVE	# EX 4	4	4	4
BONE, RIB	# EX 4	4	4	4
BONE MARROW, RIB	# EX 4	4	4	4
Hyperplasia	0 0.0	0 0.0	1 25.0	4 100.0
LYMPH NODE, MEDIASTINAL	# EX 0	0	0	2
Accumulation, pigmented macrophages	0 0.0	0 0.0	0 0.0	2 100.0
Hemorrhage	0 0.0	0 0.0	0 0.0	2 100.0
LYMPH NODE, BRONCHIAL	# EX 0	0	1	4
Accumulation, pigmented macrophage	0 0.0	0 0.0	1 100.0	4 100.0
Hemorrhage	0 0.0	0 0.0	1 100.0	1 25.0

Incidence Calculated by No. of Tissues Scored (3) - 1.0 mg base/kg/day
 (1) - 0 mg base/kg/day (4) - 4.0 mg base/kg/day
 (2) - 0.1 mg base/kg/day

DRAFT

Draft Pathology Report
Toxicology Research Laboratory
Study Number 219

SECTION III
SEVERITY SUMMARY

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

SEVERITY SUMMARY

STUDY ID : STUDY NUMBER 219
 FATE: ALL

STUDY NUMBER: SN219

SEX: MALE

GROUP:	Control (1)	Low (2)	Mid (3)	High (4)
NUMBER OF ANIMALS:	4	4	4	4
	# SEV	# SEV	# SEV	# SEV
BRAIN, FORE	# EX 4	4	4	4
Gliosis, focal	1 0.25	0 0.00	0 0.00	0 0.00
BRAIN, MID	# EX 4	4	4	4
SPINAL CORD, THORACIC	# EX 4	4	4	4
Hemorrhage	2 0.50	0 0.00	1 0.25	1 0.25
BRAIN, HIND	# EX 4	4	4	4
HEART	# EX 4	4	4	4
Angiectasis, focal, valve	0 0.00	1 0.50	0 0.00	0 0.00
BLOOD VESSEL, AORTA	# EX 4	4	4	4
TRACHEA	# EX 4	4	4	4
Inflammation, chronic	1 0.25	1 0.25	2 0.50	0 0.00
ESOPHAGUS	# EX 4	4	4	4
LUNG	# EX 4	4	4	4
Accumulation, lymphocyte, perivascular	2 0.50	2 0.50	3 0.75	2 0.50
Inflammation, chronic, interstitium	0 0.00	0 0.00	4 1.25	4 2.75
Accumulation, foamy macrophages	0 0.00	0 0.00	4 2.00	4 3.00
Hemorrhage	0 0.00	0 0.00	0 0.00	1 0.50
KIDNEY	# EX 4	4	4	4
Mineralization, medulla	4 1.00	4 1.00	4 1.00	4 1.00
Pigmentation, epithelium, cortex	0 0.00	0 0.00	2 0.50	4 2.50
Inflammation, subacute, medulla	0 0.00	1 0.50	0 0.00	0 0.00
SPLEEN	# EX 4	4	4	4
Pigmentation	2 1.00	1 0.25	3 1.25	4 2.50

Severity Calculated by No. of Tissues Scored (3) - 1.0 mg base/kg/day
 (1) - 0 mg base/kg/day (4) - 4.0 mg base/kg/day
 (2) - 0.1 mg base/kg/day

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

SEVERITY SUMMARY

STUDY ID : STUDY NUMBER 219

STUDY NUMBER: SN219

FATE: ALL

SEX: MALE

GROUP:	Control	Low	Mid	High
	(1)	(2)	(3)	(4)
NUMBER OF ANIMALS:	4	4	4	4
	# SEV	# SEV	# SEV	# SEV
SPLEEN	# EX 4	4	4	4
Congestion	0 0.00	0 0.00	1 0.50	0 0.00
PANCREAS	# EX 4	4	4	4
Inflammation, chronic, duct	1 0.25	0 0.00	1 0.25	1 0.25
INTESTINE SMALL,DUODENUM	# EX 4	4	4	4
Abscess, crypt	0 0.00	0 0.00	0 0.00	1 0.25
LIVER	# EX 4	4	4	4
Inflammation, chronic	4 1.25	4 1.00	4 1.00	4 1.00
Pigmentation, Kupffer cell	0 0.00	0 0.00	3 0.75	4 2.50
Inflammation, subacute, centrilobular	0 0.00	0 0.00	0 0.00	3 0.75
GALLBLADDER	# EX 4	4	4	4
Accumulation, lymphocyte	3 0.75	2 0.75	3 0.75	3 0.75
Pigmentation, macrophage, submucosa	0 0.00	0 0.00	0 0.00	2 1.00
ADRENAL GLAND	# EX 4	4	4	4
Congestion	0 0.00	1 0.25	0 0.00	1 0.25
SALIVARY GLAND	# EX 4	4	4	4
Inflammation, chronic	2 0.50	1 0.25	2 0.50	0 0.00
LYMPH NODE,MANDIBULAR	# EX 4	4	4	4
Pigmentation, macrophage	4 1.00	2 0.50	4 1.00	4 2.50
INTESTINE SMALL,JEJUNUM	# EX 4	4	4	4
Congestion	2 1.00	2 0.75	3 1.00	2 0.75
Congestion, Peyer's patch	0 0.00	0 0.00	0 0.00	1 0.50
INTESTINE LARGE,COLON	# EX 4	4	4	4

Severity Calculated by No. of Tissues Scored

(3) - 1.0 mg base/kg/day

(1) - 0 mg base/kg/day

(4) - 4.0 mg base/kg/day

(2) - 0.1 mg base/kg/day

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

SEVERITY SUMMARY

STUDY ID : STUDY NUMBER 219
 FATE: ALL

STUDY NUMBER: SN219

SEX: MALE

GROUP:	Control (1)	Low (2)	Mid (3)	High (4)
NUMBER OF ANIMALS:	4	4	4	4
	# SEV	# SEV	# SEV	# SEV
TONSIL	# EX 4	4	4	4
Inflammation, acute, lumen	2 0.75	1 0.25	2 0.50	4 1.00
Pigmentation, macrophage	0 0.00	0 0.00	3 0.75	4 2.50
INTESTINE SMALL, ILEUM	# EX 4	4	4	4
Congestion, mucosa	2 0.50	0 0.00	1 0.25	0 0.00
Congestion, Peyer's patch	2 1.25	1 0.50	2 0.75	1 0.50
LYMPH NODE, MESENTERIC	# EX 4	4	4	4
Hemorrhage	3 1.75	2 0.75	2 0.75	2 0.50
Pigmentation, macrophage	0 0.00	0 0.00	3 0.75	4 2.00
TONGUE	# EX 4	4	4	4
DIAPHRAGM	# EX 4	4	4	4
THYMUS	# EX 3	4	4	4
Cyst	1 0.33	0 0.00	0 0.00	0 0.00
Atrophy	1 0.67	1 0.50	0 0.00	2 0.75
URINARY BLADDER	# EX 4	4	4	4
SKELETAL MUSCLE	# EX 4	4	4	4
SKIN	# EX 4	4	4	4
MAMMARY GLAND	# EX 4	4	4	4
THYROID GLAND	# EX 4	4	4	4
PARATHYROID GLAND	# EX 4	4	4	4

Severity Calculated by No. of Tissues Scored

(1) - 0 mg base/kg/day

(2) - 0.1 mg base/kg/day

(3) - 1.0 mg base/kg/day

(4) - 4.0 mg base/kg/day

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

SEVERITY SUMMARY

STUDY ID : STUDY NUMBER 219
 FATE: ALL

STUDY NUMBER: SN219

SEX: MALE

GROUP:		Control	Low	Mid	High
		(1)	(2)	(3)	(4)
NUMBER OF ANIMALS:		4	4	4	4
		# SEV	# SEV	# SEV	# SEV
PITUITARY GLAND	# EX	4	4	4	4
Cyst		2 0.75	2 0.75	1 0.75	3 1.25
INTESTINE LARGE, CECUM	# EX	4	4	4	4
Congestion, Peyer's patch		1 0.25	0 0.00	1 0.25	0 0.00
STOMACH	# EX	4	4	4	4
Accumulation, lymphocyte		3 1.25	4 1.25	4 1.00	4 1.50
TESTES	# EX	4	4	4	4
EPIDIDYMISS	# EX	4	4	4	4
Inflammation, chronic		0 0.00	0 0.00	0 0.00	1 0.25
PERIPHERAL NERVE, SCIATIC	# EX	4	4	4	4
URETER	# EX	4	4	4	4
EYE	# EX	4	4	4	4
OPTIC NERVE	# EX	4	4	4	4
PROSTATE	# EX	4	4	4	4
Inflammation, chronic		2 0.50	0 0.00	3 0.75	0 0.00
Inflammation, chronic, active		0 0.00	0 0.00	0 0.00	1 0.50
Atrophy, focal, epithelium		0 0.00	0 0.00	3 0.75	1 0.50
BONE, RIB	# EX	4	4	4	4
BONE MARROW, RIB	# EX	4	4	4	4
Hyperplasia		0 0.00	0 0.00	1 0.25	3 1.25

Severity Calculated by No. of Tissues Scored

(1) - 0 mg base/kg/day

(2) - 0.1 mg base/kg/day

(3) - 1.0 mg base/kg/day

(4) - 4.0 mg base/kg/day

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

SEVERITY SUMMARY

STUDY ID : STUDY NUMBER 219

STUDY NUMBER: SN219

FATE: ALL

SEX: MALE

GROUP:	Control (1)	Low (2)	Mid (3)	High (4)
NUMBER OF ANIMALS:	4	4	4	4
	# SEV	# SEV	# SEV	# SEV
LYMPH NODE, MEDIASTINAL	# EX 0	1	0	2
Accumulation, pigmented macrophages	0 0.00	0 0.00	0 0.00	2 2.00
Hemorrhage	0 0.00	1 2.00	0 0.00	2 2.00
LYMPH NODE, BRONCHIAL	# EX 0	0	2	4
Accumulation, pigmented macrophage	0 0.00	0 0.00	2 2.50	4 3.00
Hemorrhage	0 0.00	0 0.00	0 0.00	1 0.50

Severity Calculated by No. of Tissues Scored

(1) - 0 mg base/kg/day

(2) - 0.1 mg base/kg/day

(3) - 1.0 mg base/kg/day

(4) - 4.0 mg base/kg/day

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

SEVERITY SUMMARY

STUDY ID : STUDY NUMBER 219
 FATE: ALL

STUDY NUMBER: SN219

SEX: FEMALE

GROUP:		Control (1)	Low (2)	Mid (3)	High (4)
NUMBER OF ANIMALS:		4	4	4	4
	# EX	# SEV	# SEV	# SEV	# SEV
BRAIN,FORE	4	4	4	4	4
BRAIN,MID	4	4	4	4	4
Inflammation, chronic, focal	1 0.25	0 0.00	0 0.00	0 0.00	0 0.00
SPINAL CORD,THORACIC	4	3	4	4	4
Hemorrhage	2 0.50	1 0.33	1 0.25	1 0.25	1 0.25
Mineralization, focal	1 0.25	0 0.00	0 0.00	0 0.00	0 0.00
BRAIN,HIND	4	4	4	4	4
HEART	4	4	4	4	4
BLOOD VESSEL,AORTA	4	4	4	4	4
TRACHEA	4	4	4	4	4
Inflammation, chronic	1 0.25	1 0.25	1 0.25	1 0.25	1 0.25
ESOPHAGUS	4	4	4	4	4
Inflammation, chronic	0 0.00	1 0.25	0 0.00	0 0.00	0 0.00
LUNG	4	4	4	4	4
Accumulation, lymphocyte, perivascular	2 0.50	3 0.75	3 0.75	3 0.75	3 0.75
Inflammation, chronic, interstitium	0 0.00	0 0.00	4 1.25	4 2.25	4 2.25
Accumulation, foamy macrophages	0 0.00	0 0.00	4 1.50	4 2.75	4 2.75
Hemorrhage	1 0.25	1 0.25	1 0.25	1 0.25	1 0.25
KIDNEY	4	4	4	4	4
Mineralization, medulla	4 1.00	4 1.00	4 1.00	4 1.00	4 1.00
Pigmentation, epithelium, cortex	0 0.00	1 0.25	0 0.00	2 0.75	2 0.75
Inflammation, chronic, interstitium	1 0.25	1 0.25	1 0.25	0 0.00	0 0.00
Nephropathy	2 0.50	0 0.00	0 0.00	3 0.75	3 0.75

Severity Calculated by No. of Tissues Scored
 (1) - 0 mg base/kg/day
 (2) - 0.1 mg base/kg/day

(3) - 1.0 mg base/kg/day
 (4) - 4.0 mg base/kg/day

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

SEVERITY SUMMARY

STUDY ID : STUDY NUMBER 219

STUDY NUMBER: SN219

FATE: ALL

SEX: FEMALE

GROUP:	Control (1)	Low (2)	Mid (3)	High (4)
NUMBER OF ANIMALS:	4	4	4	4
	# SEV	# SEV	# SEV	# SEV
SPLEEN	# EX 4	4	4	4
Pigmentation	1 0.25	2 0.50	4 2.00	4 2.00
Congestion	1 0.25	0 0.00	0 0.00	1 0.50
Mineralization, serosa	0 0.00	0 0.00	0 0.00	1 0.50
PANCREAS	# EX 4	4	4	4
Inflammation, chronic, duct	1 0.25	1 0.25	1 0.25	1 0.25
INTESTINE SMALL,DUODENUM	# EX 4	4	4	4
Abscess, crypt	2 0.50	2 0.50	0 0.00	2 0.50
LIVER	# EX 4	4	4	4
Inflammation, chronic	4 1.25	4 1.00	4 1.50	4 1.00
Pigmentation, Kupffer cell	0 0.00	2 0.50	4 2.00	4 2.00
Inflammation, subacute, centrilobular	0 0.00	0 0.00	0 0.00	2 0.50
GALLBLADDER	# EX 4	4	4	4
Accumulation, lymphocyte	3 1.00	3 0.75	2 0.75	2 0.50
Pigmentation, macrophage, submucosa	0 0.00	0 0.00	0 0.00	1 0.25
Ectopic pancreas	0 0.00	0 0.00	0 0.00	1 0.75
ADRENAL GLAND	# EX 4	4	4	4
Congestion	1 0.25	0 0.00	0 0.00	0 0.00
Vacuolation, cortex	2 0.50	1 0.25	1 0.25	0 0.00
SALIVARY GLAND	# EX 4	4	4	4
Inflammation, chronic	2 0.50	1 0.50	1 0.25	2 0.50
LYMPH NODE,MANDIBULAR	# EX 4	4	4	4
Pigmentation, macrophage	2 0.50	2 0.75	4 1.00	4 1.75
Hemorrhage	1 0.25	0 0.00	1 0.25	0 0.00

Severity Calculated by No. of Tissues Scored

(1) - 0 mg base/kg/day

(2) - 0.1 mg base/kg/day

(3) - 1.0 mg base/kg/day

(4) - 4.0 mg base/kg/day

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

SEVERITY SUMMARY

STUDY ID : STUDY NUMBER 219
 FATE: ALL

STUDY NUMBER: SN219

SEX: FEMALE

GROUP:		Control (1)	Low (2)	Mid (3)	High (4)
NUMBER OF ANIMALS:		4	4	4	4
	# EX	# SEV	# SEV	# SEV	# SEV
INTESTINE SMALL, JEJUNUM	4	4	4	4	4
Congestion	1 0.25	2 0.50	1 0.25	1 0.25	
INTESTINE LARGE, COLON	4	4	4	4	
TONSIL	4	4	4	4	
Inflammation, acute, lumen	3 0.75	3 0.75	2 0.50	3 0.75	
Pigmentation, macrophage	0 0.00	0 0.00	1 0.75	4 3.00	
INTESTINE SMALL, ILEUM	4	4	4	4	
Congestion, Peyer's patch	0 0.00	0 0.00	0 0.00	1 0.25	
LYMPH NODE, MESENTERIC	4	4	4	4	
Hemorrhage	4 1.00	4 1.00	4 1.00	2 0.50	
Pigmentation, macrophage	0 0.00	0 0.00	4 1.25	4 1.75	
TONGUE	4	4	4	4	
DIAPHRAGM	4	4	4	4	
THYMUS	4	4	4	4	
Atrophy	1 0.25	1 0.25	1 0.25	1 0.25	
URINARY BLADDER	4	4	4	4	
SKELETAL MUSCLE	4	4	4	4	
Fat infiltration	0 0.00	2 0.75	0 0.00	0 0.00	
SKIN	4	4	4	4	
MAMMARY GLAND	4	4	4	4	

Severity Calculated by No. of Tissues Scored (3) - 1.0 mg base/kg/day
 (1) - 0 mg base/kg/day (4) - 4.0 mg base/kg/day
 (2) - 0.1 mg base/kg/day

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

SEVERITY SUMMARY

STUDY ID : STUDY NUMBER 219

STUDY NUMBER: SN219

FATE: ALL

SEX: FEMALE

GROUP:		Control	Low	Mid	High
		(1)	(2)	(3)	(4)
NUMBER OF ANIMALS:		4	4	4	4
		# SEV	# SEV	# SEV	# SEV
THYROID GLAND	# EX	4	4	4	4
Inflammation, chronic		1 0.75	1 0.25	0 0.00	0 0.00
Fatty infiltration		0 0.00	0 0.00	1 0.50	0 0.00
PARATHYROID GLAND	# EX	4	4	4	4
Cyst		0 0.00	2 0.50	0 0.00	0 0.00
PITUITARY GLAND	# EX	4	4	4	4
Cyst		0 0.00	2 0.50	0 0.00	1 0.25
INTESTINE LARGE, CECUM	# EX	4	4	4	4
STOMACH	# EX	4	4	4	4
Accumulation, lymphocyte		4 1.75	4 1.00	4 1.25	3 0.75
OVARY	# EX	4	4	4	4
Mineralization, oocyte		1 0.25	0 0.00	0 0.00	0 0.00
UTERUS	# EX	4	4	4	4
Dilatation		1 0.25	0 0.00	1 0.50	0 0.00
PERIPHERAL NERVE, SCIATIC	# EX	4	4	4	4
Inflammation, chronic, perivascular		0 0.00	1 0.25	0 0.00	0 0.00
URETER	# EX	4	4	4	4
EYE	# EX	4	4	4	4
Inflammation, chronic, retina		0 0.00	0 0.00	0 0.00	1 0.50
OPTIC NERVE	# EX	4	4	4	4
BONE, RIB	# EX	4	4	4	4

Severity Calculated by No. of Tissues Scored

(3) - 1.0 mg base/kg/day

(1) - 0 mg base/kg/day

(4) - 4.0 mg base/kg/day

(2) - 0.1 mg base/kg/day

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

SEVERITY SUMMARY

STUDY ID : STUDY NUMBER 219
 FATE: ALL

STUDY NUMBER: SN219

SEX: FEMALE

GROUP:	Control (1)	Low (2)	Mid (3)	High (4)
NUMBER OF ANIMALS:	4	4	4	4
	# SEV	# SEV	# SEV	# SEV
BONE MARROW, RIB Hyperplasia	# EX 4 0 0.00	4 0 0.00	4 1 0.25	4 4 1.75
LYMPH NODE, MEDIASTINAL	# EX 0	0	0	2
Accumulation, pigmented macrophages	0 0.00	0 0.00	0 0.00	2 2.00
Hemorrhage	0 0.00	0 0.00	0 0.00	2 2.50
LYMPH NODE, BRONCHIAL	# EX 0	0	1	4
Accumulation, pigmented macrophage	0 0.00	0 0.00	1 3.00	4 3.00
Hemorrhage	0 0.00	0 0.00	1 1.00	1 0.25

Severity Calculated by No. of Tissues Scored

(1) - 0 mg base/kg/day

(2) - 0.1 mg base/kg/day

(3) - 1.0 mg base/kg/day

(4) - 4.0 mg base/kg/day

SECTION IV
TABULATED ANIMAL DATA

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219
 FATE: ALL

STUDY NUMBER: SN219
 GROUP: Control: 0 mg base/kg/day
 SEX: MALE

ANIMAL ID:	8915	8922	8909	8911
BRAIN,FORE	N	N	N	
Gliosis, focal	-	-	-	1
BRAIN,MID	N	N	N	N
SPINAL CORD,THORACIC	N	N		
Hemorrhage	-	-	1	1
BRAIN,HIND	N	N	N	N
HEART	N	N	N	N
BLOOD VESSEL,AORTA	N	N	N	N
TRACHEA	N	N	N	
Inflammation, chronic	-	-	-	1
ESOPHAGUS	N	N	N	N
LUNG	N	N		
Accumulation, lymphocyte, perivascular	-	-	1	1
KIDNEY				
Mineralization, medulla	1	1	1	1
SPLEEN		N		N
Pigmentation	2	-	2	-
PANCREAS	N	N	N	
Inflammation, chronic, duct	-	-	-	1
INTESTINE SMALL,DUODENUM	N	N	N	N
LIVER				

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

 TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219

STUDY NUMBER: SN219

FATE: ALL

GROUP: Control: 0 mg base/kg/day

SEX: MALE

ANIMAL ID:	8915	8922	8909	8911
LIVER				
Inflammation, chronic	1	2	1	1
GALLBLADDER		N		
Accumulation, lymphocyte	1	-	1	1
ADRENAL GLAND	N	N	N	N
SALIVARY GLAND	N			N
Inflammation, chronic	-	1	1	-
LYMPH NODE, MANDIBULAR				
Pigmentation, macrophage	1	1	1	1
INTESTINE SMALL, JEJUNUM		N		N
Congestion	2	-	2	-
INTESTINE LARGE, COLON	N	N	N	N
TONSIL	N			N
Bacterial colony	-	-	P	-
Inflammation, acute, lumen	-	1	2	-
INTESTINE SMALL, ILEUM		N		N
Congestion, mucosa	1	-	1	-
Congestion, Peyer's patch	2	-	3	-
LYMPH NODE, MESENTERIC		N		
Hemorrhage	2	-	3	2
TONGUE	N	N	N	N
DIAPHRAGM	N	N	N	N
THYMUS	N	U		N
Cyst	-	-	1	-

 See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

 TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219

STUDY NUMBER: SN219

FATE: ALL

GROUP: Control: 0 mg base/kg/day

SEX: MALE

ANIMAL ID:	8915	8922	8909	8911
THYMUS	N	U		N
Atrophy	-	-	2	-
URINARY BLADDER	N	N	N	N
SKELETAL MUSCLE	N	N	N	N
SKIN	N	N	N	N
MAMMARY GLAND	N	N	N	N
THYROID GLAND	N	N	N	N
PARATHYROID GLAND	N	N	N	N
PITUITARY GLAND		N		N
Cyst	2	-	1	-
INTESTINE LARGE,CECUM	N	N		N
Congestion, Peyer's patch	-	-	1	-
STOMACH			N	
Accumulation, lymphocyte	2	2	-	1
TESTES	N	N	N	N
EPIDIDYMIS	N	N	N	N
PERIPHERAL NERVE,SCIATIC	N	N	N	N
URETER	N	N	N	N
EYE	N	N	N	N
OPTIC NERVE	N	N	N	N

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219
FATE: ALL

STUDY NUMBER: SN219
GROUP: Control: 0 mg base/kg/day
SEX: MALE

ANIMAL ID:	8915	8922	8909	8911
PROSTATE		N	N	
Inflammation, chronic	1	-	-	1
BONE, RIB	N	N	N	N
BONE MARROW, RIB	N	N	N	N

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

 TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219

FATE: ALL

STUDY NUMBER: SN219

GROUP: Low: 0.1 mg base/kg/day

SEX: MALE

ANIMAL ID:	8923	8907	8924	8919
BRAIN,FORE	N	N	N	N
BRAIN,MID	N	N	N	N
SPINAL CORD,THORACIC	N	N	N	N
BRAIN,HIND	N	N	N	N
HEART	N	N	N	
Angiectasis, focal, valve	-	-	-	2
BLOOD VESSEL,AORTA	N	N	N	N
TRACHEA		N	N	N
Inflammation, chronic	1	-	-	-
ESOPHAGUS	N	N	N	N
LUNG			N	N
Accumulation, lymphocyte, perivascular	1	1	-	-
KIDNEY				
Mineralization, medulla	1	1	1	1
Inflammation, subacute, medulla	-	-	2	-
SPLEEN	N	N		
Pigmentation	-	-	1	-
Siderotic plaque	-	-	P	P
PANCREAS	N	N	N	N
INTESTINE SMALL,DUODENUM	N	N	N	N
LIVER				
Inflammation, chronic	1	1	1	1

 See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

 TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219
 FATE: ALL

STUDY NUMBER: SN219
 GROUP: Low: 0.1 mg base/kg/day
 SEX: MALE

ANIMAL ID:	8923	8907	8924	8919
GALLBLADDER			N	N
Accumulation, lymphocyte	1	2	-	-
ADRENAL GLAND	N	N	N	
Congestion	-	-	-	1
SALIVARY GLAND	N		N	N
Inflammation, chronic	-	1	-	-
LYMPH NODE, MANDIBULAR	N		N	
Pigmentation, macrophage	-	1	-	1
INTESTINE SMALL, JEJUNUM	N	N		
Congestion	-	-	2	1
INTESTINE LARGE, COLON	N	N	N	N
TONSIL	N		N	N
Bacterial colony	-	P	-	-
Inflammation, acute, lumen	-	1	-	-
INTESTINE SMALL, ILEUM	N	N	N	
Congestion, Peyer's patch	-	-	-	2
LYMPH NODE, MESENTERIC	N	N		
Hemorrhage	-	-	2	1
TONGUE	N	N	N	N
DIAPHRAGM	N	N	N	N
THYMUS	N	N	N	
Atrophy	-	-	-	2
URINARY BLADDER	N	N	N	N

 See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219
 FATE: ALL

STUDY NUMBER: SN219
 GROUP: Low: 0.1 mg base/kg/day
 SEX: MALE

ANIMAL ID:	8923	8907	8924	8919
SKELETAL MUSCLE	N	N	N	N
SKIN	N	N	N	N
MAMMARY GLAND	N	N	N	N
THYROID GLAND	N	N	N	N
PARATHYROID GLAND	N	N	N	N
PITUITARY GLAND	N			N
Cyst	-	2	1	-
INTESTINE LARGE,CECUM	N	N	N	N
STOMACH				
Accumulation, lymphocyte	1	1	1	2
TESTES	N	N	N	N
EPIDIDYMIS	N	N	N	N
PERIPHERAL NERVE,SCIATIC	N	N	N	N
URETER	N	N	N	N
EYE	N	N	N	N
OPTIC NERVE	N	N	N	N
PROSTATE	N	N	N	N
BONE, RIB	N	N	N	N
BONE MARROW, RIB	N	N	N	N

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219

STUDY NUMBER: SN219

FATE: ALL

GROUP: Low: 0.1 mg base/kg/day

SEX: MALE

ANIMAL ID:	8923	8907	8924	8919
LYMPH NODE, MEDIASTINAL Hemorrhage	-	-	2	-

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219

FATE: ALL

STUDY NUMBER: SN219

GROUP: Mid: 1.0 mg base/kg/day

SEX: MALE

ANIMAL ID:	8917	8910	8913	8914
BRAIN,FORE	N	N	N	N
BRAIN,MID	N	N	N	N
SPINAL CORD,THORACIC Hemorrhage	1	-	-	-
BRAIN,HIND	N	N	N	N
HEART	N	N	N	N
BLOOD VESSEL,AORTA	N	N	N	N
TRACHEA Inflammation, chronic	1	-	1	-
ESOPHAGUS	N	N	N	N
LUNG Accumulation, lymphocyte, perivascular	1	1	-	1
Inflammation, chronic, interstitium	1	1	1	2
Accumulation, foamy macrophages	2	2	2	2
KIDNEY Mineralization, medulla	1	1	1	1
Pigmentation, epithelium, cortex	1	1	-	-
SPLEEN Pigmentation	2	2	-	1
Congestion	2	-	-	-
Siderotic plaque	-	-	-	P
PANCREAS Inflammation, chronic, duct	-	1	-	-
INTESTINE SMALL,DUODENUM	N	N	N	N

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

 TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219

FATE: ALL

STUDY NUMBER: SN219

GROUP: Mid: 1.0 mg base/kg/day

SEX: MALE

ANIMAL ID:	8917	8910	8913	8914
LIVER				
Inflammation, chronic	1	1	1	1
Pigmentation, Kupffer cell	-	1	1	1
GALLBLADDER	N			
Accumulation, lymphocyte	-	1	1	1
ADRENAL GLAND	N	N	N	N
SALIVARY GLAND	N	N		
Inflammation, chronic	-	-	1	1
LYMPH NODE, MANDIBULAR				
Pigmentation, macrophage	1	1	1	1
INTESTINE SMALL, JEJUNUM			N	
Congestion	1	2	-	1
INTESTINE LARGE, COLON	N	N	N	N
TONSIL		N		
Bacterial colony	-	-	P	-
Inflammation, acute, lumen	-	-	1	1
Pigmentation, macrophage	1	-	1	1
INTESTINE SMALL, ILEUM			N	N
Congestion, mucosa	1	-	-	-
Congestion, Peyer's patch	2	1	-	-
LYMPH NODE, MESENTERIC			N	
Hemorrhage	1	2	-	-
Pigmentation, macrophage	1	1	-	1
TONGUE	N	N	N	N
DIAPHRAGM	N	N	N	N

 See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

 TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219

STUDY NUMBER: SN219

FATE: ALL

GROUP: Mid: 1.0 mg base/kg/day

SEX: MALE

ANIMAL ID:	8917	8910	8913	8914
THYMUS	N	N	N	N
URINARY BLADDER	N	N	N	N
SKELETAL MUSCLE	N	N	N	N
SKIN	N	N	N	N
MAMMARY GLAND	N	N	N	N
THYROID GLAND	N	N	N	N
PARATHYROID GLAND	N	N	N	N
PITUITARY GLAND	N	N		N
Cyst	-	-	3	-
INTESTINE LARGE,CECUM		N	N	N
Congestion, Peyer's patch	1	-	-	-
STOMACH				
Accumulation, lymphocyte	1	1	1	1
TESTES	N	N	N	N
EPIDIDYMIS	N	N	N	N
PERIPHERAL NERVE,SCIATIC	N	N	N	N
URETER	N	N	N	N
EYE	N	N	N	N
OPTIC NERVE	N	N	N	N
PROSTATE			N	

 See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219

FATE: ALL

STUDY NUMBER: SN219

GROUP: Mid: 1.0 mg base/kg/day

SEX: MALE

ANIMAL ID:	8917	8910	8913	8914
PROSTATE			N	
Inflammation, chronic	1	1	-	1
Atrophy, focal, epithelium	1	1	-	1
BONE, RIB	N	N	N	N
BONE MARROW, RIB	N	N		N
Hyperplasia	-	-	1	-
LYMPH NODE, BRONCHIAL				
Accumulation, pigmented macrophage	-	-	2	3

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

 TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219

STUDY NUMBER: SN219

FATE: ALL

GROUP: High: 4.0 mg base/kg/day

SEX: MALE

ANIMAL ID:	8918	8908	8926	8921
BRAIN,FORE	N	N	N	N
BRAIN,MID	N	N	N	N
SPINAL CORD,THORACIC		N	N	N
Hemorrhage	1	-	-	-
BRAIN,HIND	N	N	N	N
HEART	N	N	N	N
BLOOD VESSEL,AORTA	N	N	N	N
TRACHEA	N	N	N	N
ESOPHAGUS	N	N	N	N
LUNG				
Accumulation, lymphocyte, perivascular	-	1	-	1
Inflammation, chronic, interstitium	2	3	3	3
Accumulation, foamy macrophages	3	3	3	3
Hemorrhage	-	-	-	2
KIDNEY				
Mineralization, medulla	1	1	1	1
Pigmentation, epithelium, cortex	3	3	2	2
SPLEEN				
Pigmentation	3	3	3	1
Siderotic plaque	P	-	-	-
PANCREAS				
Inflammation, chronic, duct	-	1	-	-
INTESTINE SMALL,DUODENUM				
Abscess, crypt	1	-	-	-

 See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

 TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219
 FATE: ALL

STUDY NUMBER: SN219
 GROUP: High: 4.0 mg base/kg/day
 SEX: MALE

ANIMAL ID:	8918	8908	8926	8921
LIVER				
Inflammation, chronic	1	1	1	1
Pigmentation, Kupffer cell	2	2	3	3
Inflammation, subacute, centrilobular	1	1	-	1
GALLBLADDER				
Accumulation, lymphocyte	1	1	1	-
Pigmentation, macrophage, submucosa	2	2	-	-
ADRENAL GLAND				
Congestion	-	-	1	-
SALIVARY GLAND				
	N	N	N	N
LYMPH NODE, MANDIBULAR				
Pigmentation, macrophage	3	2	2	3
INTESTINE SMALL, JEJUNUM				
Congestion	-	2	1	-
Congestion, Peyer's patch	-	-	2	-
INTESTINE LARGE, COLON				
	N	N	N	N
TONSIL				
Bacterial colony	-	-	P	-
Inflammation, acute, lumen	1	1	1	1
Pigmentation, macrophage	3	3	1	3
INTESTINE SMALL, ILEUM				
Congestion, Peyer's patch	-	-	2	-
LYMPH NODE, MESENTERIC				
Hemorrhage	-	1	1	-
Pigmentation, macrophage	3	1	2	2
TONGUE				
	N	N	N	N

 See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

 TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219
 FATE: ALL

STUDY NUMBER: SN219
 GROUP: High: 4.0 mg base/kg/day
 SEX: MALE

ANIMAL ID:	8918	8908	8926	8921
DIAPHRAGM	N	N	N	N
THYMUS		N		N
Atrophy	2	-	1	-
URINARY BLADDER	N	N	N	N
SKELETAL MUSCLE	N	N	N	N
SKIN	N	N	N	N
MAMMARY GLAND	N	N	N	N
THYROID GLAND	N	N	N	N
PARATHYROID GLAND	N	N	N	N
PITUITARY GLAND	N			
Cyst	-	2	2	1
INTESTINE LARGE, CECUM	N	N	N	N
STOMACH				
Accumulation, lymphocyte	3	1	1	1
TESTES	N	N	N	N
EPIDIDYMIS		N	N	N
Inflammation, chronic	1	-	-	-
PERIPHERAL NERVE, SCIATIC	N	N	N	N
URETER	N	N	N	N
EYE	N	N	N	N

 See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

 TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219
 FATE: ALL

STUDY NUMBER: SN219
 GROUP: High: 4.0 mg base/kg/day
 SEX: MALE

ANIMAL ID:	8918	8908	8926	8921
OPTIC NERVE	N	N	N	N
PROSTATE	N	N		N
Inflammation, chronic, active	-	-	2	-
Atrophy, focal, epithelium	-	-	2	-
BONE, RIB	N	N	N	N
BONE MARROW, RIB				N
Hyperplasia	2	2	1	-
LYMPH NODE, MEDIASTINAL				
Accumulation, pigmented macrophages	-	-	3	1
Hemorrhage	-	-	2	2
LYMPH NODE, BRONCHIAL				
Accumulation, pigmented macrophage	3	3	3	3
Hemorrhage	-	-	-	2

 See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219
 FATE: ALL

STUDY NUMBER: SN219
 GROUP: Control: 0 mg base/kg/day
 SEX: FEMALE

ANIMAL ID:	8929	8942	8930	8938
BRAIN,FORE	N	N	N	N
BRAIN,MID	N		N	N
Inflammation, chronic, focal	-	1	-	-
SPINAL CORD,THORACIC		N		
Hemorrhage	1	-	-	1
Mineralization, focal	-	-	1	-
BRAIN,HIND	N	N	N	N
HEART	N	N	N	N
BLOOD VESSEL,AORTA	N	N	N	N
TRACHEA	N		N	N
Inflammation, chronic	-	1	-	-
ESOPHAGUS	N	N	N	N
LUNG	N			
Accumulation, lymphocyte, perivascular	-	1	-	1
Hemorrhage	-	-	1	-
KIDNEY				
Mineralization, medulla	1	1	1	1
Inflammation, chronic, interstitium	1	-	-	-
Nephropathy	-	1	1	-
SPLEEN	N			
Pigmentation	-	1	-	-
Congestion	-	-	-	1
Siderotic plaque	-	-	P	-
PANCREAS		N	N	N
Inflammation, chronic, duct	1	-	-	-

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219
 FATE: ALL

STUDY NUMBER: SN219
 GROUP: Control: 0 mg base/kg/day
 SEX: FEMALE

ANIMAL ID:	8929	8942	8930	8938
INTESTINE SMALL,DUODENUM	N	N		
Abscess, crypt	-	-	1	1
LIVER				
Inflammation, chronic	1	2	1	1
GALLBLADDER		N		
Accumulation, lymphocyte	1	-	1	2
ADRENAL GLAND	N			N
Congestion	-	1	-	-
Vacuolation, cortex	-	1	1	-
SALIVARY GLAND	N			N
Inflammation, chronic	-	1	1	-
LYMPH NODE,MANDIBULAR	N	N		
Pigmentation, macrophage	-	-	1	1
Hemorrhage	-	-	1	-
INTESTINE SMALL,JEJUNUM	N		N	N
Congestion	-	1	-	-
INTESTINE LARGE,COLON	N	N	N	N
TONSIL	N			
Bacterial colony	-	-	-	P
Inflammation, acute, lumen	-	1	1	1
INTESTINE SMALL,ILEUM	N	N	N	N
LYMPH NODE,MESENTERIC				
Hemorrhage	1	1	1	1
TONGUE	N	N	N	N

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

 TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219
 FATE: ALL

STUDY NUMBER: SN219
 GROUP: Control: 0 mg base/kg/day
 SEX: FEMALE

ANIMAL ID:	8929	8942	8930	8938
DIAPHRAGM	N	N	N	N
THYMUS	N		N	N
Atrophy	-	1	-	-
URINARY BLADDER	N	N	N	N
SKELETAL MUSCLE	N	N	N	N
SKIN	N	N	N	N
MAMMARY GLAND	N	N		N
Lactation	-	-	P	-
THYROID GLAND	N	N		N
Inflammation, chronic	-	-	3	-
PARATHYROID GLAND	N	N	N	N
PITUITARY GLAND	N	N	N	N
INTESTINE LARGE, CECUM	N	N	N	N
STOMACH				
Accumulation, lymphocyte	1	1	3	2
OVARY	N	N	N	
Mineralization, oocyte	-	-	-	1
UTERUS	N	N		N
Dilatation	-	-	1	-
PERIPHERAL NERVE, SCIATIC	N	N	N	N
URETER	N	N	N	N

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219
FATE: ALL

STUDY NUMBER: SN219
GROUP: Control: 0 mg base/kg/day
SEX: FEMALE

ANIMAL ID:	8929	8942	8930	8938
EYE	N	N	N	N
OPTIC NERVE	N	N	N	N
BONE, RIB	N	N	N	N
BONE MARROW, RIB	N	N	N	N

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

 TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219
 FATE: ALL

STUDY NUMBER: SN219
 GROUP: Low: 0.1 mg base/kg/day
 SEX: FEMALE

ANIMAL ID:	8935	8937	8934	8945
BRAIN,FORE	N	N	N	N
BRAIN,MID	N	N	N	N
SPINAL CORD,THORACIC Hemorrhage	1	-	-	-
BRAIN,HIND	N	N	N	N
HEART	N	N	N	N
BLOOD VESSEL,AORTA	N	N	N	N
TRACHEA Inflammation, chronic	-	-	1	-
ESOPHAGUS Inflammation, chronic	1	-	-	-
LUNG Accumulation, lymphocyte, perivascular Hemorrhage	1	1	-	1
	-	1	-	-
KIDNEY Mineralization, medulla	1	1	1	1
Pigmentation, epithelium, cortex	-	1	-	-
Inflammation, chronic, interstitium	-	-	-	1
SPLEEN Pigmentation	-	-	1	1
Siderotic plaque	-	-	-	P
PANCREAS Inflammation, chronic, duct	-	-	-	1
INTESTINE SMALL,DUODENUM	N		N	

 See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

 TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219
 FATE: ALL

STUDY NUMBER: SN219
 GROUP: Low: 0.1 mg base/kg/day
 SEX: FEMALE

ANIMAL ID:	8935	8937	8934	8945
INTESTINE SMALL,DUODENUM	N		N	
Abscess, crypt	-	1	-	1
LIVER				
Inflammation, chronic	1	1	1	1
Pigmentation, Kupffer cell	-	1	-	1
GALLBLADDER			N	
Accumulation, lymphocyte	1	1	-	1
ADRENAL GLAND	N		N	N
Vacuolation, cortex	-	1	-	-
SALIVARY GLAND	N		N	N
Inflammation, chronic	-	2	-	-
LYMPH NODE,MANDIBULAR	N		N	
Pigmentation, macrophage	-	2	-	1
INTESTINE SMALL,JEJUNUM	N			N
Congestion	-	1	1	-
INTESTINE LARGE,COLON	N	N	N	N
TONSIL				
Bacterial colony	P	-	P	-
Inflammation, acute, lumen	1	1	-	1
INTESTINE SMALL,ILEUM	N	N	N	N
LYMPH NODE,MESENTERIC				
Hemorrhage	1	1	1	1
TONGUE	N	N	N	N
DIAPHRAGM	N	N	N	N

 See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219
 FATE: ALL

STUDY NUMBER: SN219
 GROUP: Low: 0.1 mg base/kg/day
 SEX: FEMALE

ANIMAL ID:	8935	8937	8934	8945
THYMUS	N		N	N
Atrophy	-	1	-	-
URINARY BLADDER	N	N	N	N
SKELETAL MUSCLE		N	N	
Fat infiltration	2	-	-	1
SKIN	N	N	N	N
MAMMARY GLAND			N	N
Lactation	P	P	-	-
THYROID GLAND	N		N	N
Inflammation, chronic	-	1	-	-
PARATHYROID GLAND	N			N
Cyst	-	1	1	-
PITUITARY GLAND	N			N
Cyst	-	1	1	-
INTESTINE LARGE,CECUM	N	N	N	N
STOMACH				
Accumulation, lymphocyte	1	1	1	1
OVARY	N	N	N	N
UTERUS	N	N	N	N
PERIPHERAL NERVE,SCIATIC		N	N	N
Inflammation, chronic, perivascular	1	-	-	-
URETER	N	N	N	N

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219
FATE: ALL

STUDY NUMBER: SN219
GROUP: Low: 0.1 mg base/kg/day
SEX: FEMALE

ANIMAL ID:	8935	8937	8934	8945
EYE	N	N	N	N
OPTIC NERVE	N	N	N	N
BONE, RIB	N	N	N	N
BONE MARROW, RIB	N	N	N	N

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219
 FATE: ALL

STUDY NUMBER: SN219
 GROUP: Mid: 1.0 mg base/kg/day
 SEX: FEMALE

ANIMAL ID:	8928	8940	8931	8943
BRAIN,FORE	N	N	N	N
BRAIN,MID	N	N	N	N
SPINAL CORD,THORACIC		N	N	N
Hemorrhage	1	-	-	-
BRAIN,HIND	N	N	N	N
HEART	N	N	N	N
BLOOD VESSEL,AORTA	N	N	N	N
TRACHEA	N		N	N
Inflammation, chronic	-	1	-	-
ESOPHAGUS	N	N	N	N
LUNG				
Accumulation, lymphocyte, perivascular	1	1	-	1
Inflammation, chronic, interstitium	1	1	2	1
Accumulation, foamy macrophages	1	2	2	1
Hemorrhage	-	1	-	-
KIDNEY				
Mineralization, medulla	1	1	1	1
Inflammation, chronic, interstitium	1	-	-	-
SPLEEN				
Pigmentation	2	2	1	3
PANCREAS	N	N		N
Inflammation, chronic, duct	-	-	1	-
INTESTINE SMALL,DUODENUM	N	N	N	N

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219
 FATE: ALL

STUDY NUMBER: SN219
 GROUP: Mid: 1.0 mg base/kg/day
 SEX: FEMALE

ANIMAL ID:	8928	8940	8931	8943
LIVER				
Inflammation, chronic	2	2	1	1
Pigmentation, Kupffer cell	1	3	2	2
GALLBLADDER			N	N
Accumulation, lymphocyte	2	1	-	-
ADRENAL GLAND	N	N		N
Vacuolation, cortex	-	-	1	-
SALIVARY GLAND		N	N	N
Inflammation, chronic	1	-	-	-
LYMPH NODE, MANDIBULAR				
Pigmentation, macrophage	1	1	1	1
Hemorrhage	-	1	-	-
INTESTINE SMALL, JEJUNUM	N	N		N
Congestion	-	-	1	-
INTESTINE LARGE, COLON	N	N	N	N
TONSIL		N	N	
Inflammation, acute, lumen	1	-	-	1
Pigmentation, macrophage	-	-	-	3
INTESTINE SMALL, ILEUM	N	N	N	N
LYMPH NODE, MESENTERIC				
Hemorrhage	1	1	1	1
Pigmentation, macrophage	1	1	1	2
TONGUE	N	N	N	N
DIAPHRAGM	N	N	N	N

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

 TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219

STUDY NUMBER: SN219

FATE: ALL

GROUP: Mid: 1.0 mg base/kg/day

SEX: FEMALE

ANIMAL ID:	8928	8940	8931	8943
THYMUS	N	N		N
Atrophy	-	-	1	-
URINARY BLADDER	N	N	N	N
SKELETAL MUSCLE	N	N	N	N
SKIN	N	N	N	N
MAMMARY GLAND	N		N	
Lactation	-	P	-	P
THYROID GLAND	N	N		N
Fatty infiltration	-	-	2	-
PARATHYROID GLAND	N	N	N	N
PITUITARY GLAND	N	N	N	N
INTESTINE LARGE,CECUM	N	N	N	N
STOMACH				
Accumulation, Lymphocyte	1	1	2	1
OVARY	N	N	N	N
UTERUS	N	N	N	
Dilatation	-	-	-	2
PERIPHERAL NERVE,SCIATIC	N	N	N	N
URETER	N	N	N	N
EYE	N	N	N	N
OPTIC NERVE	N	N	N	N

 See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219
FATE: ALL

STUDY NUMBER: SN219
GROUP: Mid: 1.0 mg base/kg/day
SEX: FEMALE

ANIMAL ID:	8928	8940	8931	8943
BONE, RIB	N	N	N	N
BONE MARROW, RIB	N		N	N
Hyperplasia	-	1	-	-
LYMPH NODE, BRONCHIAL				
Accumulation, pigmented macrophage	-	3	-	-
Hemorrhage	-	1	-	-

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

 TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219

FATE: ALL

STUDY NUMBER: SN219

GROUP: High: 4.0 mg base/kg/day

SEX: FEMALE

ANIMAL ID:	8933	8936	8941	8944
BRAIN,FORE	N	N	N	N
BRAIN,MID	N	N	N	N
SPINAL CORD,THORACIC Hemorrhage	1	-	-	-
BRAIN,HIND	N	N	N	N
HEART	N	N	N	N
BLOOD VESSEL,AORTA	N	N	N	N
TRACHEA Inflammation, chronic	-	-	1	-
ESOPHAGUS	N	N	N	N
LUNG Accumulation, lymphocyte, perivascular	-	1	1	1
Inflammation, chronic, interstitium	2	2	3	2
Accumulation, foamy macrophages	3	3	3	2
Hemorrhage	-	-	1	-
KIDNEY Mineralization, medulla	1	1	1	1
Pigmentation, epithelium, cortex	-	-	2	1
Nephropathy	1	1	1	-
SPLEEN Pigmentation	3	2	2	1
Congestion	-	-	2	-
Mineralization, serosa	-	-	2	-

 See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219
 FATE: ALL
 STUDY NUMBER: SN219
 GROUP: High: 4.0 mg base/kg/day
 SEX: FEMALE

ANIMAL ID:	8933	8936	8941	8944
PANCREAS	N	N		N
Inflammation, chronic, duct	-	-	1	-
INTESTINE SMALL,DUODENUM		N		N
Abscess, crypt	1	-	1	-
LIVER				
Inflammation, chronic	1	1	1	1
Pigmentation, Kupffer cell	2	2	2	2
Inflammation, subacute, centrilobular	1	-	1	-
GALLBLADDER	N			N
Accumulation, lymphocyte	-	1	1	-
Pigmentation, macrophage, submucosa	-	-	1	-
Ectopic pancreas	-	3	-	-
ADRENAL GLAND	N	N	N	N
SALIVARY GLAND	N	N		
Inflammation, chronic	-	-	1	1
LYMPH NODE,MANDIBULAR				
Pigmentation, macrophage	2	1	2	2
INTESTINE SMALL,JEJUNUM	N	N		N
Congestion	-	-	1	-
INTESTINE LARGE,COLON	N	N	N	N
TONSIL				
Bacterial colony	-	-	-	P
Inflammation, acute, lumen	-	1	1	1
Pigmentation, macrophage	3	3	3	3
INTESTINE SMALL,ILEUM	N	N		N
Congestion, Peyer's patch	-	-	1	-

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

 TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219

STUDY NUMBER: SN219

FATE: ALL

GROUP: High: 4.0 mg base/kg/day

SEX: FEMALE

ANIMAL ID:	8933	8936	8941	8944
LYMPH NODE, MESENTERIC				
Hemorrhage	-	-	1	1
Pigmentation, macrophage	2	2	2	1
TONGUE	N	N	N	N
DIAPHRAGM	N	N	N	N
THYMUS	N		N	N
Atrophy	-	1	-	-
URINARY BLADDER	N	N	N	N
SKELETAL MUSCLE	N	N	N	N
SKIN	N	N	N	N
MAMMARY GLAND	N	N	N	N
THYROID GLAND	N	N	N	N
PARATHYROID GLAND	N	N	N	N
PITUITARY GLAND	N	N	N	
Cyst	-	-	-	1
INTESTINE LARGE, CECUM	N	N	N	N
STOMACH	N			
Accumulation, lymphocyte	-	1	1	1
OVARY	N	N	N	N
UTERUS	N	N	N	N
PERIPHERAL NERVE, SCIATIC	N	N	N	N

See Reports Code Table for Symbol Definitions

PATHOLOGY ASSOCIATES INTERNATIONAL
 ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
 TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

TABULATED ANIMAL DATA

STUDY ID : STUDY NUMBER 219

STUDY NUMBER: SN219

FATE: ALL

GROUP: High: 4.0 mg base/kg/day

SEX: FEMALE

ANIMAL ID:	8933	8936	8941	8944
URETER	N	N	N	N
EYE	N	N	N	
Inflammation, chronic, retina	-	-	-	2
OPTIC NERVE	N	N	N	N
BONE,RIB	N	N	N	N
BONE MARROW,RIB				
Hyperplasia	2	2	2	1
LYMPH NODE,MEDIASTINAL				
Accumulation, pigmented macrophages	-	2	2	-
Hemorrhage	-	2	3	-
LYMPH NODE,BRONCHIAL				
Accumulation, pigmented macrophage	3	3	3	3
Hemorrhage	-	1	-	-

See Reports Code Table for Symbol Definitions

DRAFT

Draft Pathology Report
Toxicology Research Laboratory
Study Number 219

SECTION V

CORRELATION OF GROSS AND MICROSCOPIC (MICRO) FINDINGS

PATHOLOGY ASSOCIATES INTERNATIONAL
ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

CORRELATION OF GROSS & MICRO

STUDY ID : STUDY NUMBER 219

FATE: ALL

STUDY NUMBER: SN219

GROUP: Control: 0 mg base/kg/day

SEX: MALE

Animal ID: 8909

Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:

LYMPH NODE, MESENTERIC - PIGMENTATION, MOTTLED

Related Histopathology:

LYMPH NODE, MESENTERIC - Hemorrhage

PATHOLOGY ASSOCIATES INTERNATIONAL
ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

CORRELATION OF GROSS & MICRO

STUDY ID : STUDY NUMBER 219
FATE: ALL

STUDY NUMBER: SN219
GROUP: Low: 0.1 mg base/kg/day
SEX: MALE

Animal ID: 8907
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:
LIVER - MEDIAN LOBE, ADHESION

Related Histopathology:
LIVER - No corresponding lesion

Animal ID: 8924
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:
LYMPH NODE,MEDIASTINAL - PIGMENTATION, MOTTLED

LYMPH NODE,MESENTERIC - PIGMENTATION, MOTTLED

Related Histopathology:
LYMPH NODE,MEDIASTINAL - Hemorrhage

LYMPH NODE,MESENTERIC - Hemorrhage

Animal ID: 8919
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:
HEART - ATRIOVENTRICULAR VALVE, MASS, 8X8X8 MM, RED

Related Histopathology:
HEART - Angiectasis, focal, valve

PATHOLOGY ASSOCIATES INTERNATIONAL
ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

CORRELATION OF GROSS & MICRO

STUDY ID : STUDY NUMBER 219
FATE: ALL

STUDY NUMBER: SN219
GROUP: Mid: 1.0 mg base/kg/day
SEX: MALE

Animal ID: 8917
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:
LUNG - BILATERAL, PIGMENTATION, DARK

Related Histopathology:
LUNG - No corresponding lesion

Animal ID: 8910
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:
THYMUS - SMALL

LUNG - BILATERAL, PIGMENTATION, DARK

INTESTINE SMALL, JEJUNUM - PIGMENTATION, DARK

Related Histopathology:
THYMUS - No corresponding lesion

LUNG - No corresponding lesion

INTESTINE SMALL, JEJUNUM - Congestion

Animal ID: 8913
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:
LYMPH NODE, BRONCHIAL - PIGMENTATION, MOTTLED

Related Histopathology:
LYMPH NODE, BRONCHIAL - Accumulation, pigmented
macrophage

Animal ID: 8914
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:
LUNG - BILATERAL, FOCUS, MULTIPLE, YELLOW

LYMPH NODE, BRONCHIAL - ENLARGED, MOTTLED

Related Histopathology:
LUNG - Inflammation, chronic, interstitium

LYMPH NODE, BRONCHIAL - Accumulation, pigmented
macrophage

PATHOLOGY ASSOCIATES INTERNATIONAL
ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

CORRELATION OF GROSS & MICRO

STUDY ID : STUDY NUMBER 219

STUDY NUMBER: SN219

FATE: ALL

GROUP: High: 4.0 mg base/kg/day

SEX: MALE

Animal ID: 8918

Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:

Related Histopathology:

LUNG - BILATERAL, ENLARGED

LUNG - Accumulation, foamy macrophages

LYMPH NODE, BRONCHIAL - ENLARGED

LYMPH NODE, BRONCHIAL - Accumulation, pigmented macrophage

LUNG - BILATERAL, FOCUS, YELLOW, MULTIPLE

LUNG - Inflammation, chronic, interstitium

Animal ID: 8908

Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:

Related Histopathology:

LUNG - BILATERAL, FOCUS, 4X4 MM, YELLOW, MULTIPLE

LUNG - Inflammation, chronic, interstitium

LYMPH NODE, BRONCHIAL - ENLARGED, MOTTLED

LYMPH NODE, BRONCHIAL - Accumulation, pigmented macrophage

Animal ID: 8926

Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:

Related Histopathology:

LYMPH NODE, MEDIASTINAL - PIGMENTATION, MOTTLED

LYMPH NODE, MEDIASTINAL - Hemorrhage

LYMPH NODE, BRONCHIAL - PIGMENTATION, MOTTLED

LYMPH NODE, BRONCHIAL - Accumulation, pigmented macrophage

LUNG - FOCUS, 10X10 MM, YELLOW, MULTIPLE

LUNG - Inflammation, chronic, interstitium

LUNG - ENLARGED

LUNG - Accumulation, foamy macrophages

LYMPH NODE, MESENTERIC - PIGMENTATION, MOTTLED

LYMPH NODE, MESENTERIC - Hemorrhage

PATHOLOGY ASSOCIATES INTERNATIONAL
ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

CORRELATION OF GROSS & MICRO

STUDY ID : STUDY NUMBER 219
FATE: ALL

STUDY NUMBER: SN219
GROUP: High: 4.0 mg base/kg/day
SEX: MALE

Animal ID: 8921
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:
LUNG - BILATERAL, ENLARGED

Related Histopathology:
LUNG - Accumulation, foamy macrophages

LUNG - BILATERAL, FOCUS, 10X10 MM, YELLOW, MULTIPLE

LUNG - Inflammation, chronic, interstitium

LYMPH NODE, MEDIASTINAL - PIGMENTATION, MOTTLED

LYMPH NODE, MEDIASTINAL - Hemorrhage

LYMPH NODE, BRONCHIAL - PIGMENTATION, MOTTLED

LYMPH NODE, BRONCHIAL - Hemorrhage

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PATHOLOGY ASSOCIATES INTERNATIONAL
ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

CORRELATION OF GROSS & MICRO

STUDY ID : STUDY NUMBER 219

STUDY NUMBER: SN219

FATE: ALL

GROUP: Control: 0 mg base/kg/day

SEX: FEMALE

No Gross Observations for any animal in this group

PATHOLOGY ASSOCIATES INTERNATIONAL
ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

CORRELATION OF GROSS & MICRO

STUDY ID : STUDY NUMBER 219
FATE: ALL

STUDY NUMBER: SN219
GROUP: Low: 0.1 mg base/kg/day
SEX: FEMALE

Animal ID: 8937
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:
LUNG - LEFT, RIGHT, APICAL LOBE, PIGMENTATION,
MOTTLED, DARK

Related Histopathology:
LUNG - Hemorrhage

PATHOLOGY ASSOCIATES INTERNATIONAL
ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

CORRELATION OF GROSS & MICRO

STUDY ID : STUDY NUMBER 219

STUDY NUMBER: SN219

FATE: ALL

GROUP: Mid: 1.0 mg base/kg/day

SEX: FEMALE

Animal ID: 8940

Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:

LYMPH NODE,BRONCHIAL - ENLARGED, 25X15 MM, MOTTLED

Related Histopathology:

LYMPH NODE,BRONCHIAL - Accumulation, pigmented
macrophage

LUNG - BILATERAL, FOCUS, 1X1 MM, YELLOW, MULTIPLE

LUNG - Inflammation, chronic, interstitium

Animal ID: 8931

Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:

LUNG - BILATERAL, FOCUS, YELLOW, MULTIPLE

Related Histopathology:

LUNG - Inflammation, chronic, interstitium

Animal ID: 8943

Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:

UTERUS - BILATERAL, DILATATION

Related Histopathology:

UTERUS - Dilatation

PATHOLOGY ASSOCIATES INTERNATIONAL
ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

CORRELATION OF GROSS & MICRO

STUDY ID : STUDY NUMBER 219
FATE: ALL

STUDY NUMBER: SN219
GROUP: High: 4.0 mg base/kg/day
SEX: FEMALE

Animal ID: 8933
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:
LUNG - BILATERAL, FOCUS, MULTIPLE, YELLOW

LUNG - ENLARGED

LYMPH NODE, BRONCHIAL - PIGMENTATION, MOTTLED

Related Histopathology:
LUNG - Inflammation, chronic, interstitium

LUNG - Accumulation, foamy macrophages

LYMPH NODE, BRONCHIAL - Accumulation, pigmented macrophage

Animal ID: 8936
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:
LYMPH NODE, MEDIASTINAL - PIGMENTATION, MOTTLED

GALLBLADDER - MASS, 12X9X3 MM

LUNG - BILATERAL, FOCUS, MULTIPLE, YELLOW

LUNG - BILATERAL, ENLARGED

LYMPH NODE, BRONCHIAL - ENLARGED

Related Histopathology:
LYMPH NODE, MEDIASTINAL - Hemorrhage

GALLBLADDER - Ectopic pancreas

LUNG - Inflammation, chronic, interstitium

LUNG - Accumulation, foamy macrophages

LYMPH NODE, BRONCHIAL - Accumulation, pigmented macrophage

Animal ID: 8941
Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:
SPLEEN - PARENCHYMA, FOCUS, 1X1 MM, MULTIPLE, WHITE

LYMPH NODE, MEDIASTINAL - PIGMENTATION, DARK, RED

LYMPH NODE, BRONCHIAL - PIGMENTATION, MOTTLED

LUNG - BILATERAL, FOCUS, 4X5 MM, MULTIPLE, YELLOW

Related Histopathology:
SPLEEN - Mineralization, serosa

LYMPH NODE, MEDIASTINAL - Hemorrhage

LYMPH NODE, BRONCHIAL - Accumulation, pigmented macrophage

LUNG - Inflammation, chronic, interstitium

PATHOLOGY ASSOCIATES INTERNATIONAL
ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS
TOXICOLOGY RESEARCH LABORATORY STUDY NUMBER 219

CORRELATION OF GROSS & MICRO

STUDY ID : STUDY NUMBER 219

FATE: ALL

STUDY NUMBER: SN219

GROUP: High: 4.0 mg base/kg/day

SEX: FEMALE

Animal ID: 8944

Animal Fate: Scheduled sacrifice

Reference to Necropsy Record:

LYMPH NODE,BRONCHIAL - ENLARGED, MOTTLED

Related Histopathology:

LYMPH NODE,BRONCHIAL - Accumulation, pigmented
macrophage

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Draft Pathology Report
Toxicology Research Laboratory
Study Number 219

SECTION VI
QUALITY ASSURANCE STATEMENT

QUALITY ASSURANCE STATEMENT

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This histopathology project was inspected and audited by the PAI Quality Assurance Unit (QAU) as required by the Good Laboratory Practice (GLP) standards promulgated by the U.S. Food and Drug Administration. The pathology narrative report is an accurate reflection of the recorded data. The following table is a record of the inspections/audits performed and reported by the QAU:

Date of Inspection	Phase Inspected	Date Findings Reported to Management and Study Pathologist
08/07/97	Quality Control/Checkout	08/08/97
10/20/97	Individual Animal Data	10/20/97
10/20/97	Draft Pathology Report	10/20/97
10/22/97	Second Draft Pathology Report	10/22/97

Marie Puccini
 Marie Puccini
 Quality Assurance Unit
 PAI Illinois Division

10/22/97
 Date

One Year Oral Toxicity Study of WR238605 Succinate In Dogs
 TRL Study Number 219

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SECTION VII
BONE MARROW EVALUATION REPORT



Pathology Associates International

A Company of Science Applications International Corporation



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**BONE MARROW EVALUATION REPORT
FOR**

ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS

TRL STUDY NUMBER 219

**PREPARED FOR
TOXICOLOGY RESEARCH LABORATORY**

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I. Bone Marrow Evaluation Narrative

BONE MARROW EVALUATION REPORT
ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE
IN DOGS

INTRODUCTION

This report prepared by Pathology Associates International (PAI) for Toxicology Research Laboratory (UIC/TRL), University of Illinois at Chicago, Department of Pharmacology, 1940 West Taylor Street, Chicago, IL, 60612-7353, presents the results of bone marrow evaluation from dogs administered WR238605 succinate or vehicle, orally, one time each day for at least 52 weeks. The purpose of this study was to determine specific target organ toxicity, dose-response relationships, and a no observed adverse effect level of WR238605 succinate in Beagle dogs following one year of daily oral administration.

EXPERIMENTAL DESIGN AND METHODS

Sixteen dogs of each sex will be randomly assigned to one of four dose groups. Bone marrow smears were prepared from the rib of each animal at the scheduled necropsy during week 53. The smears were fixed in methanol, stained with a Wrights-Giemsa stain, and evaluated microscopically to determine the Myeloid:Erythroid (M:E) Ratio. The M:E Ratio was determined on a cell count of 500 cells.

RESULTS

M:E Ratio data are presented by timepoint, dose group and sex in Section II.

The M:E Ratios from bone marrow smears collected during the scheduled sacrifice in this study were all within normal limits.

CONCLUSION

Under the conditions of this study, WR238605 succinate did not result in any treatment-related changes in the M:E Ratio of the bone marrow of male and female dogs evaluated on study week 53.

Lynda L. Lanning, D.V.M., D.A.B.T.
October 16, 1997

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II. M:E Ratio Data

BONE MARROW M:E RATIO DATA

Group 1

WR238605 Succinate: 0.0 mg base/kg/day

ANIMAL NO.	8929	8942	8930	8938
	266:234	257:243	277:223	269:231
RATIO	1.14:1.00	1.06:1.00	1.24:1.00	1.16:1.00

Group 2

WR238605 Succinate: 0.1 mg base/kg/day

ANIMAL NO.	8935	8937	8934	8945
	280:220	272:228	263:237	270:230
RATIO	1.27:1.00	1.19:1.00	1.11:1.00	1.17:1.00

Group 3

WR238605 Succinate: 1.0 mg base/kg/day

ANIMAL NO.	8928	8940	8931	8943
	288:212	267:233	274:226	257:243
RATIO	1.36:1.00	1.15:1.00	1.21:1.00	1.06:1.00

Group 4

WR238605 Succinate: 4.0 mg base/kg/day

ANIMAL NO.	8941	8933	8936	8944
	261:239	301:199	274:226	269:231
RATIO	1.09:1.00	1.51:1.00	1.21:1.00	1.16:1.00

BONE MARROW M:E RATIO DATA

Group 1

WR238605 Succinate: 0.0 mg base/kg/day

ANIMAL NO.	8922	8915	8911	8909
	267:233	273:227	255:245	262:238
RATIO	1.15:1.00	1.20:1.00	1.04:1.00	1.10:1.00

Group 2

WR238605 Succinate: 0.1 mg base/kg/day

ANIMAL NO.	8923	8907	8919	8924
	270:230	246:254	265:235	277:223
RATIO	1.17:1.00	0.97:1.00	1.13:1.00	1.24:1.00

Group 3

WR238605 Succinate: 1.0 mg base/kg/day

ANIMAL NO.	8917	8910	8913	8914
	269:231	271:229	253:247	261:239
RATIO	1.16:1.00	1.18:1.00	1.02:1.00	1.09:1.00

Group 4

WR238605 Succinate: 4.0 mg base/kg/day

ANIMAL NO.	8918	8908	8926	8921
	266:234	280:220	275:225	247:253
RATIO	1.14:1.00	1.27:1.00	1.22:1.00	0.98:1.00

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III. Quality Assurance Statement



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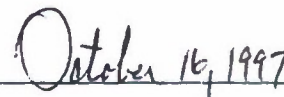
Bone Marrow Evaluation Report

**ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS**

UIC/TRL Study Number: 219

QUALITY ASSURANCE STATEMENT

This bone marrow evaluation project has been inspected and audited by the PAI Quality Assurance Unit (QAU) as required by the Good Laboratory Practice (GLP) regulations promulgated by the U.S. Food and Drug Administration. The bone marrow evaluation report is an accurate reflection of the recorded data. The following table is a record of the inspections/audits performed and reported by the QAU.

<u>Date of Inspection</u>	<u>Phase Inspected</u>	<u>Date Findings Reported to Management/ Study Pathologist</u>
09/15/97	Individual Animal Data	09/15/97
09/15/97	Draft Bone Marrow Evaluation Report	09/15/97
		
Sharon E. Abel Quality Assurance Specialist		Date

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APPENDIX N
Protocol and Protocol Amendments

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Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-9
Study No.: 219

ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS

1.0 PURPOSE OF THE STUDY:

The purpose of this study is to determine specific target organ toxicity, dose-response relationships, and a no observed adverse effect level of WR238605 succinate in Beagle dogs following one year of daily oral administration. The drug will be given as a suspension within a gelatin capsule. This study will be conducted in accordance with the specifications of the Sponsor as described in Task Order UIC-9. The protocol for this study was approved by the UIC Animal Care Committee (Appendix 1).

2.0 SPONSOR:

- 2.1 Name: U.S. Army Medical Materiel
Development Activity
- 2.2 Address: Fort Detrick
Frederick, MD 21702-5009
- 2.3 Representative: George J. Schieferstein, Ph.D.

3.0 TESTING FACILITY:

- 3.1 Name: Toxicology Research Laboratory (TRL)
- 3.2 Address: University of Illinois at Chicago (UIC)
Department of Pharmacology
1940 W. Taylor St.
Chicago, IL 60612-7353
- 3.3 Study Director: Barry S. Levine, D.Sc., D.A.B.T.

4.0 DATES:

- 4.1 Proposed Initiation of Dosing: 07/18/96
- 4.2 Proposed Necropsy Date(s): 07/17,18/97
- 4.3 Proposed Study Completion Date
(Draft Study Report): 11/18/97

5.0 TEST ARTICLE

5.1 Name or Code No: WR238605 Succinate (mole fraction = 0.8)
8-[4-Amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-(3-trifluoromethyl-phenoxy)quinoline succinate
Bottle No. BN65479
CAS No. 106635-81-8

5.2 TRL Chemical No: 0720614

5.3 Physical Description: Pale yellow powder.

5.4 Stability and Handling of Test Article:

5.4.1 Storage Conditions to Maintain Stability:

5.4.1.1 Temperature: 0 - 4°C.

5.4.1.2 Humidity: Ambient conditions.

5.4.1.3 Light: Protect from light; amber bottle or silver foil covering.

5.4.1.4 Special Requirements: None

5.4.2 Special Handling Procedures: Standard safety precautions including gloves, eye protection, mask, and lab coats.

5.4.3 Log of Test Article: The amount, date, identity of person(s) removing aliquots and the purpose for which each aliquot of the test article was removed from the batch will be documented. At termination of the study, all unused test article will be returned to the Sponsor if requested.

5.5 Analysis:

5.5.1 Identification: WR238605 Succinate Bottle No. BM12562 was previously identified by GC-MS.

5.5.2 Purity: Purity will be determined prior to dosing initiation, after approximately 6 months of dosing, and after completion of the 12 month dosing period.

6.0 PERSONNEL:

Study Director	Barry S. Levine, D.Sc., D.A.B.T.
Toxicologist	Alan P. Brown, Ph.D.
Pathologist	Robert L. Morrissey, D.V.M., Ph.D., D.A.C.V.P.
Analytical Chemist	Thomas Tolhurst, B.S.
Clinical Veterinarian	Terry Hewett, D.V.M., D.A.C.V.P.
Veterinarian Support	Documented in raw data
Clinical Laboratory	Maria Lang, A.H.T., C.V.T.
Cardiologist	Robert Hamlin, D.V.M., Ph.D., D.A.C.V.I.M.
Ophthalmologist	Samuel J. Vainisi D.V.M., D.A.V.C.O.
Tox. Lab Supervisor	Soudabeh Soura, B.S.
Lead Technician	Theresa O'Neill, B.S.
Quality Assurance	Ronald C. Schoenbeck

7.0 TEST SYSTEM:

- 7.1 Species: Dog
- 7.2 Strain: Beagle
- 7.3 Sex(s)/Number: 16 Males & 16 Females
- 7.4 Age of Animals: Approximately 7 - 8 months old upon initiation of treatment.
- 7.5 Weight of Animals: Approximately 10 - 12 kg (males) and \approx 8 - 10 kg (females) upon initiation of treatment.
- 7.6 Source of Animals: Marshall Farms, North Rose, NY.
- 7.7 Justification for Selection of Test System: The FDA requires the use of two animal species, one being a non-rodent, in preclinical toxicology studies. The dog is a standard and accepted non-rodent species for regulatory toxicology studies, and is specified by the Sponsor. This is a successive chronic toxicity study to a thirteen week oral toxicity study of WR238605 which included a thirteen week recovery period in dogs (UIC/TRL Study No. 097).
- 7.8 Procedure for Unique Identification of Test System: Upon arrival each animal will be given a facility unique number. This number will be coded on a subcutaneously implanted microchip and will also appear on a cage card visible on the front of each run. The cage card will additionally contain the study number, test article identification, treatment group number, sex and dose levels. Cage cards will be color-coded as a function of treatment group. Raw data records and specimens will also be identified by the unique test animal number.
- 7.9 Housing: The animals will be housed in an AAALAC-accredited facility. Animals will be housed in runs in a temperature (65 - 84°F) and humidity (50 \pm 20%) controlled room with a 12 hour light/12 hour dark cycle. All animals will be housed either singly or two/run within sex during the quarantine/pre-test period, but will be housed singly prior to dosing initiation and for the duration of the study. The run size, at least 15 square feet, is adequate to house dogs at the upper weight range as described in the *Guide for the Care and Use of Laboratory Animals*, DHHS (NIH) No. 86.23. All runs will be cleaned and fresh bedding replaced daily. The runs will be sanitized once every two weeks. The animal facility is redundantly wired to separate Commonwealth Edison power stations. In addition, the animal facility is tied into the UIC emergency generator.
- 7.10 Quarantine Procedure: Animals will be quarantined for approximately three weeks. During that time, the animals will be observed daily for signs of illness and all unusual observations will be reported to the Study Director, Toxicologist, or Clinical Veterinarian. Body weights and physical examinations will be done upon the dogs' arrival at the animal facility. Additionally, each dog will be lightly sprayed upon arrival with Para Pyrethrin Mist for fleas, lice, and ticks. Within a few days of arrival, hematology (to include methemoglobin level determination) and clinical chemistry tests, and fecal examination

for internal parasites will be performed. If parasites are found, the affected animal will be treated with a vermifuge approved by the Sponsor, and at least 10 days and a negative fecal examination will elapse before the animal is used on a study. Animals which demonstrate coccidia in their fecal samples will only be treated if they concurrently exhibit diarrhea. All dogs will have been vaccinated against canine distemper, infectious canine hepatitis, leptospirosis, parainfluenza, parvo, oral papilloma, and rabies by the animal supplier. In addition, the animal supplier will have conducted ECG examinations. Animals will be examined during quarantine and approved for use by the Clinical Veterinarian prior to being placed on test. Any sickly animal will be eliminated from the test animal selection process. If a selected animal appears sickly prior to initiation of treatment, it will be replaced by a healthy animal prior to treatment under the direction of the Study Director or Toxicologist. Quarantine release will be documented on the Clinical Veterinarian Log by the veterinarian prior to study initiation.

- 7.11 Food: Certified Canine Diet No. 5007 (PMI Feeds Inc., St. Louis, MO), approximately 400 g, will be provided daily from arrival until termination. Exactly 400 g will be provided when food consumption is measured. The food will be removed for an overnight fast (\approx 16 - 20 hours) prior to blood collection, overnight urine collection or scheduled sacrifice. Water will be available at all times.
- 7.12 Water: Tap water from an automatic watering system in which the room distribution lines are flushed daily will be provided *ad libitum* from arrival until termination. The water is not treated with additional chlorine or HCl.
- 7.13 There are no known contaminants in the feed or water which are expected to influence the study. A copy of the feed certification will be kept with the study records. The results of bi-monthly comprehensive chemical analyses of Chicago water are documented in files maintained by Quality Assurance.
- 7.14 It is not known if the animals will experience pain or distress during the study. Analgesic or anesthetic agents will confound the ability to determine the toxic potential of the test article, and therefore will not be used. If an animal is in severe pain or distress, following consultation with the veterinary staff, it will be euthanized in accordance with standard operating procedures.

8.0 EXPERIMENTAL DESIGN:

8.1 Treatment Groups:

<u>Treatment Group</u>	<u>Number of Males</u>	<u>Number of Females</u>	<u>Dose Level (mg base/kg/day)</u>	<u>Concentration (mg base/ml)</u>
1	4	4	0	0
2	4	4	0.1	0.625
3	4	4	1.0	6.25
4	4	4	4.0	25.0

Dose levels are selected by the Sponsor based upon the results of a previous thirteen week oral toxicity study of WR238605 with a thirteen week recovery period in dogs (UIC/TRL Study No. 097). The number of animals, 4/sex/dose, is routinely used in regulatory studies, and also is the number of animals for this species indicated in the FDA 1993 draft document entitled "Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food (Redbook II), Short-Term Toxicity Tests with Rodents and Non-Rodents". No such FDA document exists for the testing of drugs.

Upon dosing initiation, any unused dogs will become the responsibility of UIC.

- 8.2 Frequency and Route of Administration of the Test Article: The test article will be administered orally once daily as a suspension in a gelatin capsule (size 13; capacity 3.2 ml) starting on day 1 for at least 52 weeks. Control animals will receive the vehicle (i.e., the control article) within gelatin capsules. Dose volume will be 0.16 ml/kg/day. The specific volume to be administered will be adjusted on the basis of each animal's most recent body weight. The animals will be acclimated to the dosing procedure for at least three days prior to day 1 and will receive the vehicle within a gelatin capsule.
- 8.3 Justification of Route: Oral treatment is the intended clinical route and is specified by the Sponsor.
- 8.4 Procedure to Control Bias during the Assignment of Animals to Treatment Groups: The animals will be randomized separately by sex using a restricted randomization procedure, stratified by body weight. Baseline data including clinical pathology, ophthalmology and ECG data will be used to exclude animals and to select appropriate animals for randomization.
- 8.5 Test Article Vehicle: 1% Methylcellulose/0.2% Tween 80. Gelatin capsule (size 13; capacity 3.2 ml).
- 8.6 Test Article Dosage Form Preparation and Analyses: Concentrations of the dosing suspensions will be adjusted for test article purity and the base mole fraction, while the control articles comprising the vehicle will be assumed to be 100% pure. The 1% methylcellulose/0.2% Tween 80 vehicle will be prepared every two weeks by placing the required amount of deionized water in a beaker and then adding the required amount of methylcellulose and volume of Tween 80, using its specific gravity of 1.08 (1.0 g of methylcellulose and 0.2 g Tween 80 per 100 ml of deionized distilled water). One lot no. each of methylcellulose and Tween 80 will be used. The mixture will be stirred until homogeneous and then refrigerated.

The test article dosing suspensions will be prepared every two weeks. Stability data from a previously conducted dog toxicity study by gastric intubation demonstrated that WR238605 Succinate suspensions were stable for at least 28 days (UIC/TRL Study No. 047). Homogeneity data also obtained from UIC/TRL Study No. 047 demonstrated that the test article suspensions are homogeneous (coefficients of variation for sampling in the top, middle and bottom of several test suspensions were typically less than 4%).

Each test article dosing suspension will be prepared individually by adding the appropriate amount of WR238605 Succinate with the required volume of 1.0% methylcellulose/0.2% Tween 80 vehicle in a pre-calibrated beaker. The contents will be mixed with an Omni-Mixer homogenizer, for at least 5 minutes. All suspensions will be stored at 2 - 8°C, and will be allowed to warm to room temperature and stirred continuously before and during placement into gelatin capsules just prior to administration to each animal. Every other set of dosing suspensions (including controls), i.e., first, third, fifth etc., through approximately the first six months of treatment will be analyzed prior to use, and only suspensions within 10% of their target concentration will be used. Analyzed samples will also be analyzed for test article concentration after use. Tolerance of sample analysis after use will also be 10%, i.e., 10% of the "before use" assay value. If two consecutive analyses are outside of tolerance, a review of analytical chemistry procedures and personnel techniques will occur. Following Sponsor review of dosage formulation analyses through the first six months, every third set of subsequent formulations may be analyzed before and after use (approval will be provided by the Sponsor).

8.7 Type and Frequency of Observations, Tests, Analyses and Measurements:

- 8.7.1 Clinical Signs: All animals will be observed once daily for clinical signs of toxicity approximately 1 - 2 hours after dosing. Additionally, all animals will be observed for moribundity/mortality in the afternoon and immediately prior to dosing in the morning.
- 8.7.2 Clinical Observations: All animals will be subjected to a physical examination including examination of eyes and all orifices at test animal selection in the quarantine/pretest period and weekly commencing in week -1.
- 8.7.3 Body Weight: Body weights of all animals will be recorded at test animal selection in the quarantine/pretest period, weekly commencing in week -1, and at scheduled necropsy.
- 8.7.4 Food Consumption: Food consumption for all animals will be measured over an approximate 24 hour period twice during the quarantine/pretest period, and weekly during the treatment period.
- 8.7.5 Ophthalmologic Examinations: All dogs will be examined by indirect ophthalmoscopy during the quarantine/pretest period and in weeks 12, 25 and 51.
- 8.7.6 Clinical Pathology: Hematology and clinical chemistry parameters will be measured within one week of arrival (week -3), and in weeks -1, 4, 13, 26, and 52. The animals will be fasted overnight and sufficient blood will be collected from the jugular vein to measure the following parameters in random order. Water will be available *ad libitum* during all fasting periods.

Hematology

Activated partial thromboplastin time (APTT)	Mean corpuscular hemoglobin (MCH)
^a Erythrocyte count and morphology	Mean corpuscular hemoglobin concentration (MCHC)
Heinz bodies	Mean corpuscular volume (MCV)
Hematocrit	^b Methemoglobin
Hemoglobin	Platelet count
Leukocyte count, total and differential	Prothrombin time
	Reticulocyte count

^a Includes nucleated RBCs.

^b To be measured with a Co-oximeter (Instrumentation Laboratory, Model No. 482). The assay will be performed within one hour of sample collection. The specimens will be kept on wet ice prior to analysis.

Clinical Chemistry

Alanine aminotransferase (ALT)	Globulin (calculated)
Albumin	Glucose
Albumin/globulin ratio (calc.)	Haptoglobin
Aspartate aminotransferase (AST)	Lactate dehydrogenase (LDH)
Alkaline phosphatase	Inorganic phosphorus
Calcium	Potassium
Chloride	Sodium
Cholesterol	Total bilirubin
Creatinine	Total protein
Creatine kinase (CK)	Triglycerides
Gamma glutamyl transferase (GGT)	Urea nitrogen (BUN)

Urine specimens will be collected in weeks -1, 13, 26, and 52. Animals will not receive food during the overnight urine collection, but water will be available. The following parameters will be measured.

Urinalysis

Qualitative	
Bilirubin	Nitrite
Glucose	pH
Ketones	Protein
Occult Blood	Urobilinogen
Leukocytes	
Color	
Specific Gravity	
Microscopic examination of spun sediment	

DRAFT

Contract No.: DAMD17-92-C-2001

Task Order No.: UIC-9

Study No.: 219

Following anesthesia with sodium pentobarbital (I.V.; 20 - 30 mg/kg) prior to necropsy in week 53, a blood sample will be collected from the abdominal aorta for measurement of the following blood gases.

Arterial Blood Gases

pCO ₂	O ₂ Saturation
pH	pO ₂
HCO ₃ ⁻¹	Total CO ₂

- 8.7.7 Electrocardiography: Recordings from leads I, II, III, aV_F, aV_L and aV_R will be collected during the quarantine/pretest period and in weeks 12, 25, and 51. Analysis will include heart rate and duration of the P wave and PR, QRS and QT intervals.
- 8.7.8 Plasma Drug Levels: Blood samples will be collected from the jugular vein in Week -1 (when clinical pathology samples are collected), and just prior to treatment at the beginning of weeks 4, 8, 13, 26, 40 and 52 from each dog for the determination of plasma drug levels. The plasma samples will be stored frozen (-75 to -80°C) and sent to another facility as directed by the Sponsor. The plasma drug levels data will not be included in the study report.
- 8.7.9 Pathology: All animals which die on test or are killed if moribund will be necropsied. All remaining animals will be killed and necropsied in random order in Week 53. This will be accomplished by sodium pentobarbital anesthesia (i.v.; 20-30 mg/kg) and exsanguination. An extensive necropsy will be performed under the direction and supervision of the pathologist. Terminal fasted body weights will be collected prior to routine sacrifice.

The necropsy procedure will be a thorough and systematic examination and dissection of the animal viscera and carcass to include the external surface, all orifices, the cranial cavity, external surface of the brain, cross section of the spinal cord, the nasal cavity and nasal turbinates, thoracic, abdominal and pelvic cavities and their viscera, and cervical tissues and organs. The following tissues and organs will be collected and fixed in 10% neutral buffered formalin (NBF). The exception will be the eyes and optic nerve which will be fixed in 3% glutaraldehyde and the testes with epididymides which will be collected in Bouin's fixative.

REVISED PAGE	INITIAL: <i>BL</i>
STUDY NO: 219	DATE: 7/15/47

DRAFT

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-9
Study No.: 219

*Adrenal glands	*Ovaries
Aorta (thoracic)	Pancreas
*Brain (fore-, mid-, and hind-)	*Pituitary
Cecum	Prostate
Colon	Rib with costochondral junction
Diaphragm	Rib with marrow
Duodenum	Salivary gland (mandibular)
Esophagus	Sciatic nerve
Eyes and optic nerve	Skin
Gallbladder	Spinal cord (thoracic)
Gross lesions	*Spleen
*Heart	Stomach
Ileum	*Testes with epididymides
Jejunum	Thymus
*Kidneys	*Thyroid gland with parathyroids
*Liver (with gallbladder drained)	Tongue
*Lungs/Bronchi	Tonsil
Lymph nodes (mandibular and mesenteric)	Trachea
Mammary gland	Ureter
Muscle, skeletal	Urinary bladder
	Uterus

*Weighed at scheduled necropsy. Paired organs will be weighed as a unit.

The above tissues from all dogs found dead, sacrificed either *in extremis*, or sacrificed at scheduled necropsy will be embedded in paraffin, sectioned, stained with hematoxylin and eosin, and examined microscopically.

Bone marrow (rib) smears will be prepared and myeloid:erythroid (M:E) ratios will be determined for all animals at scheduled necropsy and for all animals sacrificed in a moribund state.

8.8 Statistical Analyses: For each sex, Analysis of Variance tests will be conducted on body weight, ECG measurements, hematology, clinical chemistry and organ weight data. Organ weight analyses will consider weights relative to brain weight. If a significant F ratio is obtained ($p \leq 0.05$), Dunnett's t test will be used for pairwise comparisons to the concurrent control group. Food consumption data will be analyzed by the Kruskal-Wallis test ($p \leq 0.05$). If a significant effect is seen, the Mann-Whitney U test will be used for pairwise comparisons to the control group. Frequency data such as incidence of mortality, gross necropsy observations and tissue morphology observations will be compared by Fisher's Exact Test or Chi-square analyses as necessary.

All statistical analysis procedures will compare treated to control animals at each time point. Data will not be corrected for baseline values, except that body weight analysis will include absolute values, weekly changes and total weight changes. Baseline clinical data will be used to assess the general

health of the animals, and may be used qualitatively to assist in the interpretation of potential drug-related changes following the initiation of treatment.

- 8.9 Deliverables: Quantitative data will be tabulated and presented in the report, which will include historical control clinical pathology data. In addition to the written report, individual data tables in "ASCII" form and summary data tables of parameters and variability will be transmitted to the Sponsor on magnetic media (computer diskette). The transcribed data on disk will no longer be considered GLP compliant.

9.0 RECORDS TO BE MAINTAINED:

All data generated during the conduct of the study, except those that are generated as direct computer input, shall be recorded directly, promptly, and accurately in ink in bound books with prenumbered pages or on worksheets that shall be bound during or at the conclusion of the nonclinical laboratory study. All data entries shall be dated on the day of entry and signed or initialed by the person entering the data. All appropriate computer and machine output shall be bound during or at the conclusion of the study.

Any changes in entries for whatever reason (e.g., to correct an error or transposition) shall be made so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and signed or identified at the time of data input. In automated data collection systems, the individual responsible for direct data input shall be identified at the time of data input. Any changes in automated data entries for whatever reason (e.g., to correct an error or transposition) shall be made in such a manner so as not to obscure the original entry, if possible, shall indicate the reason for such change, and shall be dated and signed by the responsible individual.

Upon completion of the study and submission of the final report, all raw data, documentation, specimens, test article reserves and other materials necessary to reconstruct the study will be stored in the UIC/TRL archives maintained by Quality Assurance.

All changes or revisions, and reasons therefore, to this protocol once it is approved shall be documented, signed by the Study Director and Sponsor, dated and maintained with the protocol.

10.0 REGULATORY REQUIREMENTS:

This study will be performed in compliance with the UIC/TRL Quality Assurance Program designed to conform with FDA Good Laboratory Practice Regulations and EPA Good Laboratory Practice Standards.

Will this study be submitted to a regulatory agency? Yes

If so, to which agency(ies)? U.S. Food and Drug Administration

Does the Sponsor Request that test article samples be returned? Possibly; direction will be provided by the Sponsor.

Does the Sponsor request that samples of the test article/carrier mixture(s) be returned to the Sponsor? No

DRAFT

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-9
Study No.: 219

11.0 PROTOCOL APPROVAL:

STUDY DIRECTOR:


Barry S. Levine, D.Sc. D.A.B.T.

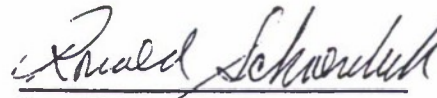
5/9/96
Date

TOXICOLOGIST:


Alan P. Brown, Ph.D.

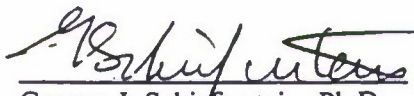
5/9/96
Date

QUALITY ASSURANCE:


Ronald Schoenbeck

5/9/96
Date

SPONSOR APPROVAL:


George J. Schieferstein, Ph.D.
Contracting Officer's
Representative (COR)

5/15/96
Date

COMMENTS FROM THE COR:

DRAFT

Office of the Vice Chancellor for Research (M/C 672)
310 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227
(312) 996-4995

Appendix 1

Manual No:

May 8, 1996

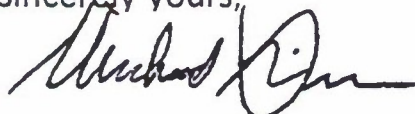
Barry S. Levine
Pharmacology
312G BGRC, M/C 868

Dear Dr. Levine:

The modifications requested in your correspondence of May 6, 1996 pertaining to your approved protocol ACC: #93-033-23: "One Year Oral Toxicity study of WR238605 Succinate in Dogs" have been reviewed in accordance with the Animal Care and Use Policies of the University of Illinois at Chicago. You will be pleased to know that the modifications were approved on May 8, 1996 and consequently the records of Animal Care Committee will be revised to reflect these changes.

Thank you for complying with the Animal Care Policies and Procedures of UIC.

Sincerely yours,



Michael W. Levine, Ph.D.
Chair, Animal Care Committee

MWL:st
XC: BRL

PROTOCOL AMENDMENT

Study No.: 219
Title: ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS

1. Page 1 Section 4.0

Add the following dates:

Proposed Initiation of Dosing: 07/18/96

Proposed Necropsy Date(s): 07/17,18/97

Proposed Study Completion Date
(Draft Study Report): 11/18/97

Reason: To indicate the study dates.

2. Page 2 Section 5.1

Change the Bottle No. from "BM12562" to "BN65479."

Reason: A different bottle number of the test article was received.

3. Page 3 Section 7.9

Change the 3rd sentence to read as follows:

"All animals will be housed either singly or two/run within sex during the quarantine/pre-test period, but will be housed singly prior to dosing initiation and for the duration of the study."

Reason: Clarification of the protocol.

4. Page 4 Section 7.10

After the 3rd sentence on the page, add the following:

"In addition, the animal supplier will have conducted ECG examinations."

Reason: To indicate that these examinations will have been conducted prior to shipment of the animals.

5. Page 4 Section 7.11

In the 3rd sentence, change "prior to blood collection or scheduled sacrifice", to read "prior to blood collection, overnight urine collection or scheduled sacrifice. Water will be available at all times."

Reason: To indicate that food will not be available during overnight urine collection and that water

PROTOCOL AMENDMENT

DRAFT

Study No.: 219
Title: ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS

will be available during overnight fasting periods.

6. Page 6 Section 8.7.6

In the 1st sentence change "in weeks -1, 5, 13, 26, and 52..." to read "in weeks -1, 4, 13, 26, and 52..."

Reason: Hematology and clinical chemistry parameters will be determined in week 4 instead of week 5 so as to coincide with collection of blood for plasma drug level analysis.

7. Page 7 Section 8.7.6

After the Clincial Chemistry section, add the following after the first sentence:

"Animals will not receive food during the overnight urine collection, but water will be available."

Reason: To indicate that food will not be available during the overnight urine collection and that water will be provided.

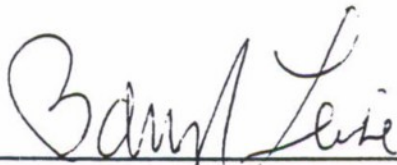
8. Page 9 Section 8.7.9

In the table under the Pathology section, change "lymph nodes (submandibular...)" to read "lymph nodes (mandibular...)"

Reason: Both terms refer to the same tissue.

APPROVALS

STUDY DIRECTOR



Barry S. Levine, D.Sc., D.A.B.T.

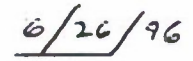


Date

TOXICOLOGIST



Alan P. Brown, Ph.D.



Date

QUALITY ASSURANCE

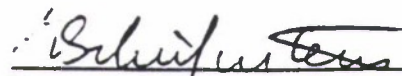


Ronald Schoenbeck

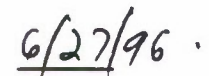


Date

SPONSOR APPROVAL



George J. Schieferstein, Ph.D.



Date

PROTOCOL AMENDMENT

DRAFT

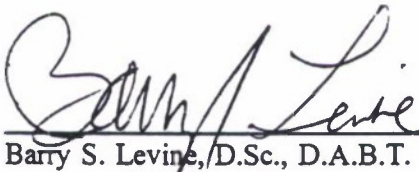
Study No.: 219
Title: ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS


9. Page 8 Section 8.7.9

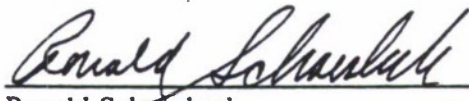
At the end of the 2nd paragraph, add the following: "The exception will be the eyes and optic nerve which will be fixed in 3% glutaraldehyde and the testes which will be collected in Bouin's fixative".

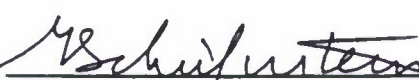
Reason: Upon request by the Pathologist, the eyes and optic nerve will be fixed in 3% glutaraldehyde and the testes will be collected in Bouin's fixative.

APPROVALS

STUDY DIRECTOR  5/1/97
Barry S. Levine, D.Sc., D.A.B.T. Date

TOXICOLOGIST  5-5-97
Alan P. Brown, Ph.D. Date

QUALITY ASSURANCE  5/8/97
Ronald Schoenbeck Date

SPONSOR APPROVAL  5/16/97
George J. Schieferstein, Ph.D. Date

PROTOCOL AMENDMENT

DRAFT

Study No.: 219
Title: ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS


10. Page 8 Section 8.7.9

Change the third sentence of the second paragraph to read "...in 3% glutaraldehyde and the testes with epididymides which will be collected...".

Reason: To indicate that the testes with epididymides will be collected in Bouin's fixative.

APPROVALS


STUDY DIRECTOR



Barry S. Levine, D.Sc., D.A.B.T.

6/17/97
Date

TOXICOLOGIST



Alan P. Brown, Ph.D.

6-17-97
Date

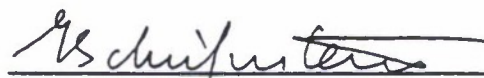
QUALITY ASSURANCE



Ronald Schönbeck

6/18/97
Date

SPONSOR APPROVAL



George J. Schieferstein, Ph.D.

6/26/97
Date

PROTOCOL AMENDMENT

DRAFT

Study No.: 219
Title: ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS


11. Page 8 Section 8.7.6

Change the sentence beginning with " Following light anesthesia. . ." to read as "Following anesthesia with sodium pentobarbital (I.V.; 20 - 30 mg/kg) prior to necropsy in week 53, a blood sample will be collected from the abdominal aorta for measurement of the following blood gases."

Reason: To indicate the procedure to be used for collecting arterial blood gas samples.

APPROVALS

STUDY DIRECTOR



Barry S. Levine, D.Sc., D.A.B.T.

7/15/97
Date

TOXICOLOGIST



Alan P. Brown, Ph.D.

7-14-97
Date

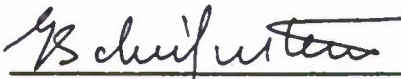
QUALITY ASSURANCE



Ronald Schoenbeck

7/15/97
Date

SPONSOR APPROVAL



George J. Schieferstein, Ph.D.

7/17/97
Date

DRAFT

APPENDIX O
Study Deviations

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

Study Deviations*

<u>Deviation Type</u>	<u>Specific Deviation</u>	<u>Effect on Study</u>
Protocol	The humidity was out of range on the following dates: 7/16/96 (Room 57), 12/22/96 (Room 59), and 5/18/97 (Room 59, 63 & 67).	None. The deviations were minimal.

* The detailed "Deviation Reports" are contained in the raw data which are archive at the Toxicology Research Laboratory, University of Illinois at Chicago, Department of Pharmacology, 1940 W. Taylor St., Chicago, IL 60612

The above deviations did not affect the integrity of the study.

Barry S. Levine, D.Sc., D.A.B.T.

Date