G-TWYST
GM PLANTS TWO YEAR SAFETY TESTING

G-TwYST Study A

Combined chronic toxicity and carcinogenicity study in rats fed GM maize NK603

Statistical report, 3 months data

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Abstract

The purpose of oral toxicity study A in the EU project G-TwYST was to assess the chronic and carcinogenic effects of genetically modified (GM) maize NK 603, grown both with and without the use of RoundUp, when fed to rats for a period of two years at incorporation rates of 11% and 33% in the feed. The effects were assessed relative to the responses for rats fed the near-isogenic non-GM maize, and the differences were compared, using a recently developed method for equivalence testing, to differences between non-GM feeds obtained in previous studies performed in the EU project GRACE.

The results of G-TwYST study A, except for the histopathological results which are reported separately, are given in five reports: four specific reports about the statistical analysis for data measured after 3, 6, 12 and 24 months, and a main report summarising all study results (Goedhart & van der Voet 2018). This report is about the results after 3 months.

Given tentative settings for regulatory parameters, for a set of 216 comparisons involving body weights, feed intake, haematology and clinical chemistry, equivalence was established in 94% of cases, close to the nominal confidence level of the test which was 95%. Equivalence was found to be more likely than lack of equivalence in 100% of cases.

In addition to this primary analysis, this report also contains results for equivalence testing using external target effect sizes for a limited set of variables, results for classical statistical analysis of differences, graphs of standardised effect sizes such as performed in the GRACE study and results of a factorial analysis.

1 Introduction

The purpose of oral toxicity study A in the EU project G-TwYST was to assess the effects of genetically modified (GM) maize NK 603, grown both with and without the use of RoundUp, when fed to rats for a period of one year (chronic toxicity study) and two years (carcinogenicity study), at incorporation rates of 11% and 33% in the feed. The effects of the GM maize were assessed relative to the responses for rats fed the near-isogenic non-GM maize. The chronic toxicity and carcinogenicity study ran in parallel. At 12 months part of the rats were euthanized and their organs were obtained, weighted and examined by the G-TwYST histopathological expert. The remaining rats were kept until 24 months, or until premature death, and were then assessed in the same way.

Rat weights and feed intake were measured weekly or bi-weekly. Haematology, clinical biochemistry in blood and urine, differential white blood cell counts, and urine volume and colour were obtained for a subset of animals after 3, 6, 12 and 24 months. This report describes in detail the results of the statistical analyses for the following data obtained after 3 months:

- Body weight at 3 months, growth rate first 3 months, mean feed intake (35 cages/group);
- Haematology (20 cages/group);
- Clinical biochemistry in blood (20 cages/group);
- Clinical biochemistry in urine (10 cages/group);
- Urine volume and colour (10 cages/group).

This report is organised as follows. Section 2 describes the data obtained after 3 months, initial data pre-processing, graphical summaries of growth and feed intake over time, outlier identification and checking of assumptions which are made in the statistical analysis. Section 3 presents detailed results of the statistical analyses. More details are provided in several appendices to this report. For a description of the statistical methods, and for a summary and discussion of results for all months, the reader is referred to the main study A report (Goedhart & van der Voet 2018).

2 Data

2.1 Data obtained after 3 months in G-TwYST study A

The available files for the data obtained after 3 months in G-TwYST study A are given in Table 1. GenStat programs “03-Males.gen” and “03-Females.gen” were used to combine all the data into single Excel files, separately for males and females. All animals survived the first 3 months, except for one female rat (Table 2). It is assumed that this single premature death is not connected to the experiment.

Some CHOL and cHGB were given as bounds; the number of such values are given in Table 3. The original Excel files with the haematology data (*Tab_5* and *Tab_6*) contain remarks given in Table 4. Values with such remarks were set to missing, see for Table 6 for details. For most Urine variables only a limited number of values have been observed, see Table 5. It is evident that a statistical analysis of uColour, uBil, uNit, uProtein, uGlu, uHemogl and uUrobili is not very useful. Therefore, only the Urine variables uVol, uVolW, uLeu, uOsmoll, uKeton and upH were statistically analysed.

Table 1 Data files for G-TwYST study A after 3 months.

Data files after 3 months	Date	Time	Size (b)
Tab_1_G_TwYST_2yr st_A_3_month_Body weight_Mal.xlsx	13-04-2017	11:14	270,434
Tab_2_G_TwYST_2yr st_A_3_month_Body weight_Fem.xlsx	13-04-2017	11:14	281,135
Correct data_rev_1_Feed consumption_12_mon_G_TwYST_A_Females.xlsx	20-10-2017	07:08	164,942
Correkt data_rev_1_Feed consumption_12_mon_G_TwYST_A_Males.xlsx	20-09-2017	12:00	168,346
Tab_5_G_TwYST_2yr st_A_3 month_Haematology_Mal.xlsx	03-01-2017	10:44	86,416
Tab_6_G_TwYST_2yr st_A_3 month_Haematology_Fem.xlsx	03-01-2017	10:46	86,525
Tab_7a_G_TwYST_2yr st_A_3 month_Clin_Chem_bl_Mal.xlsx	03-01-2017	10:48	100,197
Tab_7b_G_TwYST_2yr st_A_3 month_Clin_Chem_ur_Mal.xlsx	03-01-2017	10:49	83,115
Tab_8a_G_TwYST_2yr st_A_3 month_Clin_Chem_bl_Fem.xlsx	03-01-2017	10:51	100,248
Tab_8b_G_TwYST_2yr st_A_3 month_Clin_Chem_ur_Fem.xlsx	03-01-2017	10:52	83,070
Blood_ur_3 month_G_TwYST_2yr st_A_Fem_time image.xlsx	11-01-2017	15:00	94,320
Blood_ur_3 month_G_TwYST_2yr st_A_Mal_time image.xlsx	11-01-2017	15:03	95,985

Table 2 Animals that died before the end of month 3.

Sex	Rat	Cage	Feed	Day of Death
Female	610	555	NK11-	86

Table 3 Number of animals for which bounded values were provided. These bounds are given in the first column.

Variable	Males					Females				
	Con	NK11-	NK33-	NK11+	NK33+	Con	NK11-	NK33-	NK11+	NK33+
CHOL < 1.16	-	-	-	-	-	1	4	3	1	3
cHGB < 27.5	1	1	2	-	1	-	1	-	-	-
cHGB > 522.5	1	-	-	1	-	1	-	-	-	-

Table 4 Remarks by SZU in original Excel data files; the accompanying values have been set to missing.

Variable	Remark
WBC	High count WBC
WBC	High count of WBC and PLT, no calculated lymphocytes
WBC	Low WBC and platelet count, probably due to microclots
HGB	No calculated HGB (low blood)
PLT	Low platelet count, probably due to microclots
PLT	High count PLT
PLT	High count of WBC and PLT, no calculated lymphocytes
PLT	Low WBC and platelet count, probably due to microclots

Table 5 Urine variables with only a limited set of observed values which are given in the heading of each sub-table. The table entries give the number of times each value occurs for male and female rats. Only uLeu and uKeton were statistically analysed.

uColour	**Missing**	**2**	**3**		
Male	250	99	1		
Female	250	100	-		
uBil	**Missing**	**0**			
Male	250	100			
Female	250	100			
uLeu	**Missing**	**0**	**25**	**100**	
Male	250	63	33	4	
Female	250	81	14	5	
uNit	**Missing**	**0**	**1**		
Male	250	99	1		
Female	250	100	-		
uProtein	**Missing**	**0.00**	**0.25**	**0.75**	
Male	250	99	-	1	
Female	250	99	1	-	
uGlu	**Missing**	**1**			
Male	250	100			
Female	250	100			
uHemogl	**Missing**	**0**	**10**	**25**	**250**
Male	250	94	3	2	1
Female	250	98	1	1	-
uKeton	**Missing**	**0.0**	**0.5**	**1.5**	**5.0**
Male	250	31	27	39	3
Female	250	82	10	8	-
uUrobili	**Missing**	**1**			
Male	250	100			
Female	250	100			

2.2 Growth curves and feed intake

For each individual rat an exponential growth curve $A + B\ R^{Week}$ was fitted to the observed weights. A re-parameterization of this curve is given by $A + B\ \exp(-\gamma\ Week)$ with the growth rate γ defined by $\gamma = -\log(R)$. In Appendix 1 the observed weights are graphically displayed along with the fitted curve and, in the bottom right corner, the resulting estimate of the growth rate γ. Initially, absolute standardized residuals, resulting from the fitted curve, which were larger than 3, were marked and these were checked for errors by SZU. This led to some corrections especially for weights at the start of the experiment, see Table 6. In G-TwYST study B (Goedhart & van der Voet 2017) it was found that removing weights with large residuals only led to slightly different estimates of the growth rate. It was therefore decided to keep the weights with the large residuals. Note that in general the exponential curve fits very well and therefore the weights can be summarized by the final observed weights at week 13 and the estimated growth rate γ, further called growthRate. Thus only Weight_13 and growthRate were statistically analysed. The mean weight for each feeding group is given in Figure 1, while the mean weight gain per day per animal in each week is given in Figure 2. Feed consumption for each cage in units g/animal/day is graphically depicted in Appendix 2. The mean feed consumption for each feeding group is given in Figure 3.

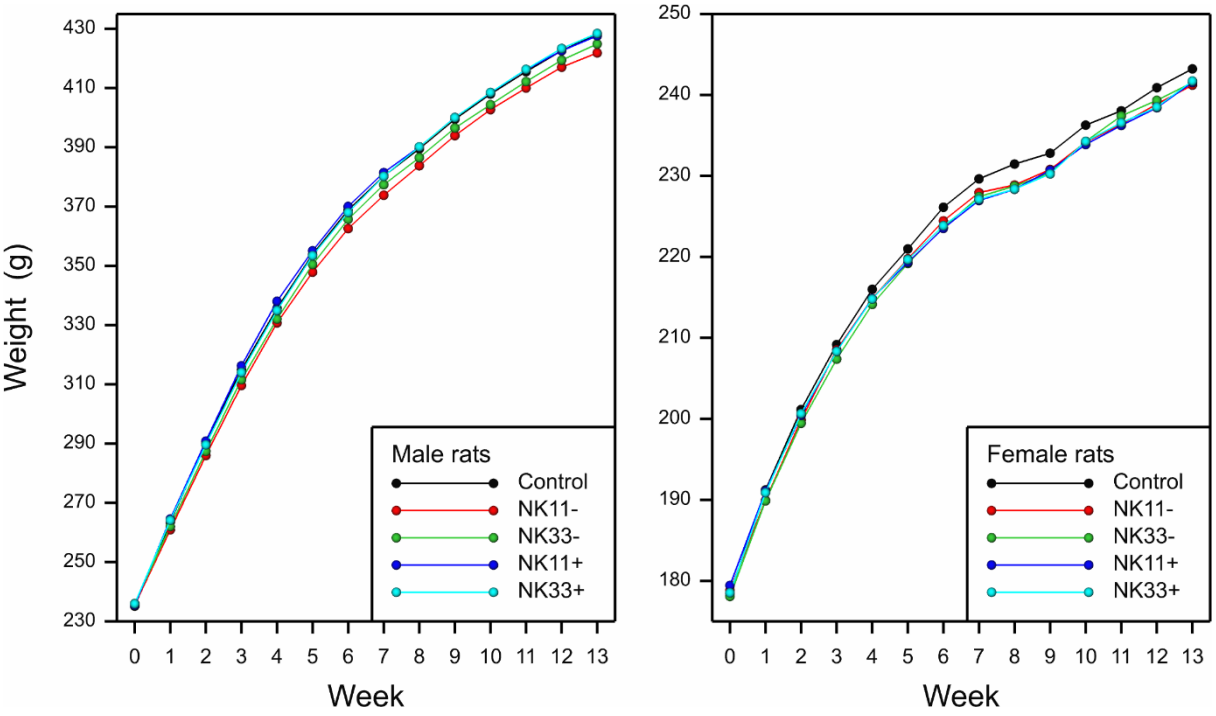

Figure 1 **Mean body weights versus week for each feeding group for male rats (left) and for female rats (right).**

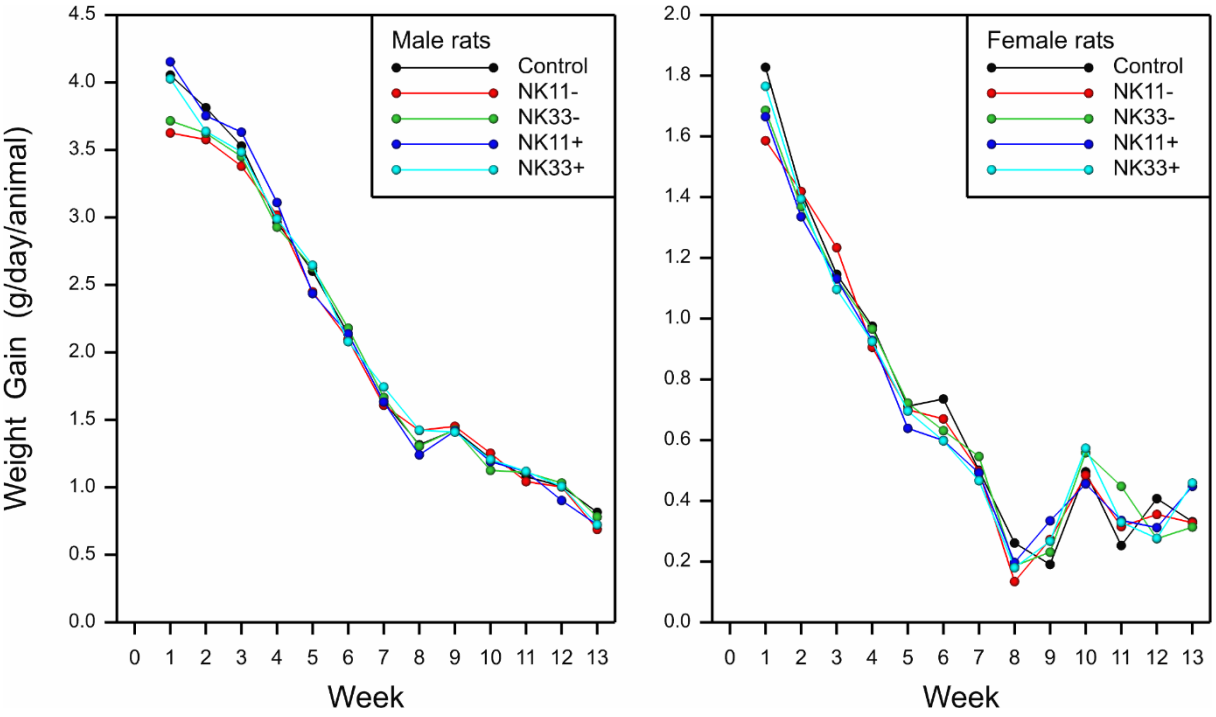

Figure 2 **Mean body weights gain (g/day/animal) versus week for each feeding group for male rats (left) and for female rats (right).**

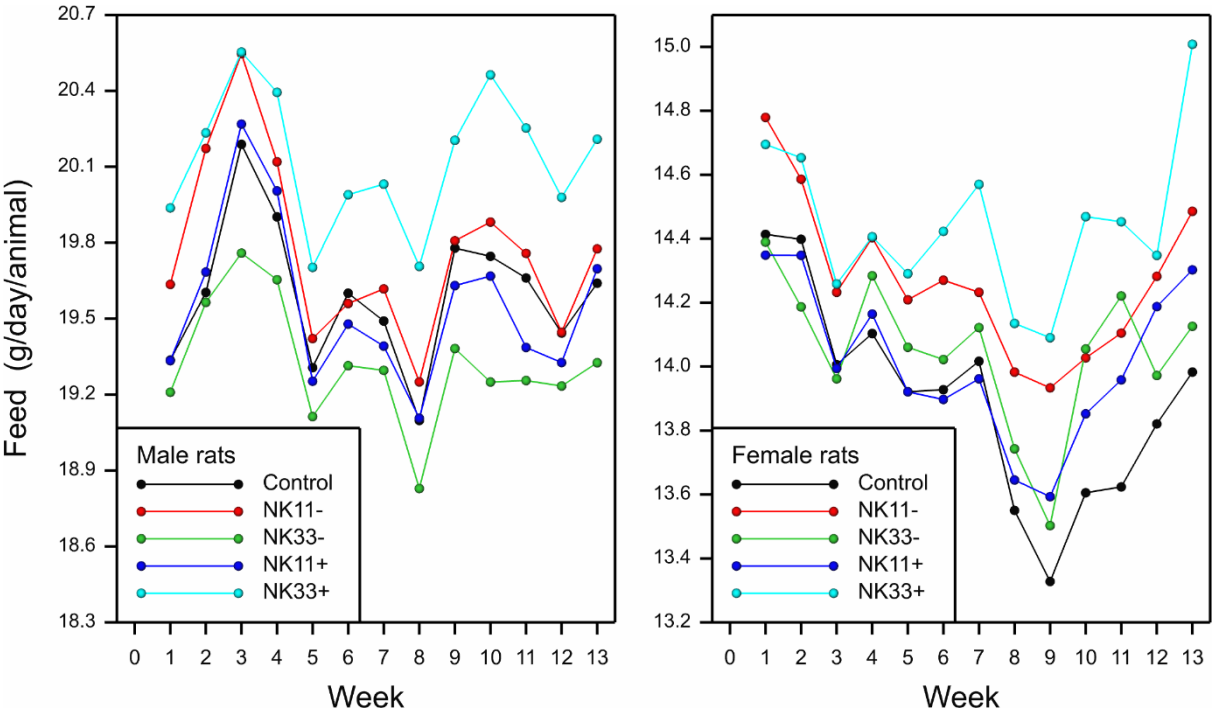

Figure 3 Mean feed consumption (g/day/animal) versus week for each feeding group for male rats (left) and for female rats (right).

2.3 Outliers and checking of ANOVA assumptions

These analyses and changes to the data were made before the feeding group codes were unblinded. The cage means, after a log transformation, for each observed variable were statistically analysed by an analysis of variance using the model “Block + Group” according to the randomized block design. Grubbs’ outlier test at the 1% level was sequentially applied to the residuals to detect outliers. This resulted in a number of outliers which were first presented to the study director and then to the G-TwYST coordinator. Outliers were classified as either (1) typos or physiologically improbable values or (2) values that might be realistic. For the first category the values were set to missing, effectively removing the outlier completely. For the second category a statistical analysis without and with these outlier was performed. The analyses presented in this report are without the outliers. Analyses including outliers are presented in Appendix 11. Table 6 lists all the initially modified values and outliers. Residual plots which include the outliers (i.e. including the yellow values in Table 6) are given in Figure 4. From this it is clear that these are indeed outliers.

Without these outliers cage means on the original scale are given in Appendix 3, while cage means after a log transformation of the individual data are given in Appendix 4. Normal probability plots of the ANOVA residuals, of an analysis on cage means after log transformation, are given in Appendix 5. To aid interpretation a 99% envelope is added to the probability plots, such that only values outside the envelop might be suspicious. Appendix 6 gives plots of residuals versus fitted values after the same analysis of variance. These residual plots are generally satisfactory implying that the ANOVA assumptions, homogeneity of variance and, less importantly, normality, are generally fulfilled.

Table 6 **Values that have been modified, deleted, or were considered as possible outliers, before unblinding of the feeding groups. Values which are not coloured were modified or deleted following comments of SZU. The red and yellow values were presented to the G-TwYST coordinator. He decided which values should be deleted (red) and which values should be considered as possible outliers (yellow). Comments by the authors of this report are given in black, while comments of the G-TwYST coordinator are given in red.**

Sex	Variable	Animal	Cage	oldValue	newValue	Comment
Male	PLT	7	4	516	delete	SZU comment in datafile: microclots
Male	PLT	79	40	494	delete	SZU comment in datafile: microclots
Male	PLT	209	105	245	delete	SZU comment in datafile: microclots
Male	PLT	231	116	305	delete	SZU comment in datafile: microclots
Male	PLT	282	141	386	delete	SZU comment in datafile: microclots
Male	PLT	299	150	31	delete	SZU comment in datafile: microclots
Male	PLT	320	160	224	delete	SZU comment in datafile: microclots
Male	WBC	98	49	19.8	delete	SZU comment in datafile: highCount
Male	Feed_2	173	87	11.6	delete	Apparent typo
Male	HGB	231	116	1.4	delete	Same animal 231; Extremely small
Male	MCH	231	116	1.6	delete	Same animal 231; Extremely small
Male	MCHC	231	116	3	delete	Same animal 231; Extremely small
Male	Na	293	147	155	outlier	Two large values in same the cage
Male	Na	294	147	152	outlier	Two large values in same the cage
Sex	**Variable**	**Animal**	**Cage**	**oldValue**	**newValue**	**Comment**
Female	PLT	521	511	237	delete	SZU comment in datafile: microclots
Female	PLT	522	511	174	delete	SZU comment in datafile: microclots
Female	PLT	588	544	1901	delete	SZU comment in datafile: highCount
Female	PLT	738	619	71	delete	SZU comment in datafile: microclots
Female	PLT	846	673	204	delete	SZU comment in datafile: microclots
Female	WBC	565	533	15.6	delete	SZU comment in datafile: highCount
Female	WBC	588	544	13.7	delete	SZU comment in datafile: highCount
Female	Weight_0	517	509	202	177.19	SZU comment: mistake in copying
Female	Weight_0	518	509	208.01	177.19	SZU comment: mistake in copying
Female	Weight_0	587	544	206.96	177.12	SZU comment: mistake in copying
Female	Weight_0	588	544	210.31	176.99	SZU comment: mistake in copying
Female	Weight_0	657	579	199.01	176.30	SZU comment: mistake in copying
Female	Weight_0	658	579	209.86	175.75	SZU comment: mistake in copying
Female	Weight_0	727	614	212.66	175.70	SZU comment: mistake in copying
Female	Weight_0	728	614	214.99	175.38	SZU comment: mistake in copying
Female	Weight_0	797	649	219.51	175.16	SZU comment: mistake in copying
Female	Weight_6	544	522	257.76	237.76	SZU comment: mistake in copying
Female	Weight_8	513	507	282.77	228.77	SZU comment: mistake in copying
Female	Weight_13	758	629	260.44	260.55	SZU comment: mistake in copying
Female	growthRate	569	535	0.347	outlier	Two large growthRates in the same cage
Female	growthRate	570	535	0.363	outlier	Two large growthRates in the same cage
Female	growthRate	583	542	0.713	outlier	Extremely large growthRate
Female	RBC	622	561	4.66	outlier	Same animal 622; very small; low value, still realistic, anaemia?
Female	HGB	622	561	10.8	outlier	Same animal 622; very small; low value, still realistic, anaemia?

Female	HCT	622	561	31.1	outlier	Same animal 622; very small; low value, still realistic, anaemia?
Female	MCV	718	609	67.3	outlier	Animal 718 has consistent large values in months 3, 6, 12; agree, possible outlier
Female	PLT	807	654	239	delete	239 is by far the smallest value, delete
Female	BIL	714	607	22.4	outlier	One value is even larger; can be realistic, haemolysis?
Female	BIL	846	673	32.8	outlier	In other months there are larger values; can be realistic, haemolysis?
Female	cHGB	714	607	456.752	outlier	522.5 is upper limit of method; I agree, possible outlier
Female	cHGB	846	673	522.5	outlier	There is one larger value; I agree, possible outlier
Female	P	662	581	3.77	outlier	Only a single value in this cage; There are larger values; I agree, possible outlier

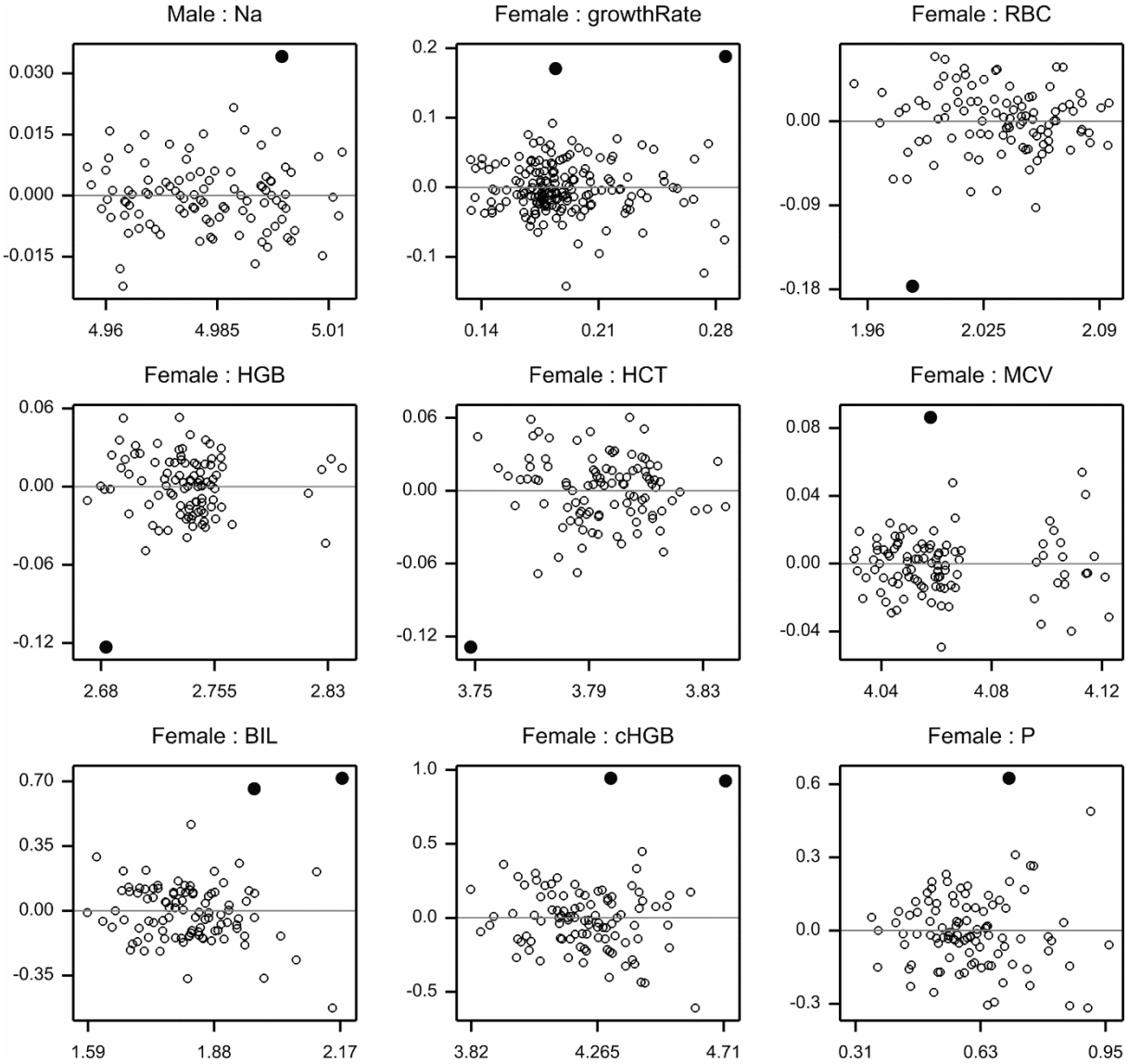

Figure 4 **Residuals along the y-axis versus fitted values along the x-axis resulting from an analysis of variance on cage means after log transforming the data. Solid symbols denote outliers found by sequentially applying Grubbs' outlier test at the 1% level to the residuals.**

2.4 Summary tables

Summary tables, on the original non-transformed scale, of number of observations, means, standard deviations and coefficients of variation (%), classified by the feeding groups, are given in Table 7 for males and in Table 8 for females. These tables were obtained by first calculating cage means and then calculating the summary statistics. The number of cages per feeding group is 35. However for haematology and clinical biochemistry data are only available for 20 cages, while urine data is available for 10 cages per feeding group.

Table 7 Summary statistics for male rats classified by the feeding groups: number of cages (N), means (Mean), standard deviations (Sd) and coefficients of variation (CV). The summary statistics are obtained from cage means.

Weights	Control				NK11-				NK33-				NK11+				NK33+			
Male	N	Mean	Sd	CV	N	Mean	Sd	CV	N	Mean	Sd	CV	N	Mean	Sd	CV	N	Mean	Sd	CV
Weight_13	35	428	24.9	5.8	35	422	27.0	6.4	35	425	30.4	7.1	35	428	28.4	6.6	35	428	27.8	6.5
growthRate	35	0.15	0.018	12.0	35	0.14	0.022	15.9	35	0.14	0.023	16.1	35	0.15	0.016	10.6	35	0.15	0.015	10.5
FeedMean	35	19.6	0.91	4.6	35	19.8	1.09	5.5	35	19.3	1.11	5.7	35	19.6	1.03	5.2	35	20.1	1.27	6.3
Haematology	**Control**				**NK11-**				**NK33-**				**NK11+**				**NK33+**			
Male	N	Mean	Sd	CV	N	Mean	Sd	CV	N	Mean	Sd	CV	N	Mean	Sd	CV	N	Mean	Sd	CV
WBC	20	10.1	1.37	13.6	20	10.2	2.08	20.5	20	11.5	1.44	12.5	20	10.9	2.39	21.8	20	11.2	2.60	23.3
RBC	20	8.64	0.32	3.6	20	8.58	0.28	3.3	20	8.61	0.25	2.9	20	8.67	0.27	3.1	20	8.60	0.29	3.3
HGB	20	16.2	0.50	3.1	20	16.1	0.42	2.6	20	16.2	0.40	2.5	20	16.0	0.43	2.7	20	16.2	0.45	2.8
HCT	20	46.5	1.66	3.6	20	46.1	1.23	2.7	20	46.5	1.36	2.9	20	46.7	1.31	2.8	20	46.6	1.52	3.3
MCV	20	53.9	1.44	2.7	20	53.8	1.45	2.7	20	54.0	1.20	2.2	20	53.8	1.20	2.2	20	54.2	1.19	2.2
MCH	20	18.7	0.65	3.5	20	18.7	0.69	3.7	20	18.9	0.55	2.9	20	18.5	0.49	2.7	20	18.8	0.66	3.5
MCHC	20	34.8	0.54	1.6	20	34.8	0.56	1.6	20	34.9	0.52	1.5	20	34.4	0.50	1.5	20	34.7	0.76	2.2
PLT	20	824	123	14.9	20	847	106	12.5	20	870	124	14.3	20	860	67	7.8	20	888	107	12.1
LYMR	20	73.3	5.21	7.1	20	72.5	5.90	8.1	20	72.2	6.84	9.5	20	73.2	4.60	6.3	20	73.7	3.74	5.1
LYMA	20	7.39	1.11	15.0	20	7.52	1.85	24.7	20	8.26	1.34	16.2	20	7.98	1.84	23.1	20	8.24	2.14	26.0
ClinChem	**Control**				**NK11-**				**NK33-**				**NK11+**				**NK33+**			
Male	N	Mean	Sd	CV	N	Mean	Sd	CV	N	Mean	Sd	CV	N	Mean	Sd	CV	N	Mean	Sd	CV
ALP	20	1.51	0.33	22.0	20	1.54	0.37	24.0	20	1.47	0.26	17.9	20	1.48	0.24	16.2	20	1.56	0.41	26.2
ALT	20	0.66	0.10	14.7	20	0.68	0.16	23.5	20	0.64	0.11	17.1	20	0.64	0.10	14.9	20	0.64	0.10	16.1
AST	20	2.27	0.47	20.7	20	2.25	0.34	15.1	20	2.18	0.30	13.6	20	2.08	0.48	23.1	20	2.12	0.28	13.4
BIL	20	6.81	3.90	57.3	20	7.16	3.12	43.6	20	7.26	4.72	65.0	20	6.68	4.63	69.3	20	6.94	4.32	62.3
ALB	20	39.7	1.92	4.8	20	39.2	2.27	5.8	20	39.4	1.86	4.7	20	38.8	1.44	3.7	20	39.9	2.78	7.0
TP	20	67.7	2.12	3.1	20	67.6	2.57	3.8	20	67.1	2.06	3.1	20	67.4	1.86	2.8	20	68.0	3.04	4.5
Glu	20	5.99	0.83	13.9	20	5.86	0.73	12.4	20	5.86	0.91	15.6	20	6.12	0.79	13.0	20	6.24	0.91	14.6
CHOL	20	2.13	0.21	9.8	20	2.17	0.22	10.3	20	2.14	0.25	11.8	20	2.08	0.22	10.7	20	2.17	0.24	11.2
TAG	20	1.01	0.23	23.1	20	1.14	0.34	29.5	20	1.14	0.33	28.8	20	1.16	0.37	31.9	20	1.03	0.25	24.6
Crea	20	37.4	4.34	11.6	20	35.4	4.64	13.1	20	35.9	5.59	15.6	20	36.2	4.29	11.9	20	36.0	4.79	13.3
Urea	20	5.85	0.65	11.2	20	5.61	1.06	18.8	20	5.70	0.85	14.9	20	5.69	0.68	12.0	20	5.78	0.58	10.0
cHGB	20	85	54.3	64.0	20	100	63.6	63.4	20	94	66.1	70.4	20	87	63.1	72.7	20	95	82.7	87.5

Ca	20	2.54	0.096	3.8	20	2.55	0.087	3.4	20	2.55	0.094	3.7	20	2.54	0.084	3.3	20	2.54	0.095	3.7
Cl	20	104	2.72	2.6	20	104	1.63	1.6	20	104	1.98	1.9	20	103	1.46	1.4	20	105	2.09	2.0
K	20	5.34	0.62	11.6	20	5.42	0.55	10.1	20	5.39	0.74	13.6	20	5.35	0.53	10.0	20	5.47	0.86	15.8
Na	19	146	3.28	2.3	20	145	2.20	1.5	20	146	1.90	1.3	20	146	2.15	1.5	20	146	2.33	1.6
P	20	2.57	0.22	8.4	20	2.43	0.25	10.3	20	2.56	0.34	13.1	20	2.48	0.19	7.7	20	2.47	0.27	10.8
Urine	**Control**				**NK11-**				**NK33-**				**NK11+**				**NK33+**			
Male	N	Mean	Sd	CV	N	Mean	Sd	CV	N	Mean	Sd	CV	N	Mean	Sd	CV	N	Mean	Sd	CV
uVol	10	26.4	7.22	27.3	10	26.3	5.47	20.8	10	21.4	9.08	42.5	10	24.9	5.34	21.5	10	26.0	6.97	26.8
uVolW	10	6.30	1.93	30.6	10	6.29	1.62	25.8	10	5.04	1.97	39.1	10	5.93	1.75	29.5	10	6.01	1.43	23.9
uLeu	10	7.5	10.5	140.5	10	6.2	10.6	170.0	10	21.2	23.6	111.1	10	8.8	11.9	135.5	10	17.5	19.7	112.7
uOsmoll	10	324	105	32.4	10	296	67	22.5	10	394	132	33.5	10	338	90	26.5	10	362	226	62.4
uKeton	10	0.83	0.97	117.0	10	0.82	0.74	89.3	10	1.12	0.54	48.3	10	0.70	0.54	76.8	10	0.88	0.99	113.7
upH	10	6.90	0.17	2.5	10	6.72	0.22	3.3	10	6.88	0.21	3.1	10	6.85	0.54	7.9	10	6.75	0.26	3.9

Table 8 Summary statistics for female rats classified by the feeding groups: number of cages (N), means (Mean), standard deviations (Sd) and coefficients of variation (CV). The summary statistics are obtained from cage means.

Weights	**Control**				**NK11-**				**NK33-**				**NK11+**				**NK33+**			
Female	N	Mean	Sd	CV	N	Mean	Sd	CV	N	Mean	Sd	CV	N	Mean	Sd	CV	N	Mean	Sd	CV
Weight_13	35	243	13.3	5.5	35	241	12.8	5.3	35	242	13.2	5.5	35	242	15.0	6.2	35	242	14.8	6.1
growthRate	35	0.19	0.041	20.8	35	0.19	0.049	25.9	35	0.19	0.047	25.4	35	0.18	0.042	23.2	34	0.18	0.046	25.1
FeedMean	35	13.9	0.75	5.4	35	14.3	0.98	6.9	35	14.0	0.90	6.4	35	14.0	0.90	6.4	35	14.4	0.94	6.5
Haematology	**Control**				**NK11-**				**NK33-**				**NK11+**				**NK33+**			
Female	N	Mean	Sd	CV	N	Mean	Sd	CV	N	Mean	Sd	CV	N	Mean	Sd	CV	N	Mean	Sd	CV
WBC	20	7.54	1.63	21.6	20	7.88	1.24	15.7	20	7.80	2.24	28.8	20	7.28	1.12	15.4	20	8.02	1.36	16.9
RBC	20	7.62	0.33	4.3	20	7.62	0.31	4.0	20	7.73	0.35	4.6	20	7.70	0.29	3.7	20	7.73	0.37	4.8
HGB	20	15.5	0.59	3.8	20	15.4	0.52	3.4	20	15.6	0.57	3.7	20	15.4	0.52	3.4	20	15.4	0.51	3.3
HCT	20	44.4	1.31	2.9	20	44.2	1.35	3.1	20	44.9	1.03	2.3	20	44.6	1.09	2.5	20	44.8	1.74	3.9
MCV	20	58.4	2.27	3.9	20	58.4	1.50	2.6	20	58.0	1.90	3.3	20	58.0	1.52	2.6	20	58.0	1.73	3.0
MCH	20	20.4	1.15	5.6	20	20.4	1.10	5.4	20	20.2	0.89	4.4	20	20.0	0.86	4.3	20	20.0	0.76	3.8
MCHC	20	34.9	0.94	2.7	20	34.9	1.52	4.3	20	34.8	0.99	2.8	20	34.6	1.14	3.3	20	34.5	0.95	2.7
PLT	20	828	71.1	8.6	20	799	81.0	10.1	20	787	87.4	11.1	20	813	83.9	10.3	19	846	78.8	9.3
LYMR	20	73.7	5.05	6.9	20	71.3	7.26	10.2	20	72.7	6.30	8.7	20	72.5	8.03	11.1	20	74.1	6.25	8.4

LYMA	20	5.56	1.22	22.0	20	5.69	1.15	20.3	20	5.57	1.41	25.4	20	5.22	0.83	15.8	20	6.02	1.38	22.8
ClinChem	**Control**				**NK11-**				**NK33-**				**NK11+**				**NK33+**			
Female	N	Mean	Sd	CV	N	Mean	Sd	CV	N	Mean	Sd	CV	N	Mean	Sd	CV	N	Mean	Sd	CV
ALP	20	0.68	0.14	20.3	20	0.69	0.13	18.8	20	0.71	0.18	25.5	20	0.73	0.14	18.6	20	0.71	0.21	29.4
ALT	20	0.52	0.12	22.9	20	0.53	0.16	29.5	20	0.51	0.10	19.8	20	0.48	0.08	16.3	20	0.57	0.14	24.4
AST	20	2.14	0.37	17.5	20	2.11	0.40	19.1	20	2.28	0.30	13.3	20	2.09	0.36	17.1	20	2.43	0.48	19.8
BIL	20	6.36	1.03	16.2	20	5.89	0.88	15.0	20	6.87	2.03	29.5	20	6.14	1.36	22.1	20	6.39	1.27	19.9
ALB	20	45.8	2.87	6.3	20	45.8	4.52	9.9	20	45.7	2.96	6.5	20	46.0	3.10	6.7	20	45.2	4.50	10.0
TP	20	71.3	3.34	4.7	20	70.7	4.41	6.2	20	70.8	3.13	4.4	20	71.5	3.64	5.1	20	70.9	4.01	5.7
Glu	20	5.15	0.53	10.4	20	5.20	0.81	15.6	20	4.93	0.74	15.0	20	5.20	0.77	14.9	20	4.89	0.57	11.6
CHOL	20	1.98	0.34	17.0	20	1.90	0.33	17.2	20	1.83	0.34	18.7	20	1.78	0.22	12.5	20	1.85	0.33	17.6
TAG	20	0.70	0.13	18.7	20	0.68	0.16	23.3	20	0.63	0.11	17.0	20	0.61	0.13	20.8	20	0.65	0.08	12.2
Crea	20	44.5	4.04	9.1	20	46.2	5.08	11.0	20	45.2	3.43	7.6	20	47.2	5.23	11.1	20	46.0	4.87	10.6
Urea	20	5.76	0.54	9.4	20	5.89	0.83	14.2	20	5.83	0.51	8.8	20	5.88	0.50	8.4	20	6.13	0.81	13.2
cHGB	20	72.1	18.9	26.2	20	68.4	13.6	19.9	20	85.3	33.3	39.1	20	61.9	11.9	19.2	20	72.4	18.1	25.0
Ca	20	2.51	0.062	2.5	20	2.52	0.076	3.0	20	2.53	0.073	2.9	20	2.52	0.076	3.0	20	2.52	0.062	2.5
Cl	20	100	2.44	2.4	20	101	2.70	2.7	20	101	1.99	2.0	20	101	3.49	3.4	20	101	2.94	2.9
K	20	4.46	0.41	9.1	20	4.52	0.27	6.0	20	4.54	0.32	7.0	20	4.46	0.39	8.7	20	4.57	0.39	8.6
Na	20	142	2.14	1.5	20	143	2.52	1.8	20	143	2.49	1.7	20	143	2.98	2.1	20	143	2.77	1.9
P	20	1.78	0.33	18.8	20	1.87	0.25	13.7	20	2.00	0.33	16.2	19	1.77	0.43	24.5	20	1.96	0.64	32.9
Urine	**Control**				**NK11-**				**NK33-**				**NK11+**				**NK33+**			
Female	N	Mean	Sd	CV	N	Mean	Sd	CV	N	Mean	Sd	CV	N	Mean	Sd	CV	N	Mean	Sd	CV
uVol	10	20.2	5.12	25.3	10	19.1	6.02	31.6	10	23.7	6.54	27.7	10	18.2	7.78	42.7	10	16.4	6.10	37.1
uVolW	10	8.45	1.78	21.1	10	7.98	2.27	28.4	10	9.71	2.62	27.0	10	7.45	3.18	42.7	10	6.88	2.46	35.7
uLeu	10	8.8	15.6	178.8	10	5.0	6.5	129.1	10	10.0	16.5	164.6	10	12.5	20.4	163.3	10	6.2	15.9	253.9
uOsmoll	10	323	56	17.5	10	334	120	35.9	10	288	98	33.9	10	391	98	25.2	10	399	107	26.7
uKeton	10	0.10	0.24	241.5	10	0.05	0.11	210.8	10	0.17	0.31	178.8	10	0.33	0.37	115.0	10	0.20	0.31	153.7
upH	10	6.40	0.32	4.9	10	6.15	0.32	5.1	10	6.42	0.29	4.5	10	6.25	0.26	4.2	10	6.38	0.52	8.1

3 Statistical analysis

The statistical methods are described in the main study A report (Goedhart & van der Voet 2018).

3.1 Equivalence testing using historical data

The sample size in the current study, i.e. the number of cages per feeding group, equals 35 for the weight variables and 20 for haematology and clinical biochemistry. These sample sizes were used as the regulatory replication n_0 in the equivalence analysis. Moreover regulatory values $\alpha = 0.05$ and $\beta = 0.05$ were employed. Equivalence testing was only performed for those variables that were also observed in the GRACE study.

Each GMO feed was tested for equivalence with respect to the control feed. The DWE intervals showing the main results of the equivalence tests for 27 variables are given in Figure 5 to Figure 8. The hypothesis of no difference is rejected in case the interval does not contain zero, which is denoted by fuchsia coloured estimates. The non-equivalence hypothesis is rejected when the interval fully lies inside the interval (-1,1). For further interpretation the 95% confidence intervals for the ratios are given in Table 9 and Table 10. These confidence intervals at the ratio scale are also given in Figure 9 to Figure 16, with inclusion of the estimated equivalence limits (red bars) and their uncertainty (blue bars). Note that the latter graphs cannot be used directly for performing the equivalence test. However, they show the effects and equivalence limits at a more familiar scale.

The DWE equivalence test depends, among other things, on the ratio of the residual variance of the current study and the residual variance of the historical studies. In case this variance ratio (VR) is small the corresponding DWE interval will generally be short, and when VR is large the interval will large. The ratio of the residual variances is given in Figure 17. Large ratios are observed in males for MCV and MCHC, and in females for growthRate, MCHC, CHOL and P.

Among 8×27 = 216 equivalence tests, there were 13 failures (6%) to prove equivalence (i.e. reject the hypothesis of non-equivalence), which is close to the 5% level of the test. In all these 13 cases the median estimate was within the equivalence limits, therefore equivalence is still more likely than lack of equivalence according to the terminology of EFSA (2011a). These 13 cases were observed for MCV (4x) in males, while the remaining 9 cases are observed in females for growthRate (4x), MCHC (1x), CHOL (3x) and P (1x). From Figure 17 it can be seen that these are all cases where, on average, G-TwYST study A was less precise than the historical GRACE study.

Although not the primary result of the equivalence analysis, it can also be observed from the fuchsia symbols in Figure 5 to Figure 8 and from Table 9 and Table 10 that, for those variables for which the equivalence test is performed, the number of significant differences, employing classical two-sided t-tests at the 5% level, equals 13 (6% of 216 difference tests, 3 for males and 10 for females), which is again close to the 5% level of the test. Only in two of these cases (females P for NK33-, females CHOL for NK11+) there was both a significant difference and a failure to show equivalence.

For all difference tests, i.e. including those for which the equivalence test was not performed, 17 out of 288 t-tests were significant which is 6% of the tests (Table 9 and Table 10).

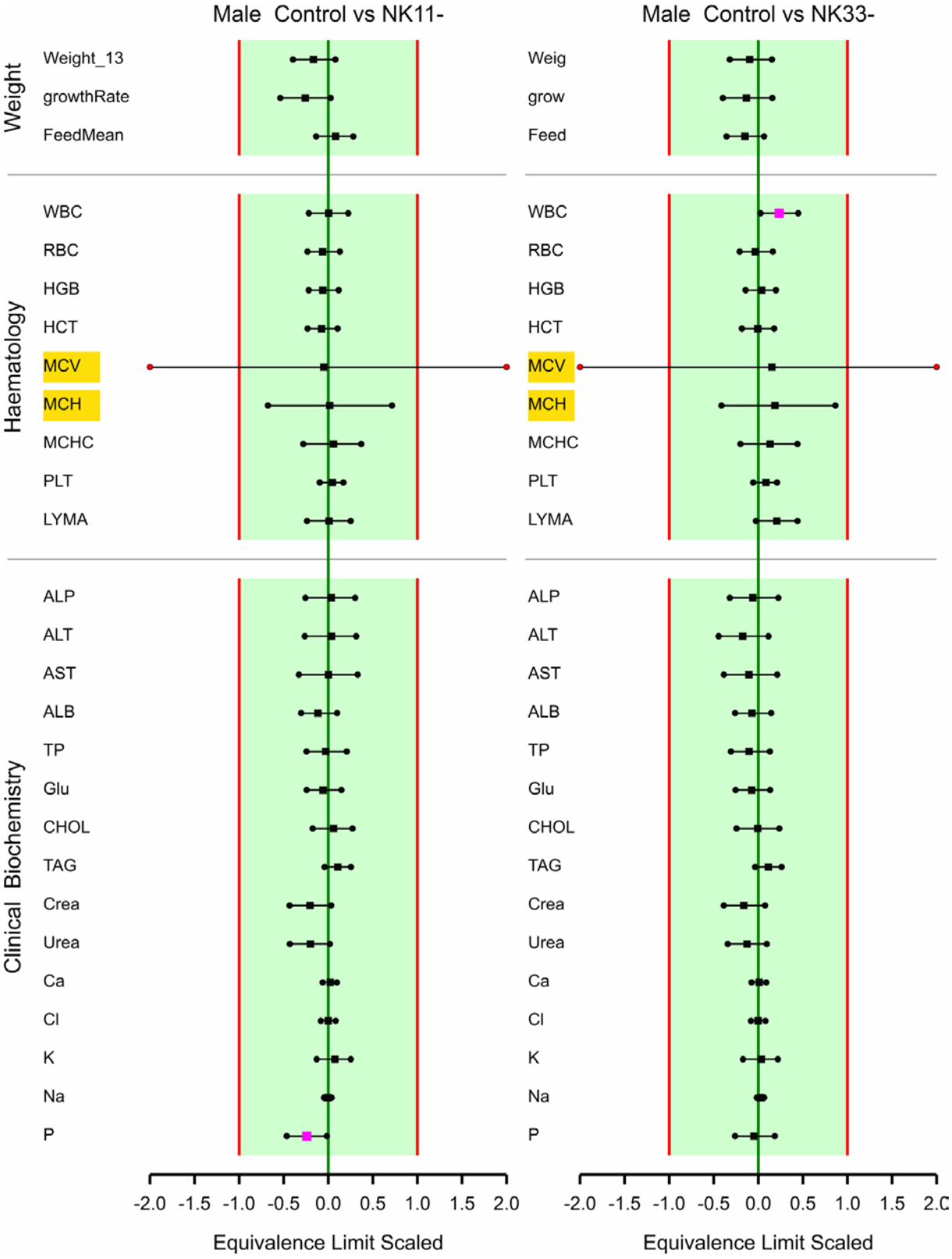

Figure 5 **Equivalence testing of NK11- and NK33- versus the control feed for males. For estimates (square symbols) on the left of zero the GM feed has a smaller mean than the control feed. See Table 9, Figure 9 and Figure 10 for further interpretation. Endpoints labelled with a golden background have a large residual variance compared to the historical studies (VR>150%). Fuchsia coloured symbols denote a significant difference.**

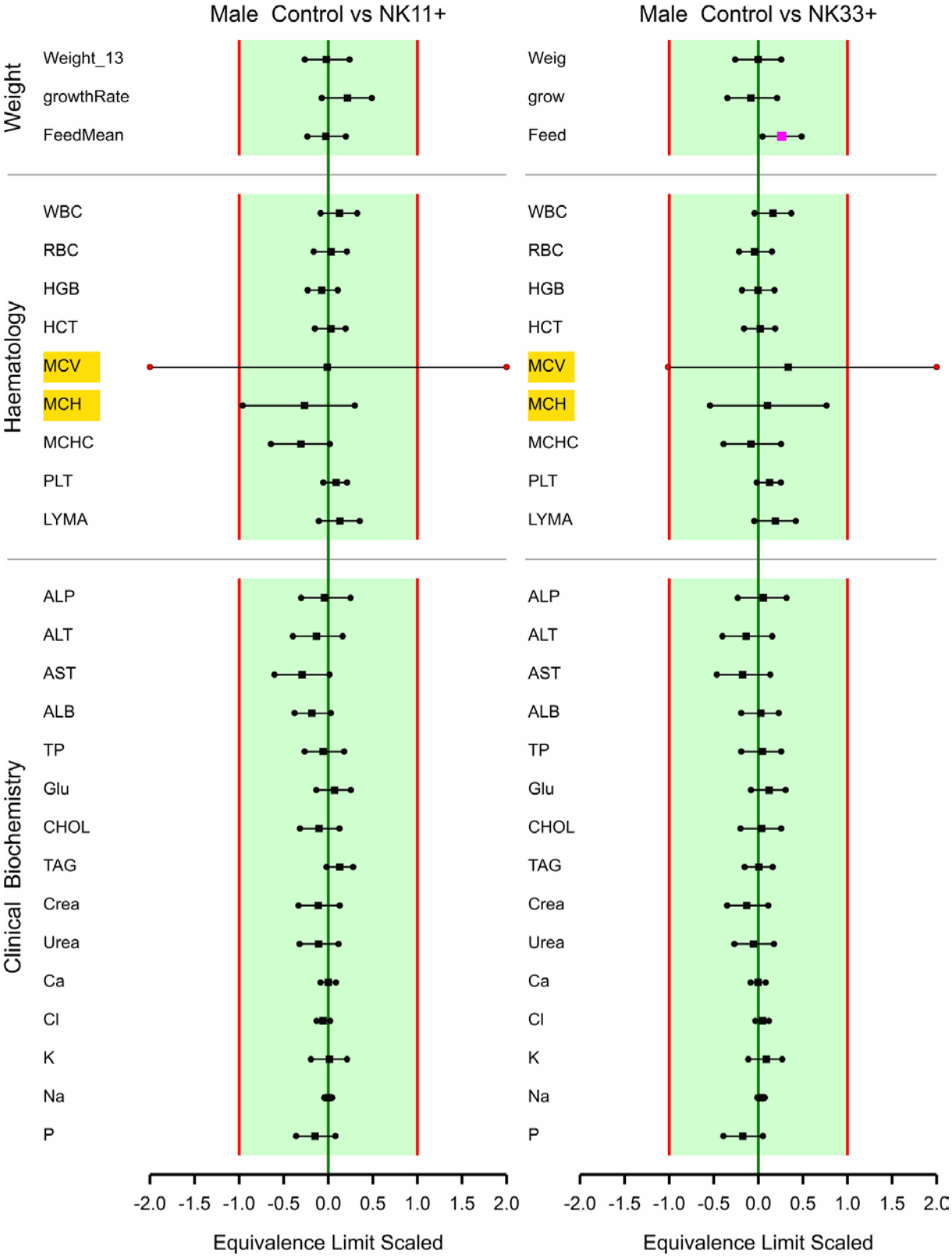

Figure 6 **Equivalence testing of NK11+ and NK33+ versus the control feed for males. For estimates (square symbols) on the left of zero the GM feed has a smaller mean than the control feed. See Table 9, Figure 11 and Figure 12 for further interpretation. Endpoints labelled with a golden background have a large residual variance compared to the historical studies (VR>150%). Fuchsia coloured symbols denote a significant difference.**

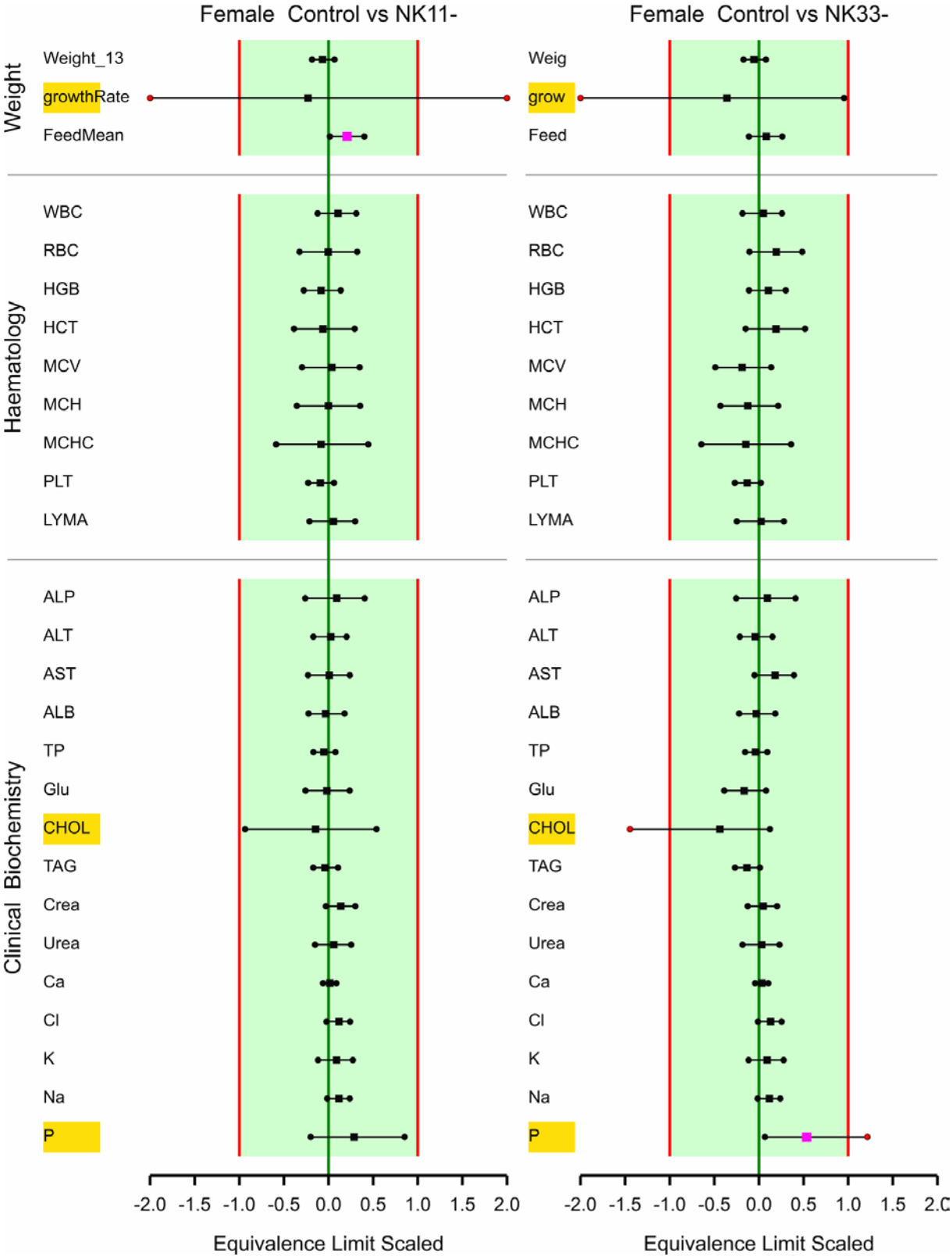

Figure 7 **Equivalence testing of NK11- and NK33- versus the control feed for females. For estimates (square symbols) on the left of zero the GM feed has a smaller mean than the control feed. See Table 10, Figure 13 and Figure 14 for further interpretation. Endpoints labelled with a golden background have a large residual variance compared to the historical studies (VR>150%). Fuchsia coloured symbols denote a significant difference.**

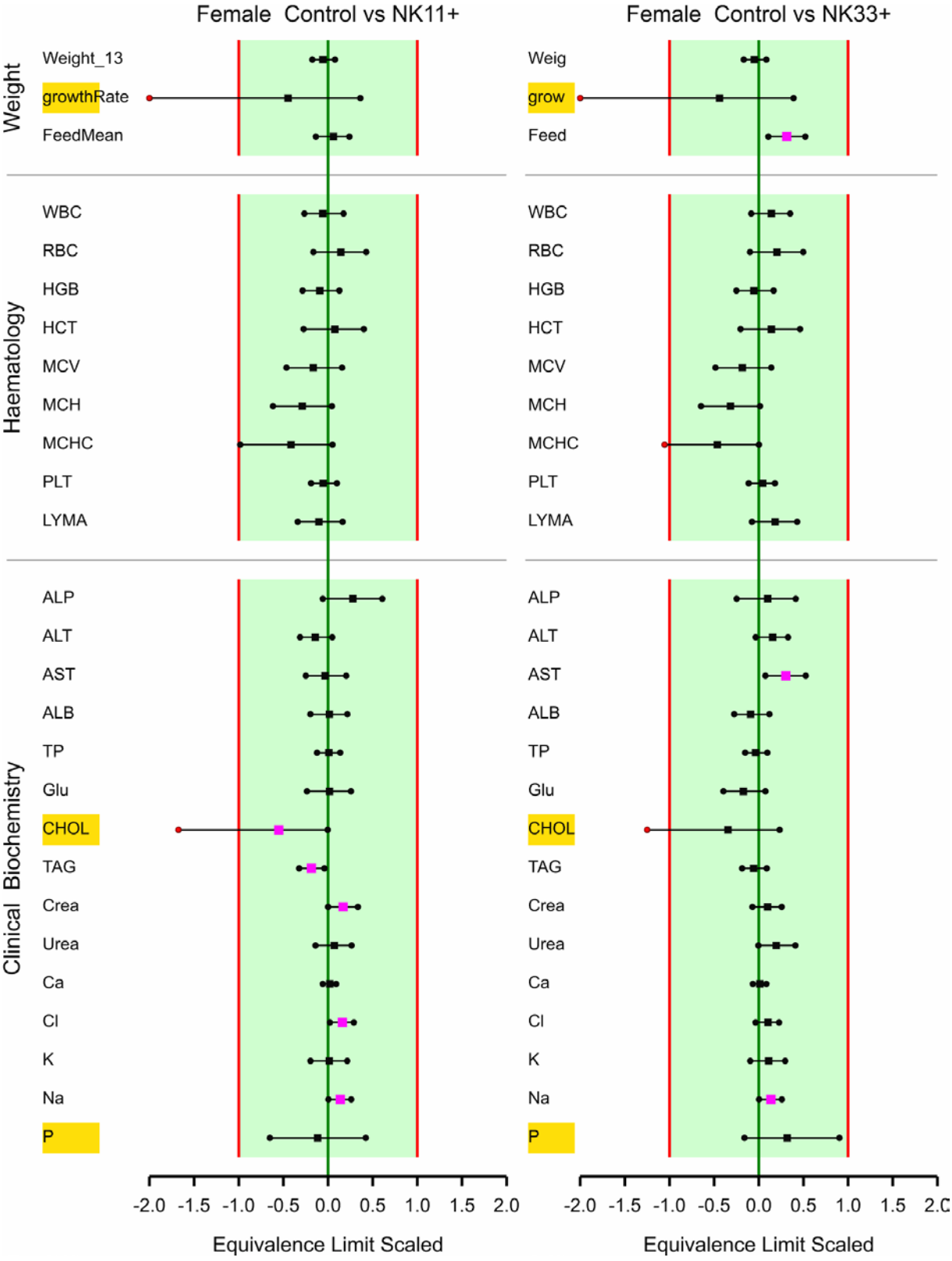

Figure 8 **Equivalence testing of NK11+ and NK33+ versus the control feed for females. For estimates (square symbols) on the left of zero the GM feed has a smaller mean than the control feed. See Table 10, Figure 15 and Figure 16 for further interpretation. Endpoints labelled with a golden background have a large residual variance compared to the historical studies (VR>150%). Fuchsia coloured symbols denote a significant difference.**

Table 9 95% Confidence interval plus estimate for the ratio Δ of the GMO feeds versus the Control feed for males. Intervals are based on an ANOVA with 5 feeding groups. Ratios with corresponding Intervals that do not encompass the value 1 are coloured red; this is equivalent to a significant difference according to a t-test with significance level 5%.

Weights	**NK11- vs Control**			**NK33- vs Control**			**NK11+ vs Control**			**NK33+ vs Control**		
Males	Lower	Ratio	Upper	Lower	Ratio	Upper	Lower	Ratio	Upper	Lower	Ratio	Upper
Weight_13	0.962	0.985	1.007	0.969	0.991	1.014	0.975	0.998	1.021	0.977	1.000	1.023
growthRate	0.984	0.992	1.001	0.987	0.996	1.005	0.998	1.007	1.015	0.989	0.997	1.006
FeedMean	0.987	1.008	1.029	0.965	0.985	1.006	0.977	0.997	1.018	1.005	1.026	1.048
Haematology	**NK11- vs Control**			**NK33- vs Control**			**NK11+ vs Control**			**NK33+ vs Control**		
Males	Lower	Ratio	Upper	Lower	Ratio	Upper	Lower	Ratio	Upper	Lower	Ratio	Upper
WBC	0.899	1.003	1.119	1.013	1.131	1.261	0.958	1.069	1.193	0.978	1.091	1.217
RBC	0.972	0.993	1.014	0.976	0.996	1.017	0.983	1.003	1.025	0.975	0.995	1.016
HGB	0.977	0.994	1.011	0.987	1.004	1.021	0.976	0.993	1.010	0.983	1.000	1.017
HCT	0.973	0.992	1.011	0.980	0.999	1.019	0.984	1.003	1.023	0.983	1.002	1.022
MCV	0.983	0.999	1.015	0.987	1.003	1.019	0.984	1.000	1.016	0.991	1.007	1.023
MCH	0.980	1.001	1.022	0.986	1.008	1.029	0.968	0.989	1.011	0.983	1.004	1.026
MCHC	0.991	1.002	1.013	0.994	1.004	1.015	0.980	0.990	1.001	0.987	0.997	1.008
PLT	0.947	1.027	1.113	0.969	1.050	1.138	0.970	1.051	1.139	0.991	1.074	1.164
LYMR	0.947	0.987	1.029	0.939	0.979	1.020	0.956	0.997	1.039	0.965	1.005	1.048
LYMA	0.895	1.005	1.128	0.987	1.108	1.243	0.950	1.067	1.198	0.979	1.099	1.234
ClinChem	**NK11- vs Control**			**NK33- vs Control**			**NK11+ vs Control**			**NK33+ vs Control**		
Males	Lower	Ratio	Upper	Lower	Ratio	Upper	Lower	Ratio	Upper	Lower	Ratio	Upper
ALP	0.917	1.012	1.117	0.886	0.978	1.080	0.892	0.985	1.087	0.924	1.020	1.126
ALT	0.942	1.009	1.080	0.896	0.959	1.027	0.905	0.969	1.037	0.904	0.968	1.036
AST	0.910	1.000	1.099	0.881	0.968	1.064	0.831	0.914	1.004	0.862	0.947	1.040
BIL	0.873	1.046	1.253	0.873	1.046	1.253	0.788	0.944	1.131	0.847	1.015	1.216
ALB	0.963	0.987	1.011	0.968	0.992	1.016	0.955	0.979	1.003	0.979	1.003	1.028
TP	0.978	0.998	1.017	0.972	0.991	1.011	0.976	0.995	1.015	0.985	1.004	1.024
Glu	0.916	0.980	1.049	0.911	0.975	1.044	0.957	1.024	1.096	0.973	1.042	1.115
CHOL	0.955	1.017	1.083	0.937	0.998	1.063	0.912	0.971	1.034	0.949	1.011	1.076
TAG	0.968	1.093	1.235	0.972	1.098	1.240	0.984	1.112	1.256	0.890	1.006	1.136
Crea	0.878	0.941	1.010	0.889	0.953	1.022	0.902	0.967	1.037	0.897	0.962	1.032
Urea	0.896	0.949	1.005	0.914	0.967	1.024	0.918	0.972	1.029	0.931	0.985	1.043

cHGB	0.864	1.121	1.455	0.828	1.075	1.395	0.725	0.941	1.221	0.815	1.057	1.372
Ca	0.991	1.003	1.016	0.989	1.002	1.014	0.987	1.000	1.013	0.987	0.999	1.012
Cl	0.991	1.000	1.009	0.990	1.000	1.009	0.984	0.993	1.002	0.996	1.006	1.015
K	0.970	1.018	1.067	0.961	1.008	1.057	0.957	1.003	1.052	0.974	1.022	1.071
Na	0.993	0.999	1.005	0.998	1.004	1.009	0.994	1.000	1.006	0.999	1.004	1.010
P	0.899	0.947	0.997	0.939	0.989	1.041	0.918	0.967	1.018	0.913	0.961	1.012
Urine	**NK11- vs Control**			**NK33- vs Control**			**NK11+ vs Control**			**NK33+ vs Control**		
Males	Lower	Ratio	Upper	Lower	Ratio	Upper	Lower	Ratio	Upper	Lower	Ratio	Upper
uVol	0.797	1.020	1.305	0.606	0.776	0.992	0.734	0.939	1.201	0.741	0.949	1.213
uVolW	0.795	1.028	1.331	0.604	0.782	1.012	0.725	0.938	1.214	0.721	0.932	1.206
uLeu	0.662	0.947	1.353	1.028	1.469	2.100	0.739	1.056	1.510	0.871	1.246	1.781
uOsmoll	0.730	0.940	1.209	0.929	1.196	1.539	0.830	1.068	1.375	0.793	1.020	1.313
uKeton	0.660	1.145	1.984	1.034	1.793	3.109	0.652	1.130	1.960	0.689	1.194	2.070
upH	0.641	0.839	1.099	0.745	0.975	1.277	0.726	0.951	1.246	0.657	0.861	1.127

Table 10 95% Confidence interval plus estimate for the ratio Δ of the GMO feeds versus the Control feed for females. Intervals are based on an ANOVA with 5 feeding groups. Ratios with corresponding Intervals that do not encompass the value 1 are coloured red; this is equivalent to a significant difference according to a t-test with significance level 5%.

Weights	**NK11- vs Control**			**NK33- vs Control**			**NK11+ vs Control**			**NK33+ vs Control**		
Females	Lower	Ratio	Upper	Lower	Ratio	Upper	Lower	Ratio	Upper	Lower	Ratio	Upper
Weight_13	0.975	0.991	1.008	0.976	0.993	1.010	0.976	0.993	1.010	0.977	0.994	1.011
growthRate	0.975	0.994	1.012	0.972	0.990	1.009	0.970	0.988	1.006	0.970	0.988	1.007
FeedMean	1.002	1.026	1.050	0.987	1.010	1.034	0.984	1.008	1.032	1.014	1.039	1.063
Haematology	**NK11- vs Control**			**NK33- vs Control**			**NK11+ vs Control**			**NK33+ vs Control**		
Females	Lower	Ratio	Upper	Lower	Ratio	Upper	Lower	Ratio	Upper	Lower	Ratio	Upper
WBC	0.935	1.060	1.201	0.908	1.027	1.162	0.856	0.969	1.096	0.956	1.081	1.222
RBC	0.977	1.000	1.023	0.992	1.015	1.038	0.988	1.011	1.034	0.993	1.015	1.038
HGB	0.980	0.994	1.009	0.993	1.007	1.022	0.979	0.994	1.008	0.982	0.996	1.011
HCT	0.978	0.996	1.016	0.992	1.011	1.030	0.986	1.004	1.023	0.989	1.008	1.027
MCV	0.989	1.001	1.014	0.981	0.993	1.005	0.982	0.994	1.006	0.981	0.993	1.005
MCH	0.980	1.000	1.020	0.974	0.993	1.012	0.964	0.983	1.002	0.963	0.982	1.001
MCHC	0.986	0.998	1.010	0.984	0.996	1.008	0.977	0.989	1.001	0.976	0.988	1.000

PLT	0.908	0.965	1.025	0.895	0.950	1.008	0.922	0.979	1.039	0.958	1.017	1.081
LYMR	0.919	0.961	1.006	0.941	0.984	1.029	0.936	0.979	1.023	0.959	1.003	1.049
LYMA	0.899	1.029	1.177	0.887	1.013	1.156	0.832	0.949	1.083	0.962	1.098	1.253
ClinChem	**NK11- vs Control**			**NK33- vs Control**			**NK11+ vs Control**			**NK33+ vs Control**		
Females	Lower	Ratio	Upper	Lower	Ratio	Upper	Lower	Ratio	Upper	Lower	Ratio	Upper
ALP	0.928	1.027	1.137	0.931	1.028	1.136	0.983	1.086	1.200	0.932	1.030	1.138
ALT	0.909	1.014	1.131	0.877	0.977	1.087	0.829	0.922	1.027	0.980	1.091	1.215
AST	0.908	1.003	1.108	0.980	1.081	1.192	0.894	0.986	1.087	1.032	1.138	1.255
BIL	0.829	0.927	1.038	0.945	1.056	1.179	0.860	0.960	1.073	0.901	1.007	1.124
ALB	0.953	0.994	1.036	0.954	0.994	1.036	0.963	1.003	1.045	0.943	0.982	1.023
TP	0.966	0.990	1.015	0.969	0.993	1.017	0.978	1.002	1.026	0.970	0.993	1.017
Glu	0.919	0.994	1.075	0.879	0.949	1.025	0.931	1.005	1.086	0.877	0.947	1.023
CHOL	0.873	0.972	1.082	0.827	0.919	1.021	0.809	0.899	0.999	0.842	0.936	1.040
TAG	0.863	0.969	1.088	0.803	0.900	1.008	0.772	0.865	0.969	0.853	0.956	1.071
Crea	0.990	1.044	1.102	0.963	1.015	1.070	1.000	1.054	1.111	0.979	1.032	1.088
Urea	0.958	1.018	1.082	0.951	1.010	1.072	0.962	1.021	1.084	0.998	1.060	1.125
cHGB	0.831	0.956	1.098	0.996	1.142	1.310	0.768	0.880	1.010	0.902	1.034	1.186
Ca	0.990	1.003	1.015	0.993	1.006	1.018	0.991	1.003	1.016	0.990	1.002	1.014
Cl	0.998	1.008	1.017	0.999	1.009	1.018	1.001	1.011	1.020	0.998	1.007	1.016
K	0.972	1.022	1.074	0.973	1.022	1.074	0.955	1.003	1.054	0.978	1.027	1.079
Na	0.999	1.008	1.016	0.999	1.008	1.016	1.000	1.009	1.017	1.000	1.009	1.017
P	0.960	1.064	1.180	1.015	1.123	1.242	0.879	0.975	1.080	0.969	1.072	1.186
Urine	**NK11- vs Control**			**NK33- vs Control**			**NK11+ vs Control**			**NK33+ vs Control**		
Females	Lower	Ratio	Upper	Lower	Ratio	Upper	Lower	Ratio	Upper	Lower	Ratio	Upper
uVol	0.710	0.943	1.251	0.911	1.198	1.574	0.675	0.888	1.167	0.648	0.851	1.119
uVolW	0.719	0.949	1.253	0.903	1.180	1.543	0.665	0.869	1.137	0.650	0.850	1.112
uLeu	0.629	0.913	1.324	0.737	1.056	1.514	0.737	1.056	1.514	0.625	0.896	1.284
uOsmoll	0.818	1.075	1.413	0.653	0.851	1.108	0.929	1.210	1.576	0.963	1.254	1.634
uKeton	0.722	1.017	1.434	0.791	1.102	1.536	1.028	1.432	1.996	0.836	1.164	1.623
upH	0.544	0.750	1.034	0.752	1.025	1.398	0.631	0.861	1.174	0.715	0.975	1.330

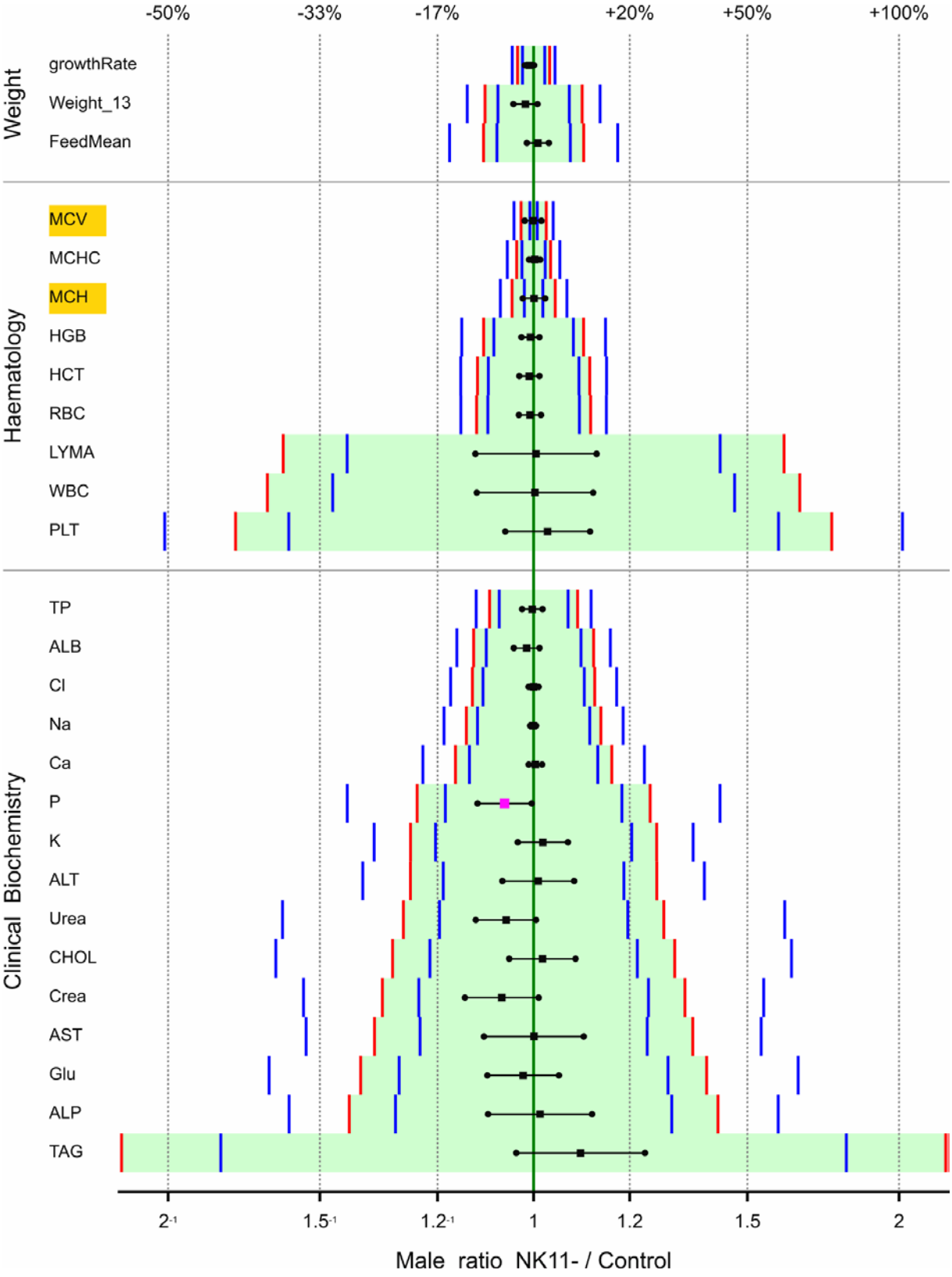

Figure 9 **95% confidence intervals for the ratio of NK11- and the Control feed for males with added intervals for the equivalence limits (blue and red bars, see text). Endpoints labelled with a golden background have a large residual variance compared to the historical studies (VR>150%).**

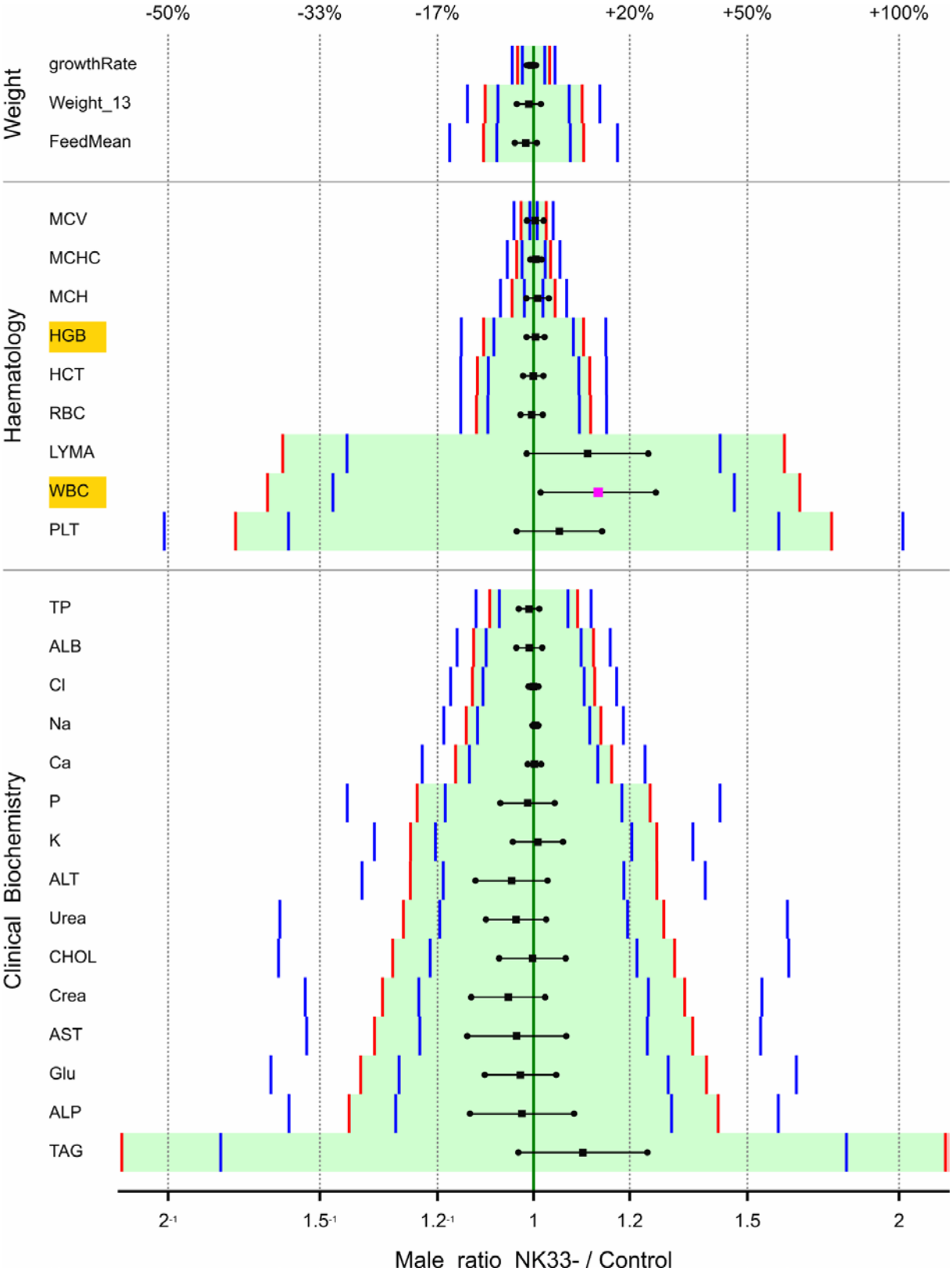

Figure 10 95% confidence intervals for the ratio of NK33- and the Control feed for males with added intervals for the equivalence limits (blue and red bars, see text). Endpoints labelled with a golden background have a large residual variance compared to the historical studies (VR>150%).

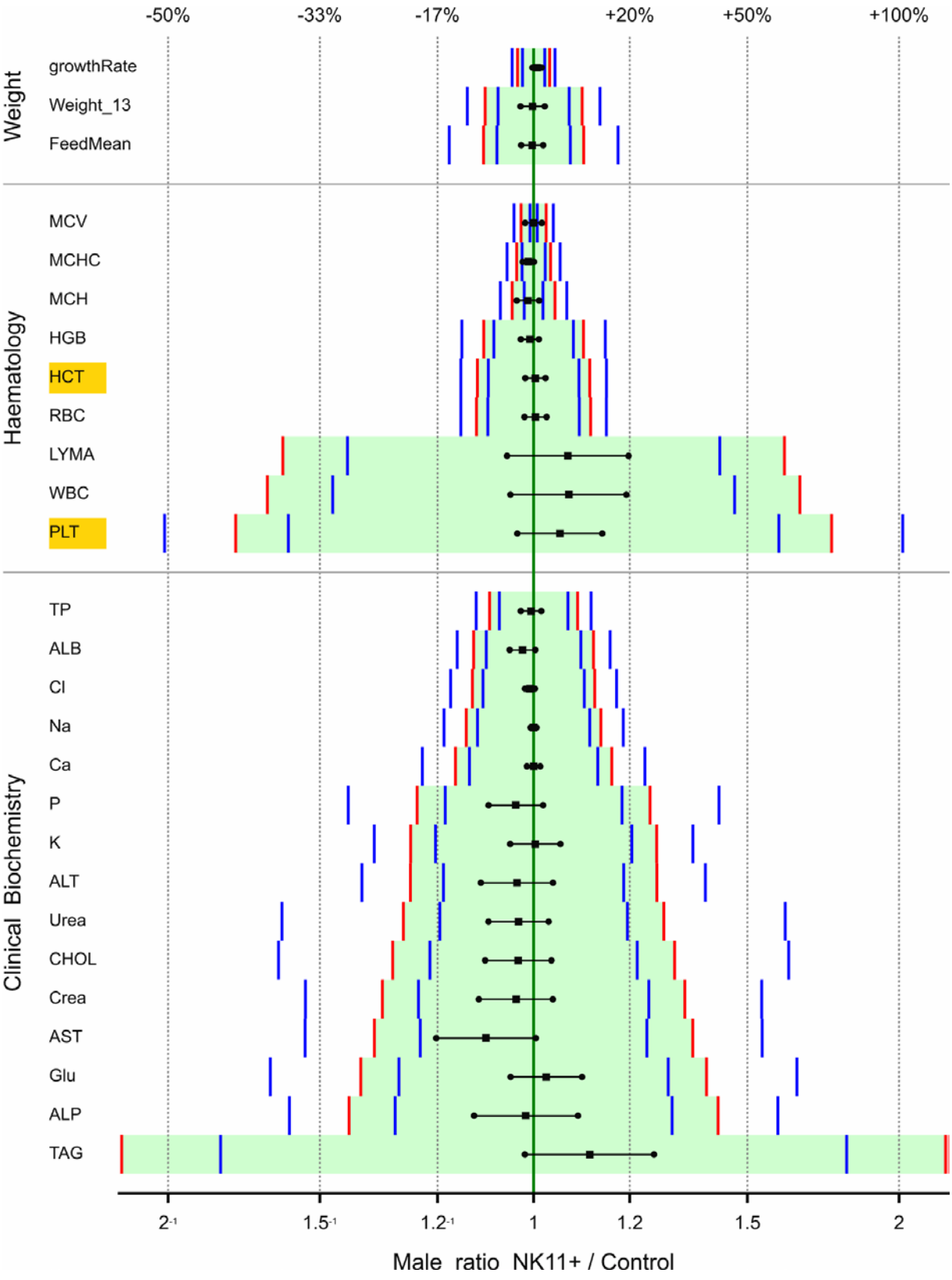

Figure 11 95% confidence intervals for the ratio of NK11+ and the Control feed for males with added intervals for the equivalence limits (blue and red bars, see text). Endpoints labelled with a golden background have a large residual variance compared to the historical studies (VR>150%).

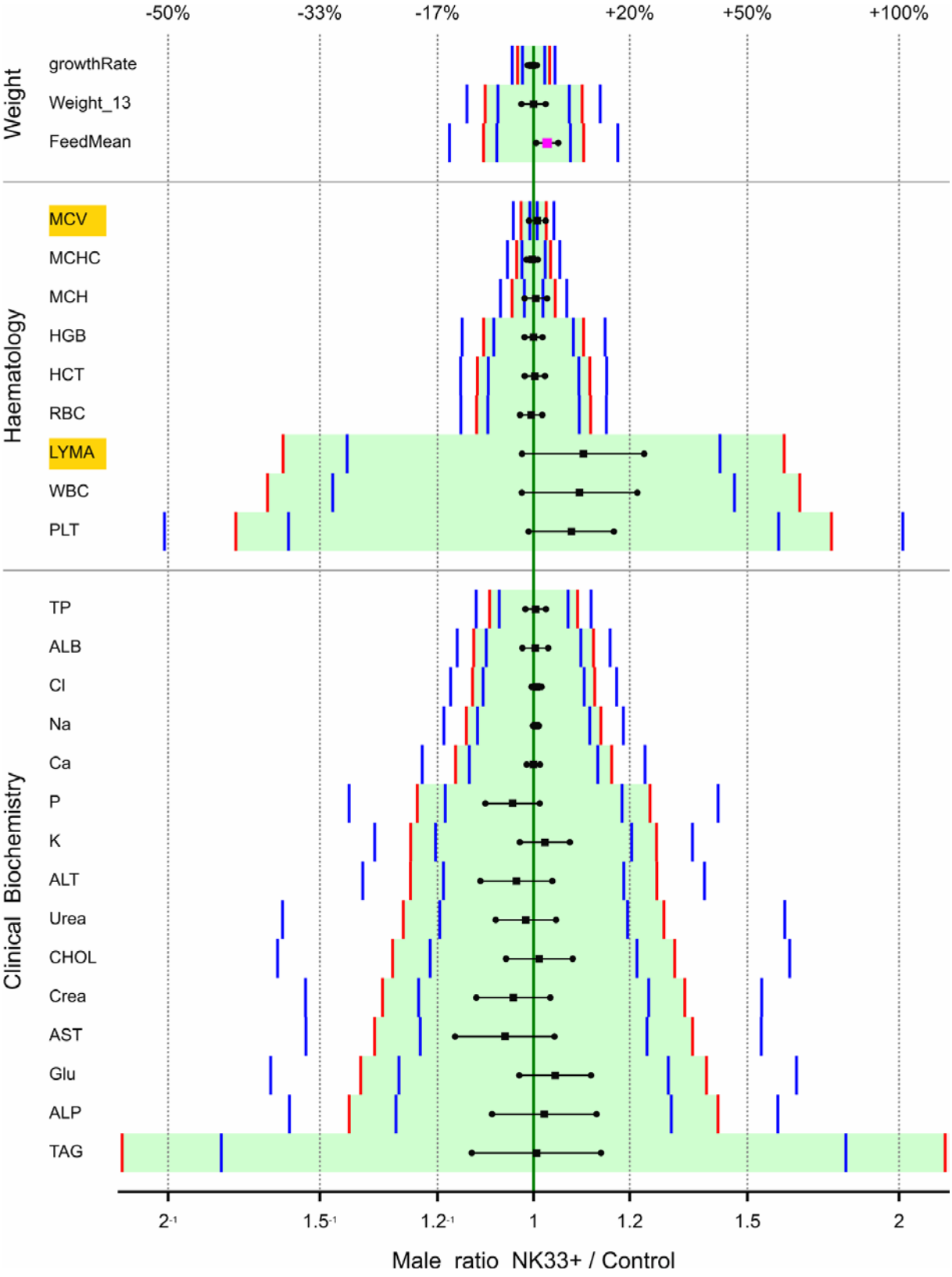

Figure 12 95% confidence intervals for the ratio of NK33+ and the Control feed for males with added intervals for the equivalence limits (blue and red bars, see text). Endpoints labelled with a golden background have a large residual variance compared to the historical studies (VR>150%).

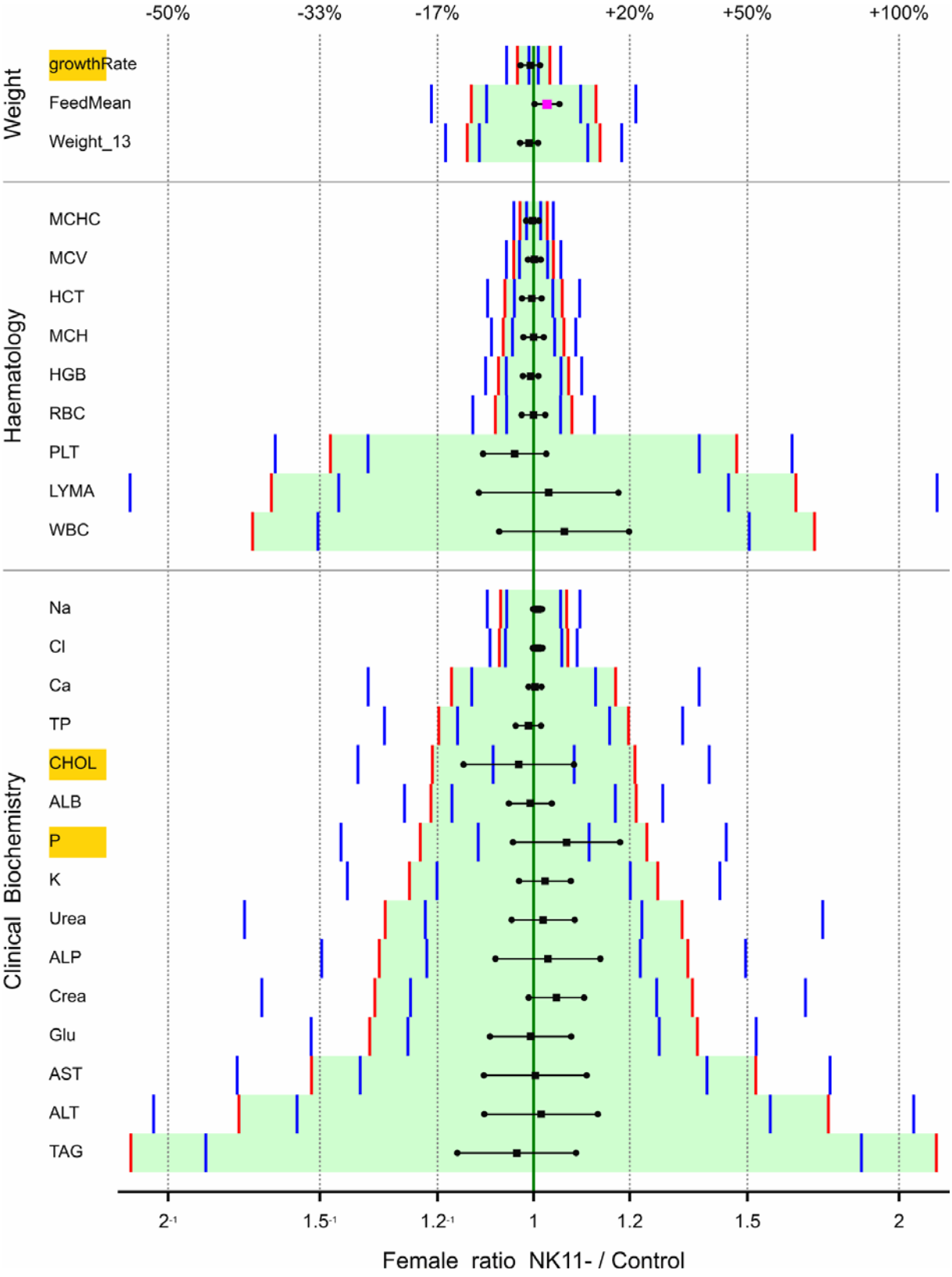

Figure 13 95% confidence intervals for the ratio of NK11- and the Control feed for females with added intervals for the equivalence limits (blue and red bars, see text). Endpoints labelled with a golden background have a large residual variance compared to the historical studies (VR>150%).

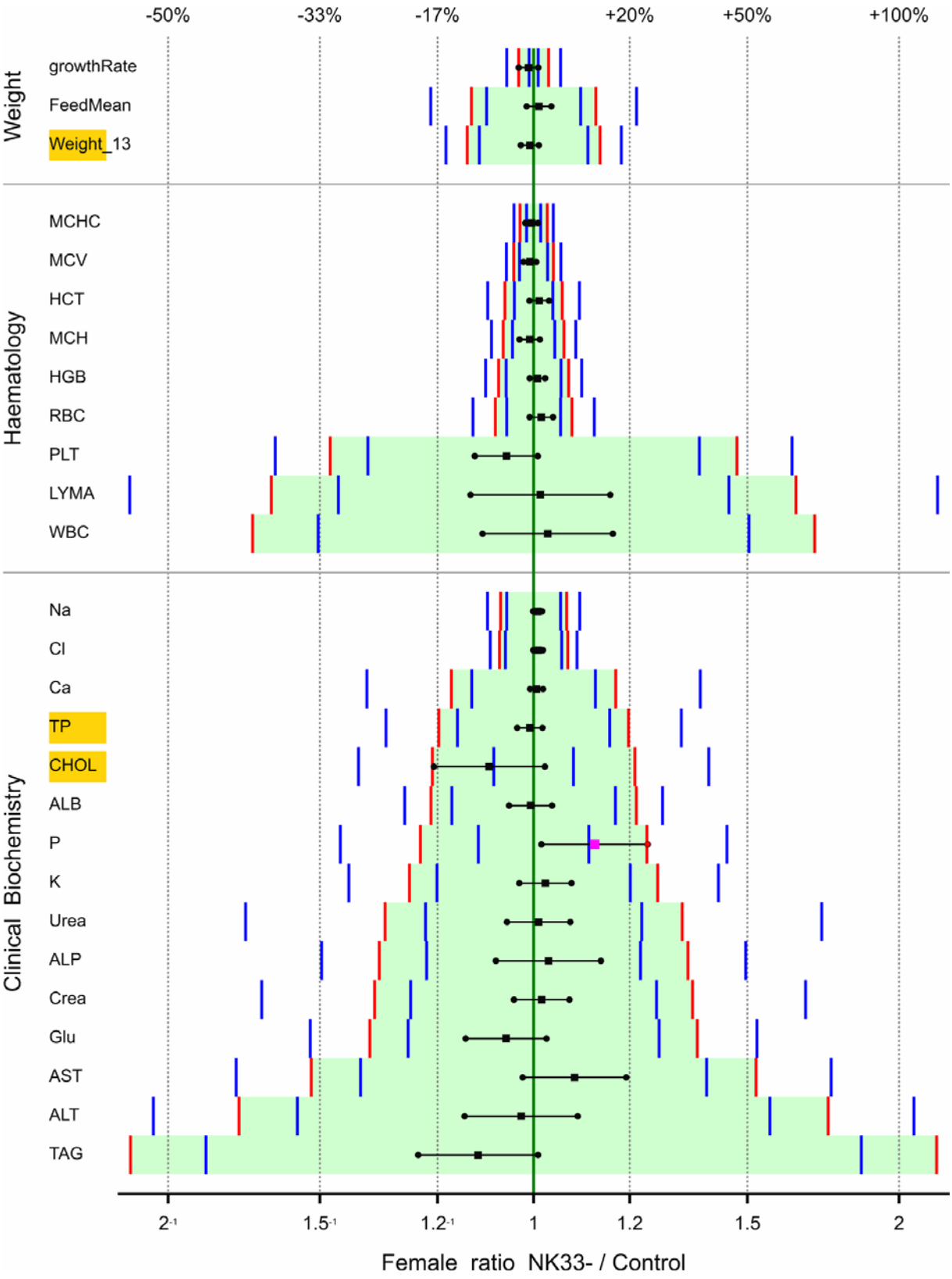

Figure 14 95% confidence intervals for the ratio of NK33- and the Control feed for females with added intervals for the equivalence limits (blue and red bars, see text). Endpoints labelled with a golden background have a large residual variance compared to the historical studies (VR>150%).

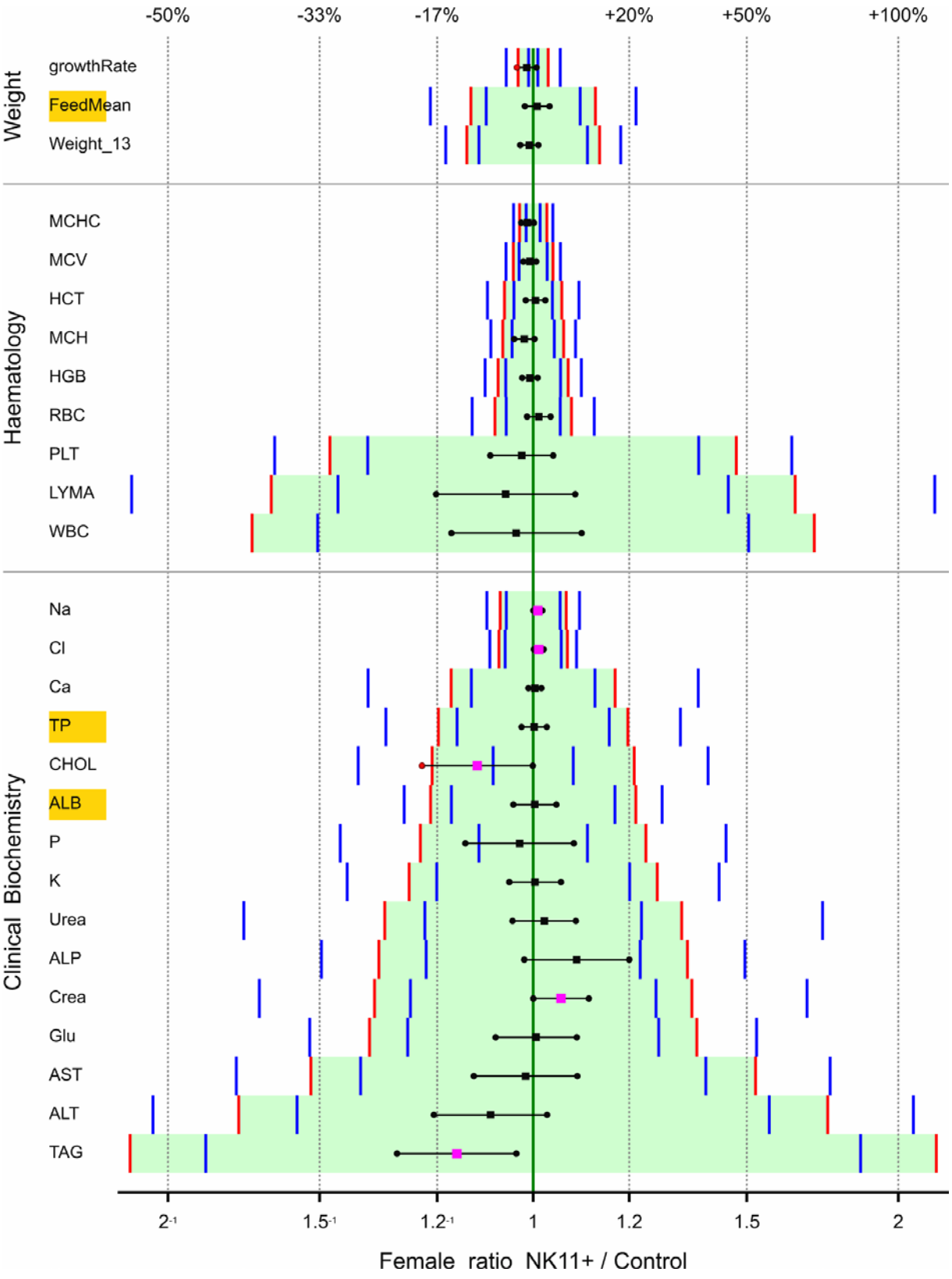

Figure 15 95% confidence intervals for the ratio of NK11+ and the Control feed for females with added intervals for the equivalence limits (blue and red bars, see text). Endpoints labelled with a golden background have a large residual variance compared to the historical studies (VR>150%).

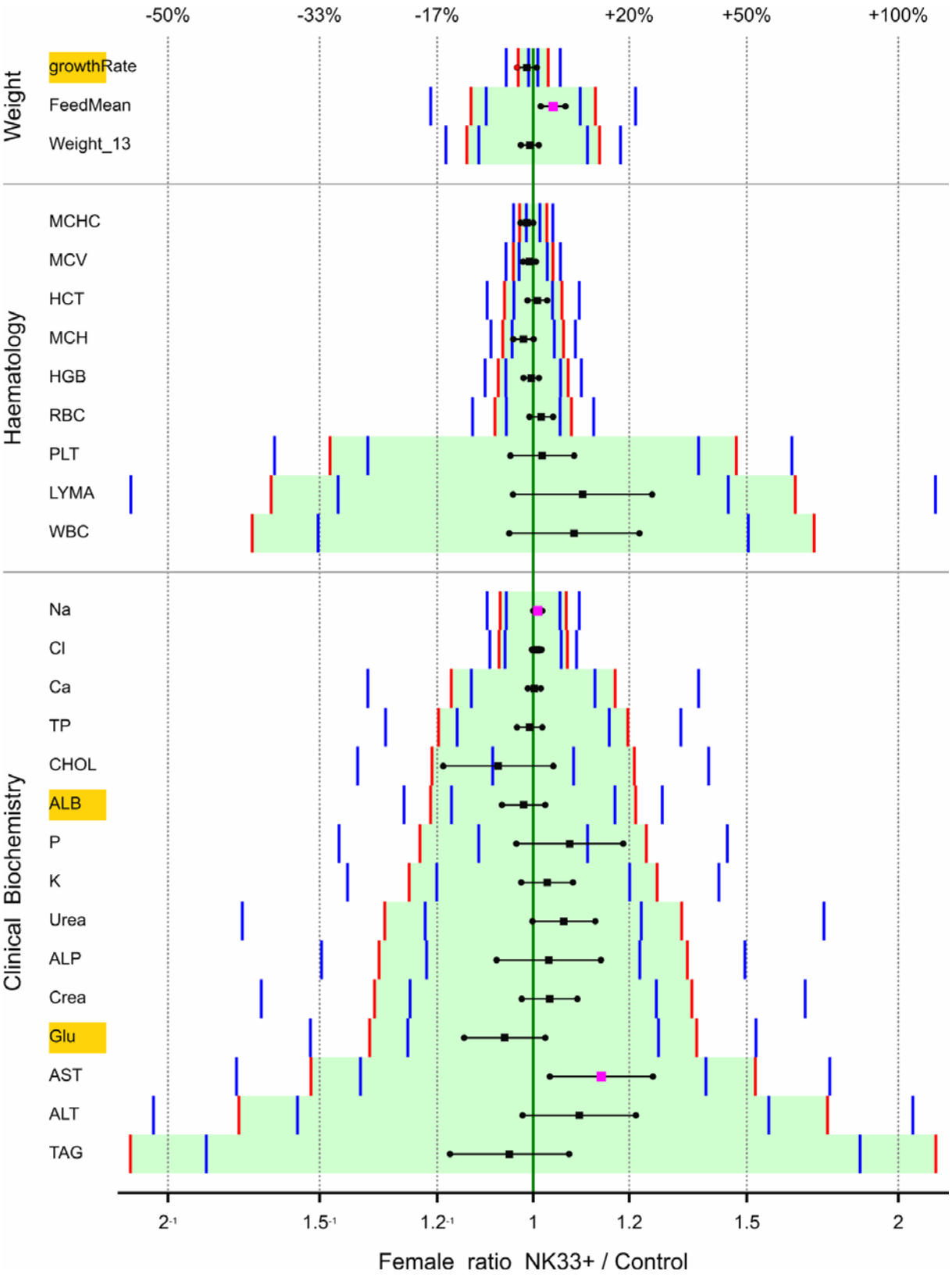

Figure 16 95% confidence intervals for the ratio of NK33+ and the Control feed for females with added intervals for the equivalence limits (blue and red bars, see text).

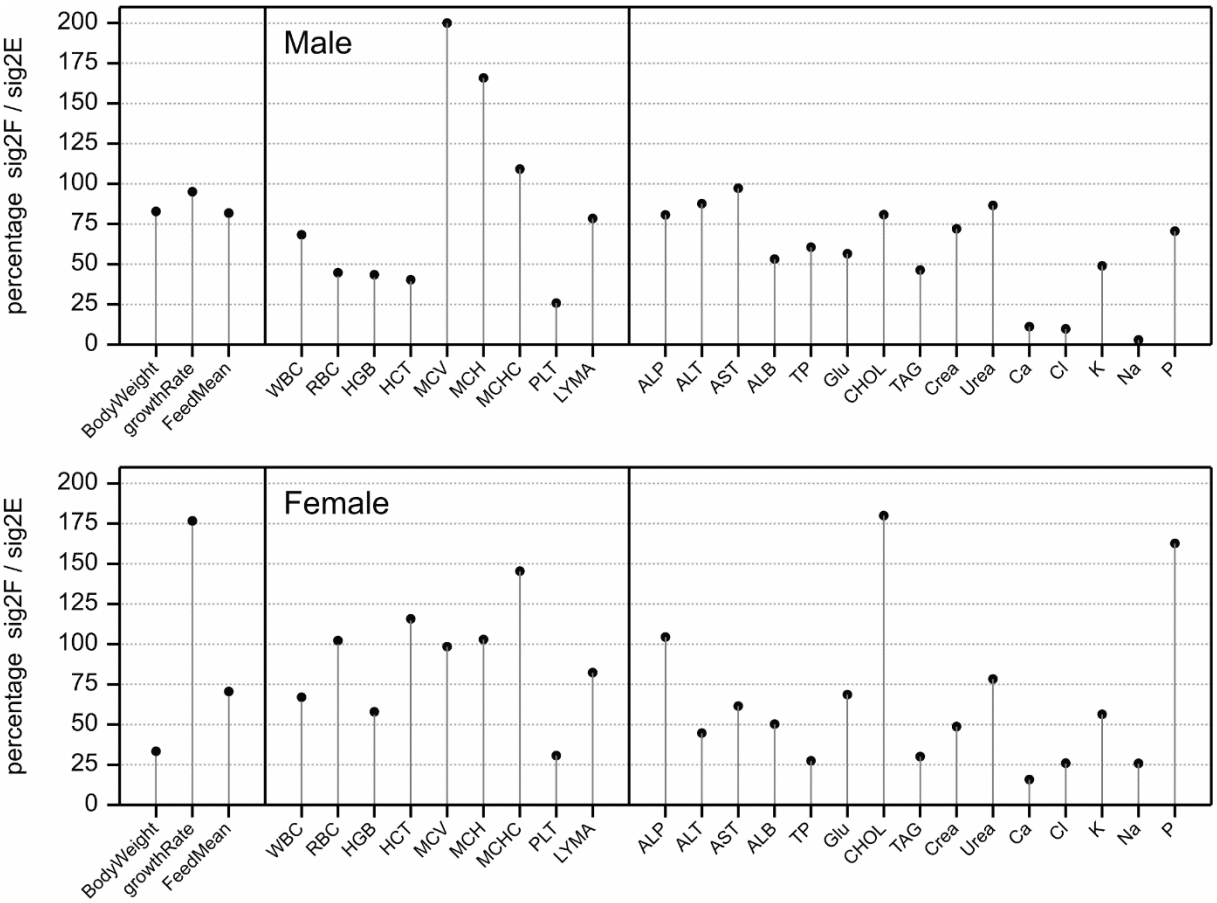

Figure 17 Residual variance (sig2F or σ_F^2) in the current G-TwYST A study as a percentage of the residual variance (sig2E or σ_E^2) in the historical GRACE studies for males (top panel) and females (bottom panel).

3.2 Equivalence testing using target effect sizes

90% confidence intervals for 7 variables, with equivalence limits according to the targeted effect sizes in Hong *et al.* (2017), are given in Figure 18 for males and in Figure 19 for females. Note that these are 90% intervals, rather than the 95% intervals in Figure 9 to Figure 16. In all cases the null hypothesis of non-equivalence is rejected with a p-value smaller than 0.01 (Table 11).

Table 11 P-values of equivalence tests for the ratio of the mean of the GMO feed versus the mean of the control feed using targeted effect sizes of Hong *et al.* (2017) as equivalence limits. P-values smaller than 0.01/0.05 have a gold/yellow background.

Variable	Males				Females			
	NK11-	NK33-	NK11+	NK33+	NK11-	NK33-	NK11+	NK33+
Weight_13	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
WBC	0.000	0.007	0.000	0.001	0.001	0.000	0.000	0.002
LYMA	0.000	0.004	0.001	0.002	0.000	0.000	0.000	0.007
ALP	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Crea	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Urea	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CHOL	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

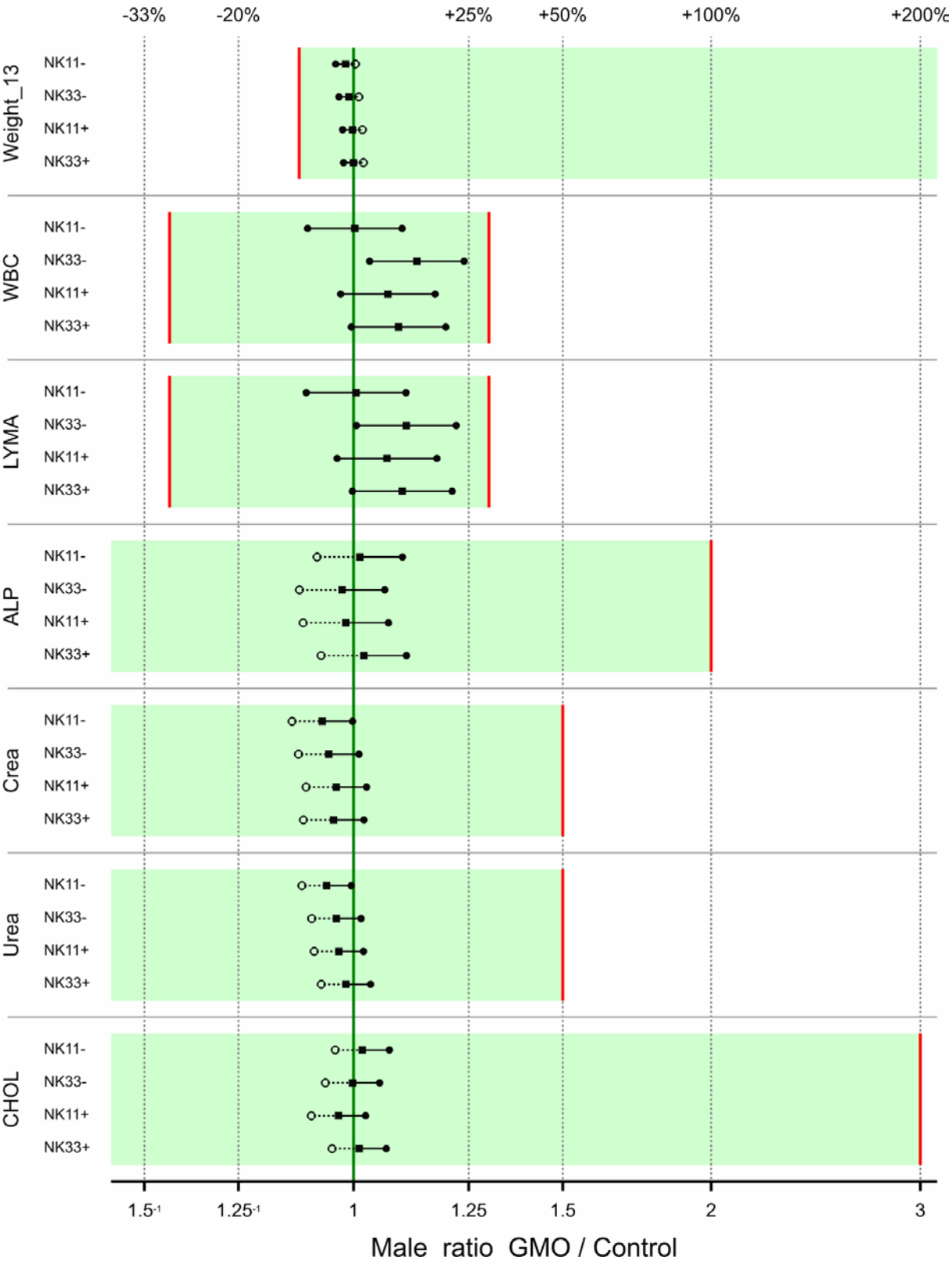

Figure 18 90% confidence intervals for the ratio of the mean of the GMO feed and the control feed for selected variables for males along with equivalence intervals defined by targeted effect sizes of Hong *et al.* (2017).

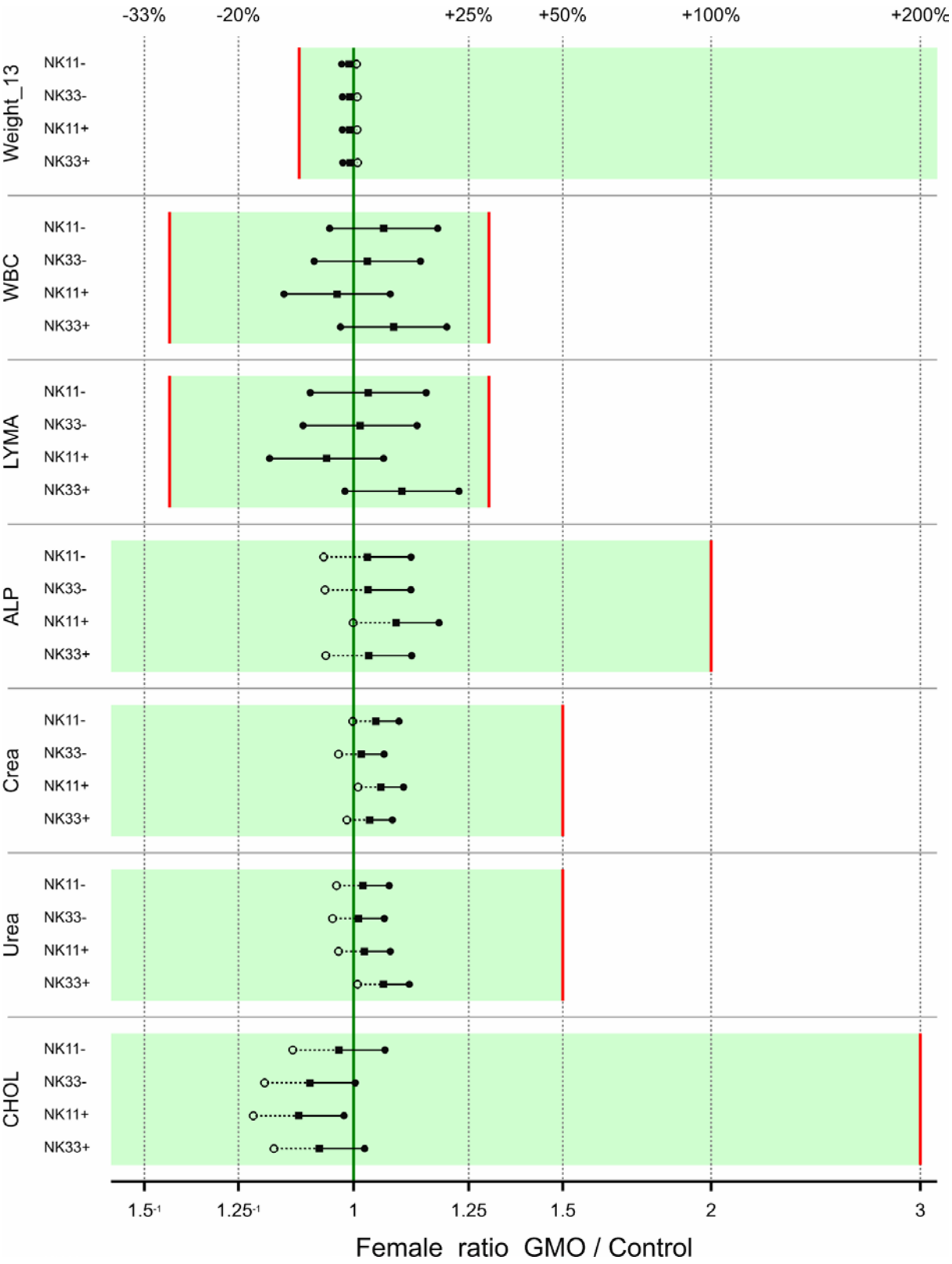

Figure 19 90% confidence intervals for the ratio of the mean of the GMO feed and the control feed for selected variables for females along with equivalence intervals defined by targeted effect sizes of Hong *et al.* (2017).

3.3 Classical statistical analysis

A classical analysis of variance was performed on the cage means after log transforming the data. Note that the ANOVA residuals were already assessed by means of a normal probability plot (Appendix 5) and a plot of residuals versus fitted values (Appendix 6). Table 12 (males) and Table 13 (females) present the results of the t-tests, of Dunnett's tests and of Wilcoxon tests for the 36 variables divided in four groups. For ease of interpretation results are expressed as means and coefficients of variation on the original scale, rather than as means and standard deviations on the log scale. Note however that 95% confidence intervals on the ratio scale are given in Table 9 (males) and Table 10 (females).

Results of the t-test and Dunnett's test for the difference are summarized by letters which indicate significance at 5% and at 1%. Results for the non-parametric Wilcoxon test, where each test only uses data for the specific GM feed and the non-GM Control feed, are summarized in the same way. Exact p-values for these tests are given in Appendix 9.

It can be seen (Table 12 and Table 13) that the relative precision of variables ranges from high to low precision. For example CVs smaller than 5% are observed for e.g. HGB, MCV, MCHC, TP and Na, while CVs larger than 50% are found for cHGB, uLeu and uKeton. For some variables there is a difference in precision for males and females, e.g. BIL for males has a CV in the range 44-69%, while for females the range equals 15-30%.

In 26 cases (9.0% of the 288 comparisons) a difference was significant in at least one of the tests at the 5% level. On their own, Dunnett's test resulted in 3 significant differences (1.0%), the t-test resulted in 17 significant differences (5.9%), and Wilcoxon's test resulted in 19 significant differences (6.6%). Note that cells coloured red in Table 9 and Table 10, with 95% confidence intervals for ratios, correspond to cells coloured red in Table 12 and Table 13 with letters "t", "T", "d" or "D".

Results of the Shapiro-Wilks test for normality and Bartlett's and Levene's test for homogeneity of variance are given in Appendix 10. Bartlett's' test is significant at the 5% level for males for 4 variables (WBC, PLT, LYMR, upH) and for females for 0 variables. Levene's test is significant for WBC and Cl (males), and WBC (females). This implies the important assumption of homogeneity of variance is generally fulfilled. For these significant cases, one might resort to Wilcoxon's test which is significant for WBC in males (NK33-) and PLT in males (NK33+).

The Shapiro-Wilks test for non-normality for separate feeding groups (Appendix 10) is frequently significant. However the normality assumptions is not very important. Moreover normal probability plots (Appendix 5) and plots of residuals versus fitted values (Appendix 6) were generally satisfactory. Also, graphs of cage means on the log scale in Appendix 4 indicate that significance of non-normality seems mostly due to one outlying observation in a feeding group.

3.4 Standardized effect sizes

SES intervals were calculated for all 36 variables. Results for the four treatment groups, separately for males and females, are given in Figure 20 to Figure 23. The number of intervals that extend outside the -/+ 1 SD limits equals 106 out of 288 (37%).

Table 12 Means and coefficient of variation (CV) for male rats. Means of GM feeds which are significantly different from the non-GM Control feed are marked, with red background colouring, as follows: D: P<0.01 by Dunnett-test, d: P<0.05 by Dunnett-test, T: P<0.01 by t-test but not by Dunnett-test, t: P<0.05 by t-test but not by Dunnett-test, W: P<0.01 by Wilcoxon signed rank test, w: P<0.05 by Wilcoxon signed rank test. Dunnett- and t-tests are based on an ANOVA with 5 treatment groups, while Wilcoxon tests only uses data for the specific GM feed and the control feed.

Weights	**Control**		**NK11-**			**NK33-**			**NK11+**			**NK33+**		
Males	Mean	CV	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig
Weight_13	428.3	5.8	421.8	6.4		424.8	7.1		427.6	6.6		428.4	6.5	
growthRate	0.148	12.0	0.140	15.9		0.144	16.1		0.154	10.6		0.145	10.5	
FeedMean	19.60	4.6	19.77	5.5		19.32	5.7		19.55	5.2		20.13	6.3	tw
Haematology	**Control**		**NK11-**			**NK33-**			**NK11+**			**NK33+**		
Males	Mean	CV	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig
WBC	10.09	13.6	10.17	20.5		11.47	12.5	tW	10.93	21.8		11.16	23.3	
RBC	8.641	3.6	8.580	3.3		8.606	2.9		8.672	3.1		8.603	3.3	
HGB	16.16	3.1	16.06	2.6		16.22	2.5		16.04	2.7		16.16	2.8	
HCT	46.53	3.6	46.13	2.7		46.48	2.9		46.66	2.8		46.63	3.3	
MCV	53.86	2.7	53.80	2.7		54.03	2.2		53.84	2.2		54.23	2.2	
MCH	18.72	3.5	18.74	3.7		18.87	2.9		18.53	2.7		18.81	3.5	
MCHC	34.75	1.6	34.82	1.6		34.91	1.5		34.41	1.5		34.66	2.2	
PLT	824.5	14.9	846.8	12.5		869.5	14.3		860.5	7.8		887.7	12.1	w
LYMR	73.34	7.1	72.54	8.1		72.16	9.5		73.17	6.3		73.67	5.1	
LYMA	7.388	15.0	7.520	24.7		8.258	16.2		7.982	23.1		8.245	26.0	
ClinChem	**Control**		**NK11-**			**NK33-**			**NK11+**			**NK33+**		
Males	Mean	CV	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig
ALP	1.508	22.0	1.544	24.0		1.466	17.9		1.475	16.2		1.556	26.2	
ALT	0.662	14.7	0.679	23.5		0.638	17.1		0.642	14.9		0.643	16.1	
AST	2.269	20.7	2.252	15.1		2.181	13.6		2.082	23.1		2.125	13.4	
BIL	6.810	57.3	7.162	43.6		7.265	65.0		6.683	69.3		6.935	62.3	
ALB	39.71	4.8	39.19	5.8		39.38	4.7		38.84	3.7	w	39.87	7.0	
TP	67.72	3.1	67.56	3.8		67.13	3.1		67.37	2.8		68.01	4.5	
Glu	5.990	13.9	5.856	12.4		5.863	15.6		6.122	13.0		6.243	14.6	
CHOL	2.134	9.8	2.169	10.3		2.136	11.8		2.077	10.7		2.167	11.2	
TAG	1.014	23.1	1.138	29.5		1.144	28.8		1.160	31.9		1.031	24.6	

Crea	37.37	11.6	35.44	13.1		35.87	15.6		36.23	11.9		35.98	13.3	
Urea	5.851	11.2	5.611	18.8		5.697	14.9		5.691	12.0		5.776	10.0	
cHGB	84.8	64.0	100.4	63.4		93.9	70.4		86.8	72.7		94.5	87.5	
Ca	2.545	3.8	2.553	3.4		2.548	3.7		2.545	3.3		2.544	3.7	
Cl	104.1	2.6	104.1	1.6		104.1	1.9		103.4	1.4		104.7	2.0	
K	5.342	11.6	5.425	10.1		5.395	13.6		5.350	10.0		5.467	15.8	
Na	145.6	2.3	145.5	1.5		146.1	1.3		145.6	1.5		146.2	1.6	
P	2.568	8.4	2.431	10.3	tw	2.557	13.1		2.482	7.7		2.473	10.8	
Urine	**Control**		**NK11-**			**NK33-**			**NK11+**			**NK33+**		
Males	Mean	CV	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig
uVol	26.40	27.3	26.25	20.8		21.35	42.5	t	24.85	21.5		25.95	26.8	
uVolW	6.296	30.6	6.292	25.8		5.044	39.1		5.929	29.5		6.014	23.9	
uLeu	7.50	140.5	6.25	170.0		21.25	111.1	t	8.75	135.5		17.50	112.7	
uOsmoll	323.8	32.4	296.4	22.5		394.4	33.5		338.3	26.5		362.4	62.4	
uKeton	0.825	117.0	0.825	89.3		1.125	48.3	t	0.700	76.8		0.875	113.7	
upH	6.900	2.5	6.725	3.3		6.875	3.1		6.850	7.9		6.750	3.9	

Table 13 Means and coefficient of variation (CV) for female rats. Means of GMO feeds which are significantly different from the Control feed are marked, with red background colouring, as follows: D: P<0.01 by Dunnett-test, d: P<0.05 by Dunnett-test, T: P<0.01 by t-test but not by Dunnett-test, t: P<0.05 by t-test but not by Dunnett-test, W: P<0.01 by Wilcoxon signed rank test, w: P<0.05 by Wilcoxon signed rank test. Note that Dunnett- and t-tests are based on a ANOVA with 5 treatment groups, while Wilcoxon tests only uses data for the specific GM feed and the control feed.

Weights	**Control**		**NK11-**			**NK33-**			**NK11+**			**NK33+**		
Females	Mean	CV	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig
Weight_13	243.2	5.5	241.1	5.3		241.5	5.5		241.5	6.2		241.7	6.1	
growthRate	0.195	20.8	0.189	25.9		0.185	25.4		0.183	23.2		0.184	25.1	
FeedMean	13.90	5.4	14.27	6.9	tw	14.05	6.4		14.01	6.4		14.45	6.5	DW
Haematology	**Control**		**NK11-**			**NK33-**			**NK11+**			**NK33+**		
Females	Mean	CV	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig
WBC	7.543	21.6	7.878	15.7		7.798	28.8		7.282	15.4		8.020	16.9	
RBC	7.618	4.3	7.618	4.0		7.731	4.6		7.697	3.7		7.734	4.8	
HGB	15.51	3.8	15.42	3.4		15.61	3.7		15.41	3.4		15.44	3.3	

HCT	44.41	2.9	44.23	3.1		44.89	2.3		44.60	2.5		44.78	3.9	
MCV	58.41	3.9	58.38	2.6		57.97	3.3		58.01	2.6		57.97	3.0	
MCH	20.40	5.6	20.39	5.4		20.23	4.4		20.04	4.3	w	20.00	3.8	
MCHC	34.92	2.7	34.90	4.3		34.79	2.8		34.55	3.3	w	34.51	2.7	
PLT	827.8	8.6	798.6	10.1		787.0	11.1		812.9	10.3		846.2	9.3	
LYMR	73.75	6.9	71.34	10.2		72.70	8.7		72.47	11.1		74.08	8.4	
LYMA	5.562	22.0	5.690	20.3		5.570	25.4		5.225	15.8		6.025	22.8	
ClinChem	**Control**		**NK11-**			**NK33-**			**NK11+**			**NK33+**		
Females	Mean	CV	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig
ALP	0.681	20.3	0.694	18.8		0.709	25.5		0.733	18.6		0.711	29.4	
ALT	0.522	22.9	0.532	29.5		0.507	19.8		0.475	16.3		0.569	24.4	
AST	2.136	17.5	2.115	19.1		2.282	13.3		2.091	17.1		2.428	19.8	dw
BIL	6.360	16.2	5.888	15.0		6.875	29.5		6.145	22.1		6.387	19.9	
ALB	45.85	6.3	45.84	9.9		45.67	6.5		46.02	6.7		45.16	10.0	
TP	71.34	4.7	70.66	6.2		70.84	4.4		71.48	5.1		70.89	5.7	
Glu	5.148	10.4	5.199	15.6		4.932	15.0		5.201	14.9		4.892	11.6	
CHOL	1.980	17.0	1.900	17.2		1.827	18.7		1.778	12.5	t	1.852	17.6	
TAG	0.696	18.7	0.677	23.3		0.626	17.0	w	0.608	20.8	d	0.655	12.2	
Crea	44.49	9.1	46.16	11.0		45.24	7.6		47.16	11.1	tw	46.01	10.6	
Urea	5.760	9.4	5.886	14.2		5.834	8.8		5.878	8.4		6.133	13.2	w
cHGB	72.05	26.2	68.40	19.9		85.25	39.1		61.89	19.2	w	72.43	25.0	
Ca	2.513	2.5	2.522	3.0		2.528	2.9		2.522	3.0		2.518	2.5	
Cl	100.3	2.4	101.0	2.7		101.1	2.0	w	101.4	3.4	t	101.0	2.9	
K	4.458	9.1	4.520	6.0		4.543	7.0		4.463	8.7		4.568	8.6	
Na	141.9	1.5	143.0	1.8		143.0	1.7	w	143.2	2.1	tw	143.2	1.9	tw
P	1.780	18.8	1.865	13.7		2.002	16.2	tW	1.765	24.5		1.957	32.9	
Urine	**Control**		**NK11-**			**NK33-**			**NK11+**			**NK33+**		
Females	Mean	CV	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig
uVol	20.25	25.3	19.05	31.6		23.65	27.7		18.20	42.7		16.45	37.1	
uVolW	8.453	21.1	7.980	28.4		9.711	27.0		7.449	42.7		6.878	35.7	
uLeu	8.75	178.8	5.00	129.1		10.00	164.6		12.50	163.3		6.25	253.9	
uOsmoll	323.1	17.5	333.8	35.9		287.9	33.9		390.9	25.2		398.9	26.7	
uKeton	0.100	241.5	0.050	210.8		0.175	178.8		0.325	115.0	t	0.200	153.7	
upH	6.400	4.9	6.150	5.1		6.425	4.5		6.250	4.2		6.375	8.1	

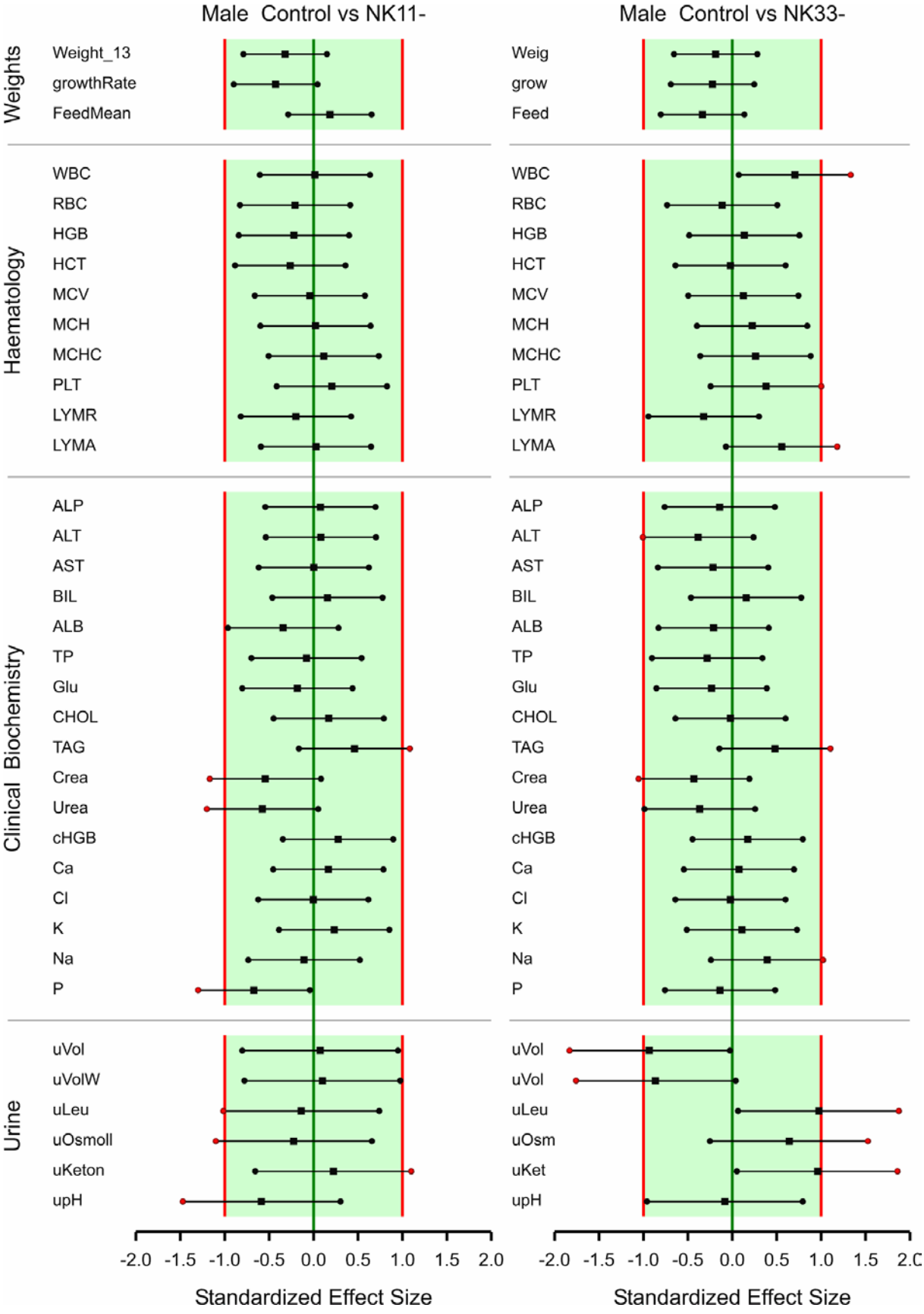

Figure 20 Confidence intervals for Standardized Effect Sized (SES) for male rats for GMO feeds NK11- and NK33- versus the control feed.

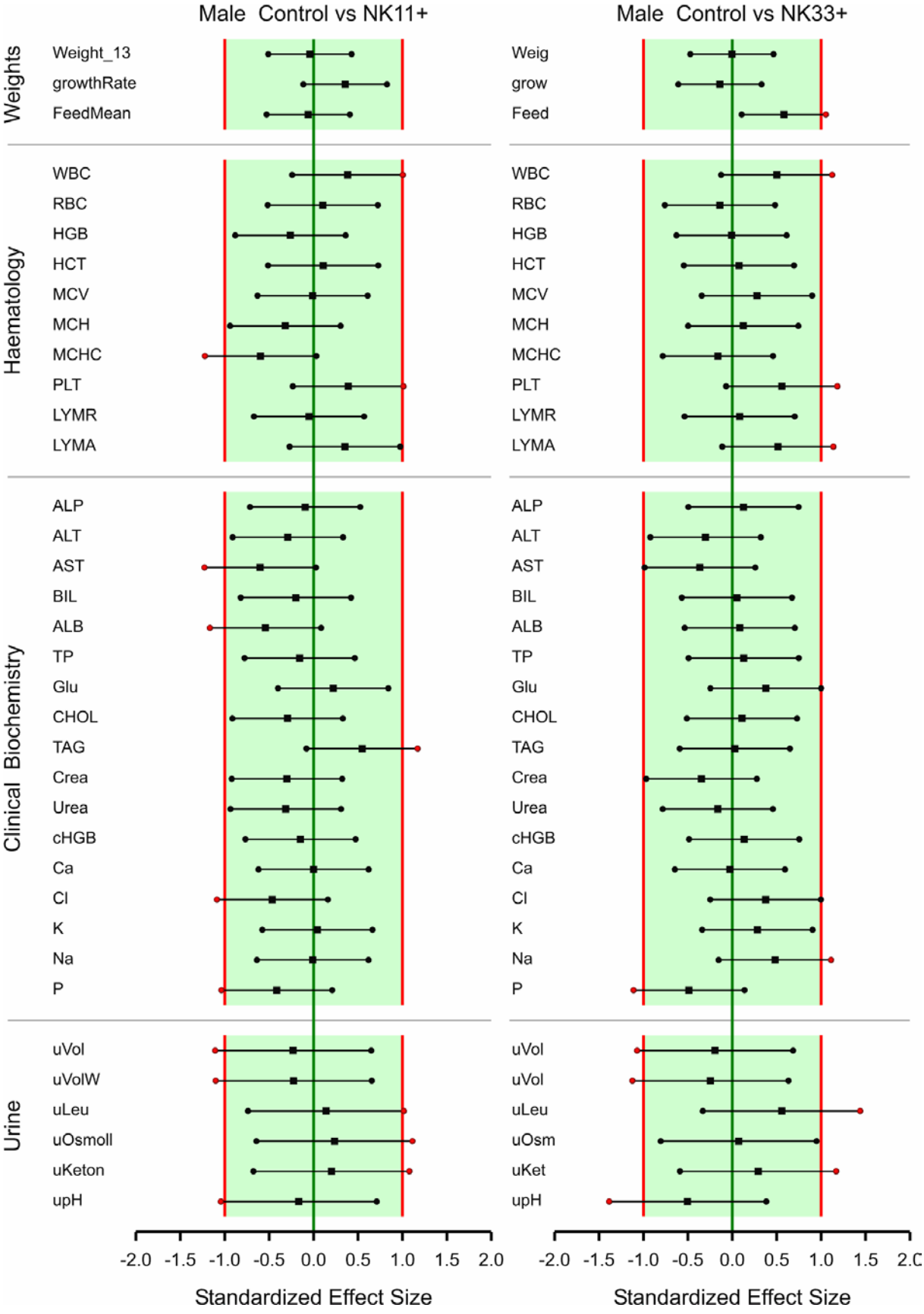

Figure 21 Confidence intervals for Standardized Effect Sized (SES) for male rats for GMO feeds NK11+ and NK33+ versus the control feed.

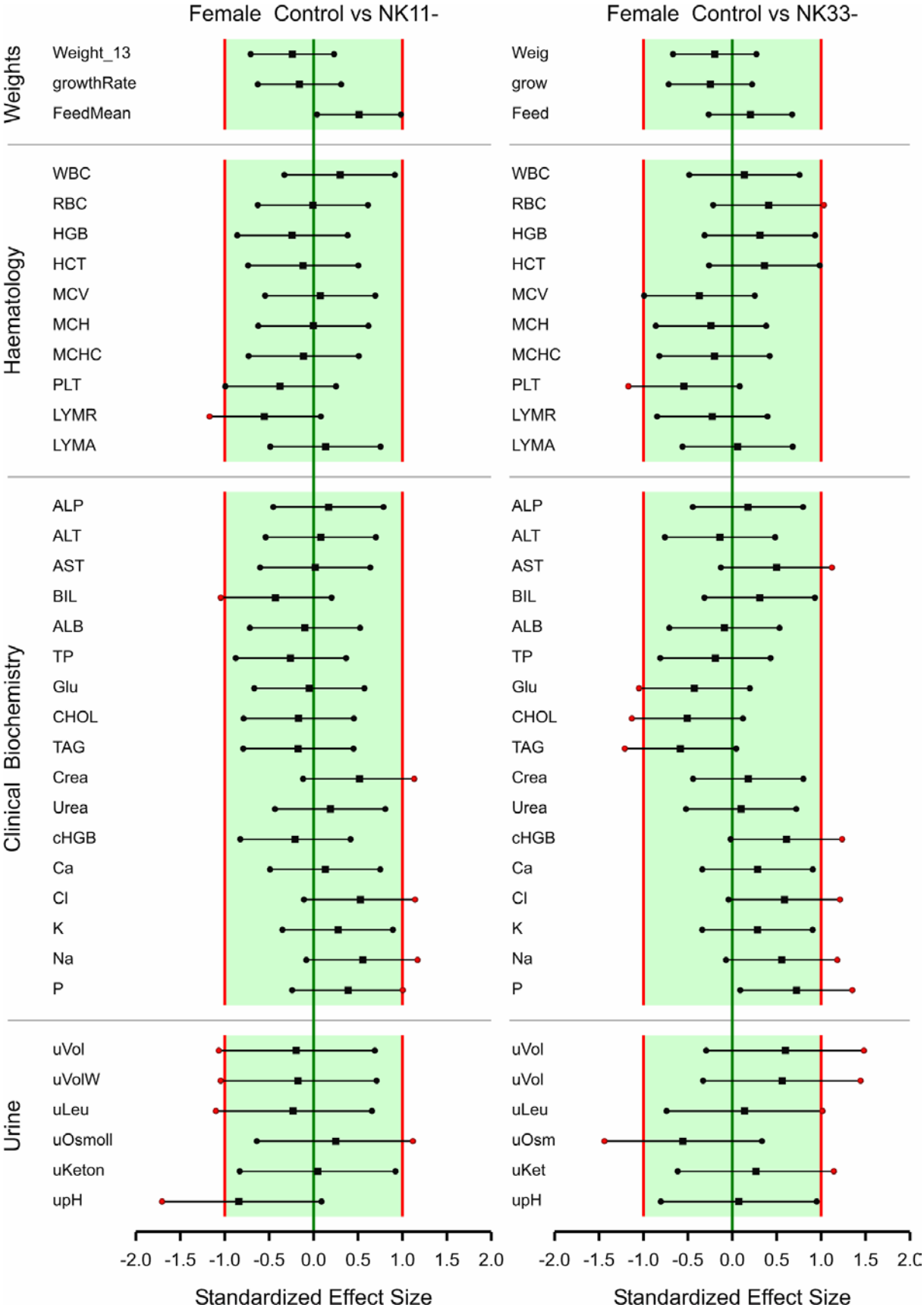

Figure 22 Confidence intervals for Standardized Effect Sized (SES) for female rats for GMO feeds NK11- and NK33- versus the control feed.

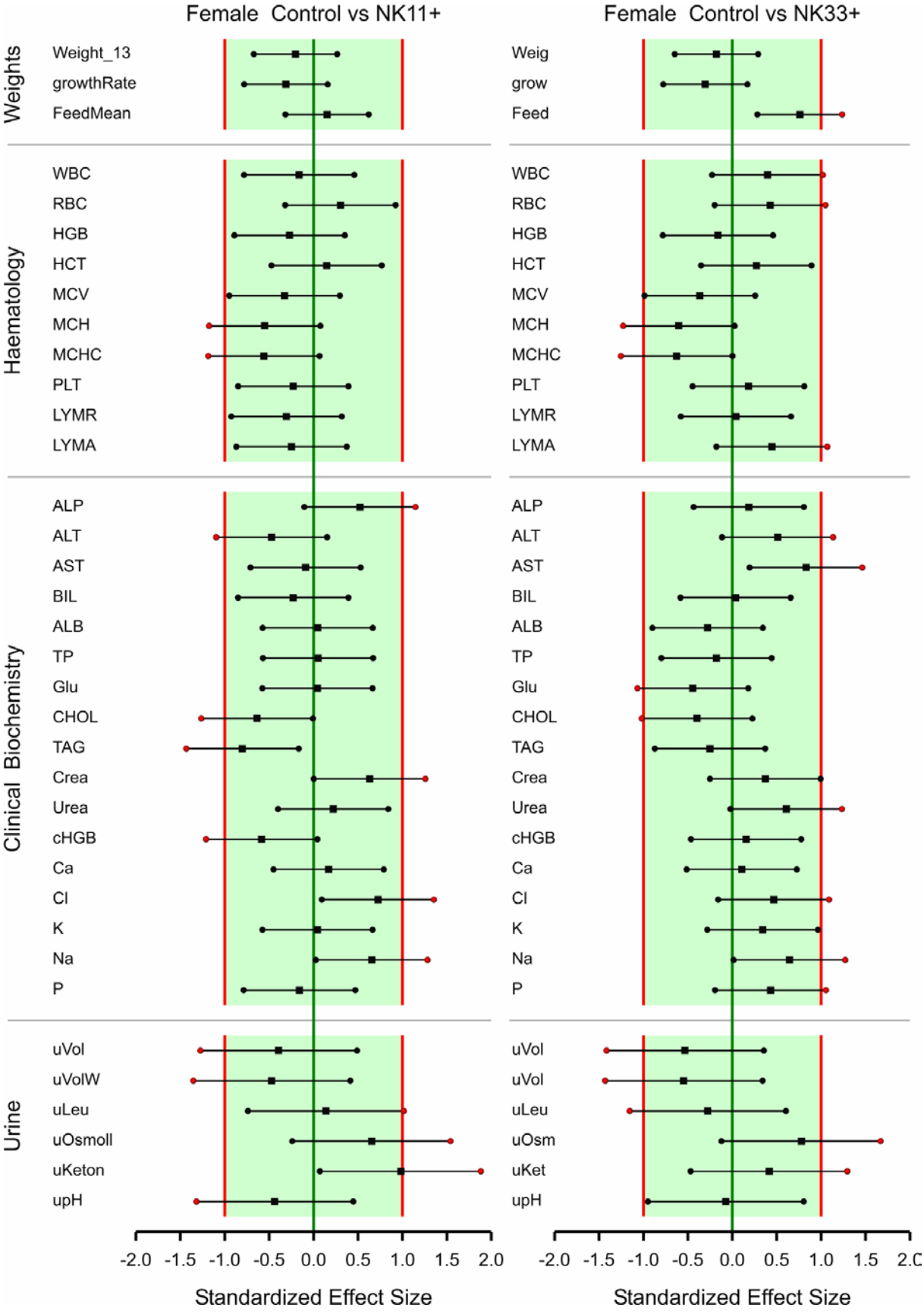

Figure 23 Confidence intervals for Standardized Effect Sized (SES) for female rats for GMO feeds NK11+ and NK33+ versus the control feed.

3.5 Factorial analysis

The significance results from fitting the factorial model to the 36 variables are given in Table 14. The ratios for the significant cases are shown in Table 15 and Table 16.

As an example, consider the results for FeedMean. The interaction was significant for both males and females. The effect of GM inclusion rate was negative for GM feeds without Roundup, while it was positive for GM feeds with Roundup. However the differences were quite small. Larger interaction effects were found for ALT and TAG in females. Main significant GM inclusion rate effects larger than 10% were observed for uLeu (males) and AST, cHGB and upH (females). Significant main Roundup effect larger than 10% were observed for uVol, uVolW and upH (females).

The p-values in Table 14 can be summarized as follows. In 3 out of 72 cases (4.2%) there was a significant difference at the 5% level between the mean of the GM feeds and the non-GM feed. In 5 cases (7%) there was a significant interaction term at the 5% level. In these latter cases the main effects should not be used for assessing effects of GM inclusion rate or Roundup. Among the remaining 67 cases, i.e. where the interaction is not significant, there were 7 cases (10%) with a significant differences between GM inclusion rates, and 8 cases (11%) with a significant difference between the GM feeds with and without Roundup.

Table 14 P values for significance of effects obtained with the factorial model. P-values smaller than 0.01/0.05 have a gold/yellow background.

Response	Males				Females			
Weights	GMO	InclRate	Roundup	Interact	GMO	InclRate	Roundup	Interact
Weight_13	0.465	0.613	0.173	0.777	0.280	0.842	0.872	0.962
growthRate	0.567	0.393	0.011	0.040	0.178	0.815	0.534	0.779
FeedMean	0.627	0.717	0.049	0.001	0.033	0.371	0.561	0.008
Haematology	GMO	InclRate	Roundup	Interact	GMO	InclRate	Roundup	Interact
WBC	0.113	0.074	0.715	0.204	0.494	0.366	0.644	0.101
RBC	0.721	0.743	0.522	0.452	0.250	0.219	0.457	0.505
HGB	0.723	0.176	0.682	0.817	0.711	0.134	0.252	0.314
HCT	0.920	0.638	0.300	0.539	0.501	0.168	0.688	0.413
MCV	0.728	0.310	0.682	0.784	0.314	0.272	0.366	0.354
MCH	0.960	0.153	0.328	0.593	0.156	0.513	0.041	0.674
MCHC	0.702	0.196	0.013	0.522	0.128	0.723	0.048	0.960
PLT	0.129	0.445	0.421	0.989	0.325	0.577	0.049	0.188
LYMR	0.625	0.979	0.220	0.566	0.288	0.126	0.242	0.966
LYMA	0.151	0.126	0.528	0.412	0.687	0.160	1.000	0.081
ClinChem	GMO	InclRate	Roundup	Interact	GMO	InclRate	Roundup	Interact
ALP	0.973	0.993	0.831	0.328	0.284	0.456	0.407	0.432
ALT	0.373	0.289	0.519	0.311	0.983	0.083	0.825	0.007
AST	0.241	0.966	0.096	0.311	0.202	0.002	0.607	0.315
BIL	0.869	0.574	0.306	0.573	0.748	0.024	0.871	0.281
ALB	0.315	0.093	0.833	0.272	0.669	0.472	0.917	0.448
TP	0.696	0.852	0.457	0.278	0.556	0.715	0.463	0.498
Glu	0.856	0.812	0.026	0.644	0.372	0.050	0.867	0.803
CHOL	0.973	0.637	0.456	0.189	0.083	0.830	0.417	0.192
TAG	0.133	0.270	0.415	0.232	0.067	0.744	0.504	0.031
Crea	0.108	0.882	0.464	0.724	0.086	0.177	0.481	0.860
Urea	0.159	0.422	0.301	0.896	0.256	0.495	0.219	0.280
cHGB	0.664	0.688	0.303	0.393	0.976	0.001	0.061	0.857
Ca	0.831	0.795	0.550	0.885	0.478	0.840	0.744	0.625
Cl	0.909	0.069	0.885	0.059	0.021	0.649	0.861	0.469
K	0.507	0.794	0.974	0.418	0.336	0.482	0.695	0.510
Na	0.451	0.029	0.677	0.985	0.016	0.982	0.669	0.977
P	0.091	0.305	0.835	0.178	0.161	0.037	0.058	0.559
Urine	GMO	InclRate	Roundup	Interact	GMO	InclRate	Roundup	Interact
uVol	0.369	0.133	0.495	0.107	0.699	0.286	0.034	0.132
uVolW	0.387	0.128	0.644	0.145	0.641	0.281	0.025	0.187
uLeu	0.285	0.020	0.827	0.278	0.866	0.936	0.936	0.202
uOsmoll	0.611	0.275	0.863	0.112	0.410	0.268	0.007	0.133
uKeton	0.243	0.198	0.282	0.312	0.213	0.571	0.080	0.200
upH	0.348	0.792	1.000	0.192	0.349	0.041	0.676	0.371

Table 15 Ratios for significant variables at the 5% level in the factorial analysis for males. Main effects are "GM vs Contrl" (ratio of the mean of the four GM feeds vs the control feed), "33 vs 11" (ratio of the two GM feeds with 33% GM inclusion rate vs the two feeds with 11% GM inclusion rate) and "+RU vs -RU" (ratio of the two GM feeds with roundup vs the two feeds without roundup). The interaction ratios are scaled such that NK11- equals 1. The InclRate and RndUp main effects are only given when the interaction is not significant.

Males Group	Variable	GM vs Contrl	33 vs 11	+RU vs -RU	Interaction			
					NK11-	NK33-	NK11+	NK33+
Weights	growthRate	-	-	-	1.00	1.00	1.01	1.01
Weights	FeedMean	-	-	-	1.00	0.98	0.99	1.02
Haematology	MCHC	-	-	0.99	-	-	-	-
ClinChem	Glu	-	-	1.06	-	-	-	-
ClinChem	Na	-	1.00	-	-	-	-	-
Urine	uLeu	-	1.35	-	-	-	-	-

Table 16 Ratios for significant variables at the 5% level in the factorial analysis for females. Main effects are "GM vs Contrl" (ratio of the mean of the four GM feeds vs the control feed), "33 vs 11" (ratio of the two GM feeds with 33% GM inclusion rate vs the two feeds with 11% GM inclusion rate) and "+RU vs -RU" (ratio of the two GM feeds with roundup vs the two feeds without roundup). The interaction ratios are scaled such that NK11- equals 1. The InclRate and RndUp main effects are only given when the interaction is not significant.

Females Group	Variable	GM vs Contrl	33 vs 11	+RU vs -RU	Interaction			
					NK11-	NK33-	NK11+	NK33+
Weights	FeedMean	1.02	-	-	1.00	0.98	0.98	1.01
Haematology	MCH	-	-	0.99	-	-	-	-
Haematology	MCHC	-	-	0.99	-	-	-	-
Haematology	PLT	-	-	1.04	-	-	-	-
ClinChem	ALT	-	-	-	1.00	0.96	0.91	1.08
ClinChem	AST	-	1.12	-	-	-	-	-
ClinChem	BIL	-	1.09	-	-	-	-	-
ClinChem	TAG	-	-	-	1.00	0.93	0.89	0.99
ClinChem	cHGB	-	1.19	-	-	-	-	-
ClinChem	Cl	1.01	-	-	-	-	-	-
ClinChem	Na	1.01	-	-	-	-	-	-
ClinChem	P	-	1.08	-	-	-	-	-
Urine	uVol	-	-	0.82	-	-	-	-
Urine	uVolW	-	-	0.81	-	-	-	-
Urine	uOsmoll	-	-	1.29	-	-	-	-
Urine	upH	-	1.24	-	-	-	-	-

References

Goedhart, P.W. & van der Voet, H. (2017). G TwYST Study B. A 90-day toxicity study in rats fed GM maize NK603. Statistical report. Report 31.10.17, Biometris, Wageningen, The Netherlands.

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Hong B, Du Y, Mukerji P, Roper JM, Appenzeller LM (2017). Safety assessment of food and feed from GM crops in Europe: Evaluating EFSA's alternative framework for the rat 90-day feeding study. Journal of Agricultural and Food Chemistry, 65(27): 5545-5560. http://dx.doi.org/10.1021/acs.jafc.7b01492.

List of Tables

Table 13 Means and coefficient of variation (CV) for female rats. Means of GMO feeds which are significantly different from the Control feed are marked, with red background colouring, as follows: D: P<0.01 by Dunnett-test, d: P<0.05 by Dunnett-test, T: P<0.01 by t-test but not by Dunnett-test, t: P<0.05 by t-test but not by Dunnett-test, W: P<0.01 by Wilcoxon signed rank test, w: P<0.05 by Wilcoxon signed rank test. Note that Dunnett- and t-tests are based on a ANOVA with 5 treatment groups, while Wilcoxon tests only uses data for the specific GM feed and the control feed.

Table 14 P values for significance of effects obtained with the factorial model. P-values smaller than 0.01/0.05 have a gold/yellow background.

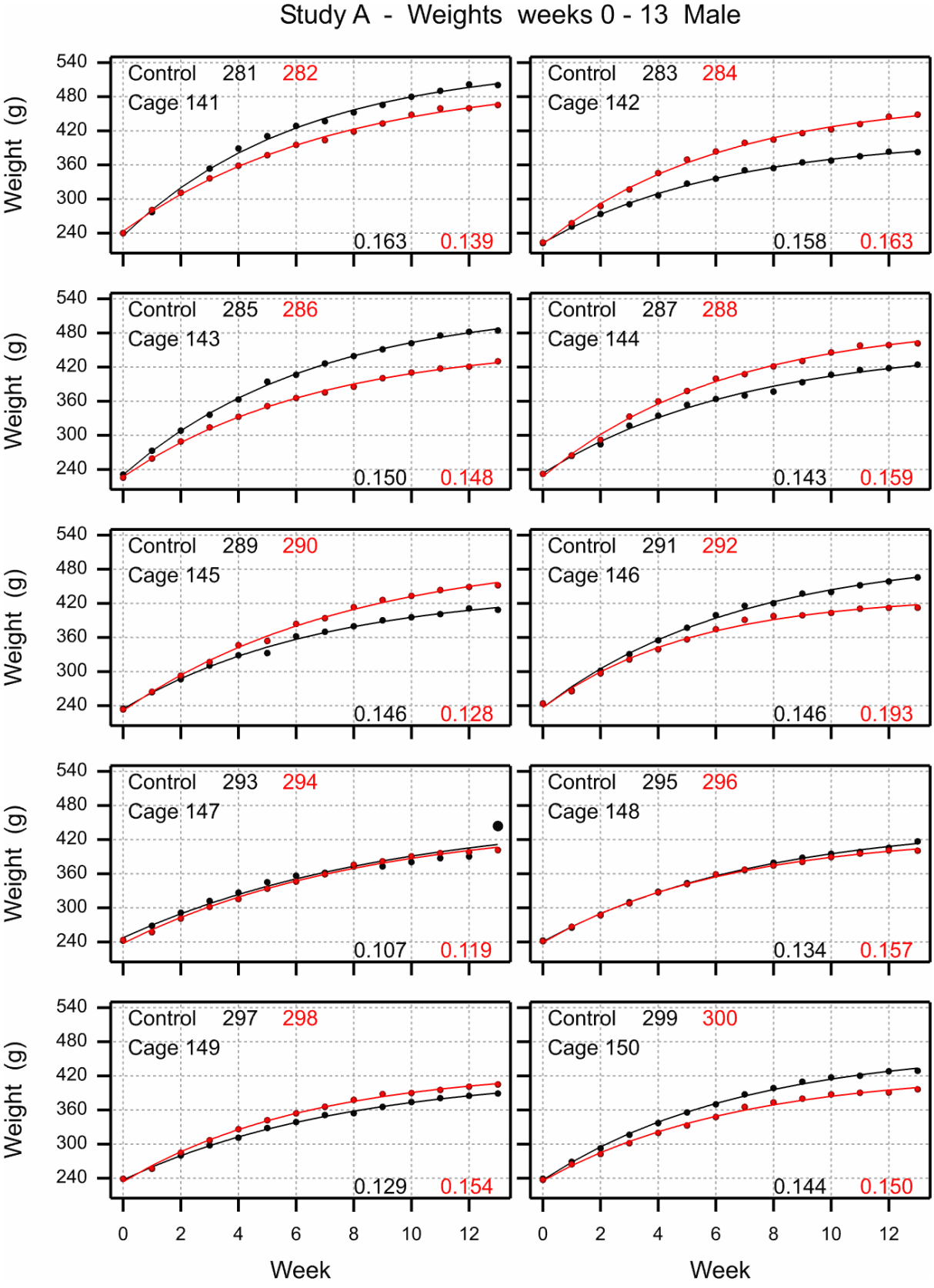
Table 15 Ratios for significant variables at the 5% level in the factorial analysis for males. Main effects are “GM vs Contrl” (ratio of the mean of the four GM feeds vs the control feed), “33 vs 11” (ratio of the two GM feeds with 33% GM inclusion rate vs the two feeds with 11% GM inclusion rate) and “+RU vs -RU“ (ratio of the two GM feeds with roundup vs the two feeds without roundup). The interaction ratios are scaled such that NK11- equals 1. The InclRate and RndUp main effects are only given when the interaction is not significant.

Table 16 Ratios for significant variables at the 5% level in the factorial analysis for females. Main effects are “GM vs Contrl” (ratio of the mean of the four GM feeds vs the control feed), “33 vs 11” (ratio of the two GM feeds with 33% GM inclusion rate vs the two feeds with 11% GM inclusion rate) and “+RU vs -RU“ (ratio of the two GM feeds with roundup vs the two feeds without roundup). The interaction ratios are scaled such that NK11- equals 1. The InclRate and RndUp main effects are only given when the interaction is not significant.

List of Figures

Appendix 1. Growth curves per animal pair

The feed group and animal numbers are given in the left top corner of the graph, while the estimated growth rate, i.e. $\gamma = -\log(R)$, is given in the right-bottom corner.



Appendix 1. Growth curves per animal pair (continued)

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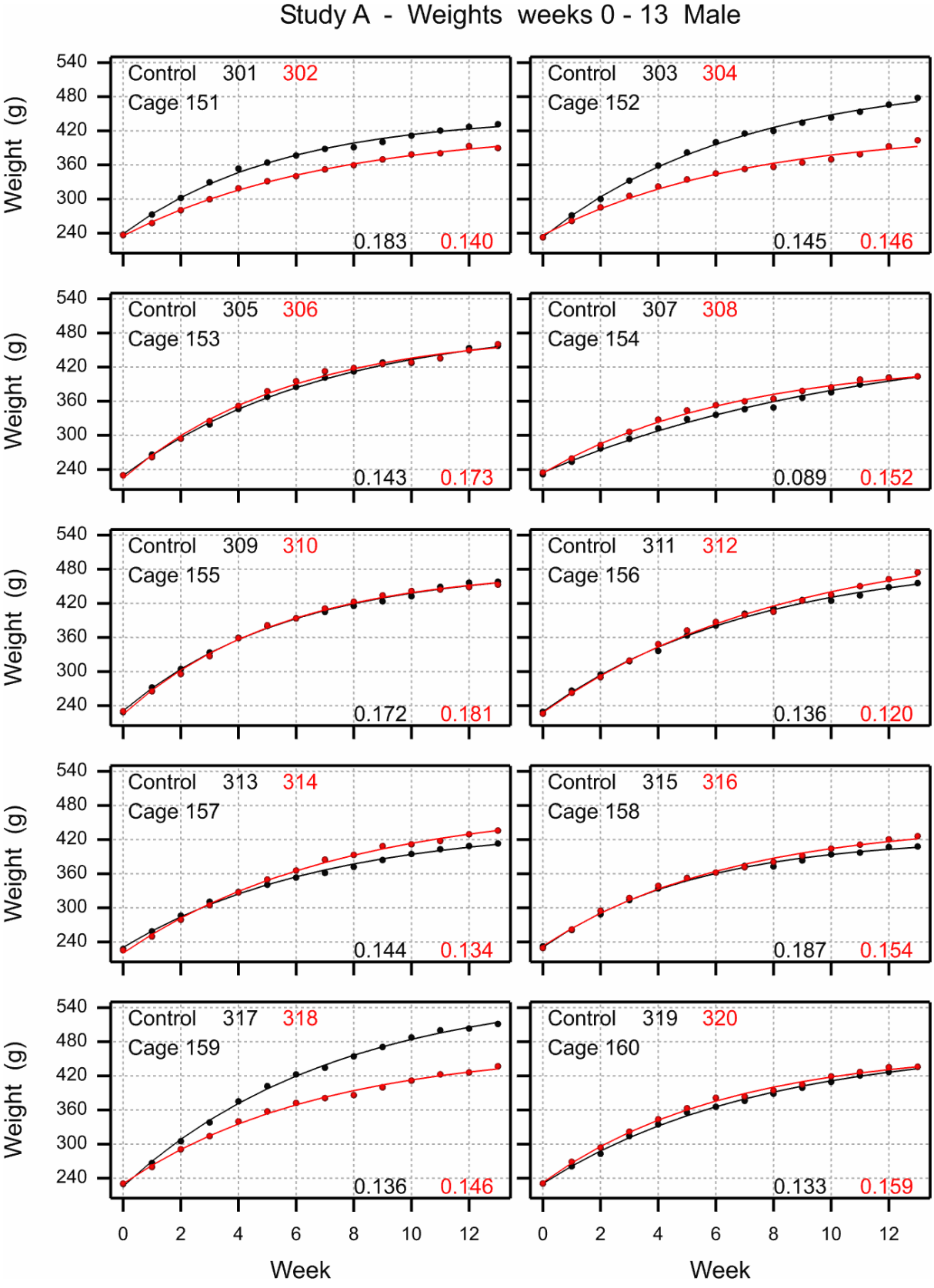

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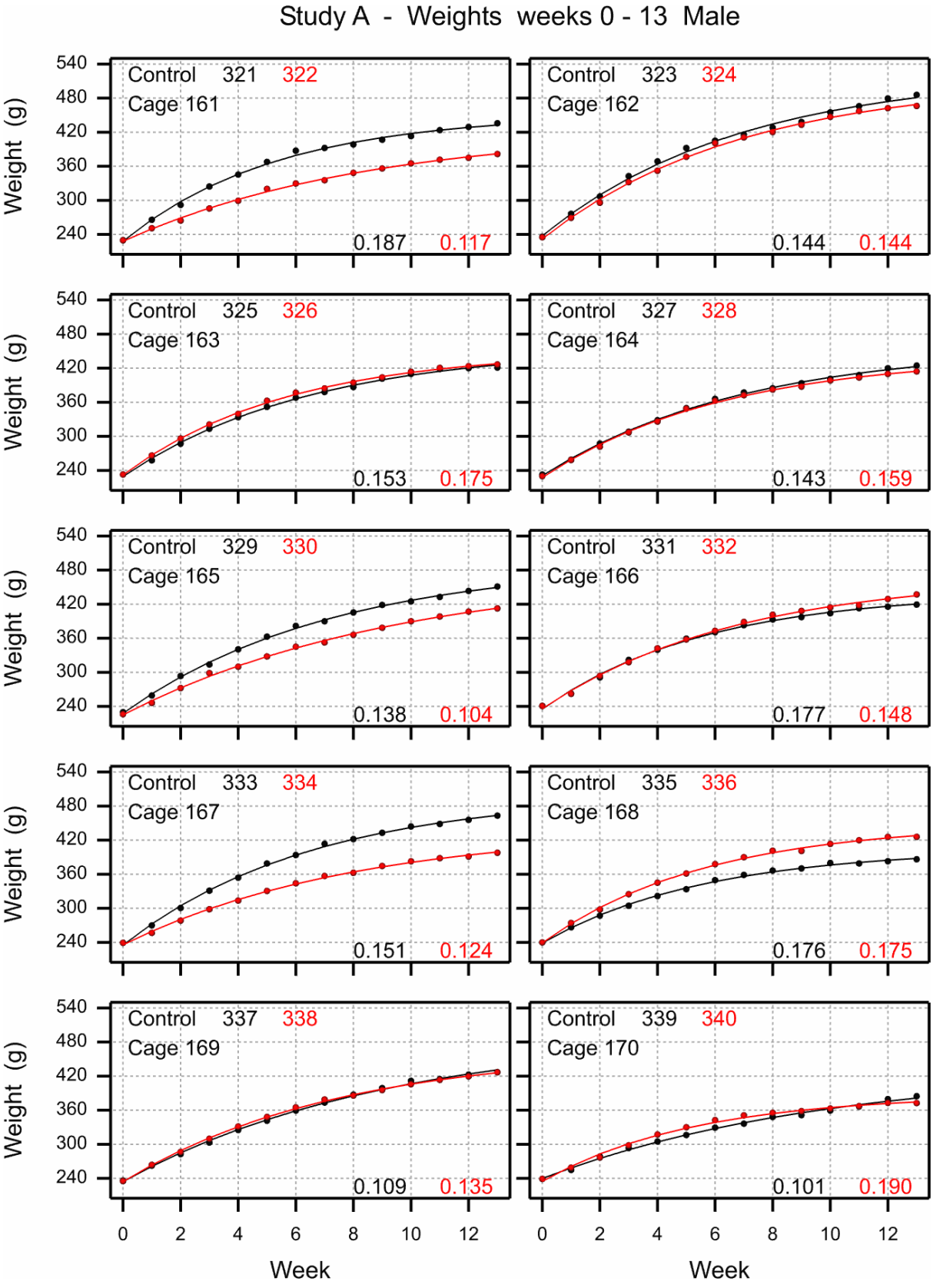

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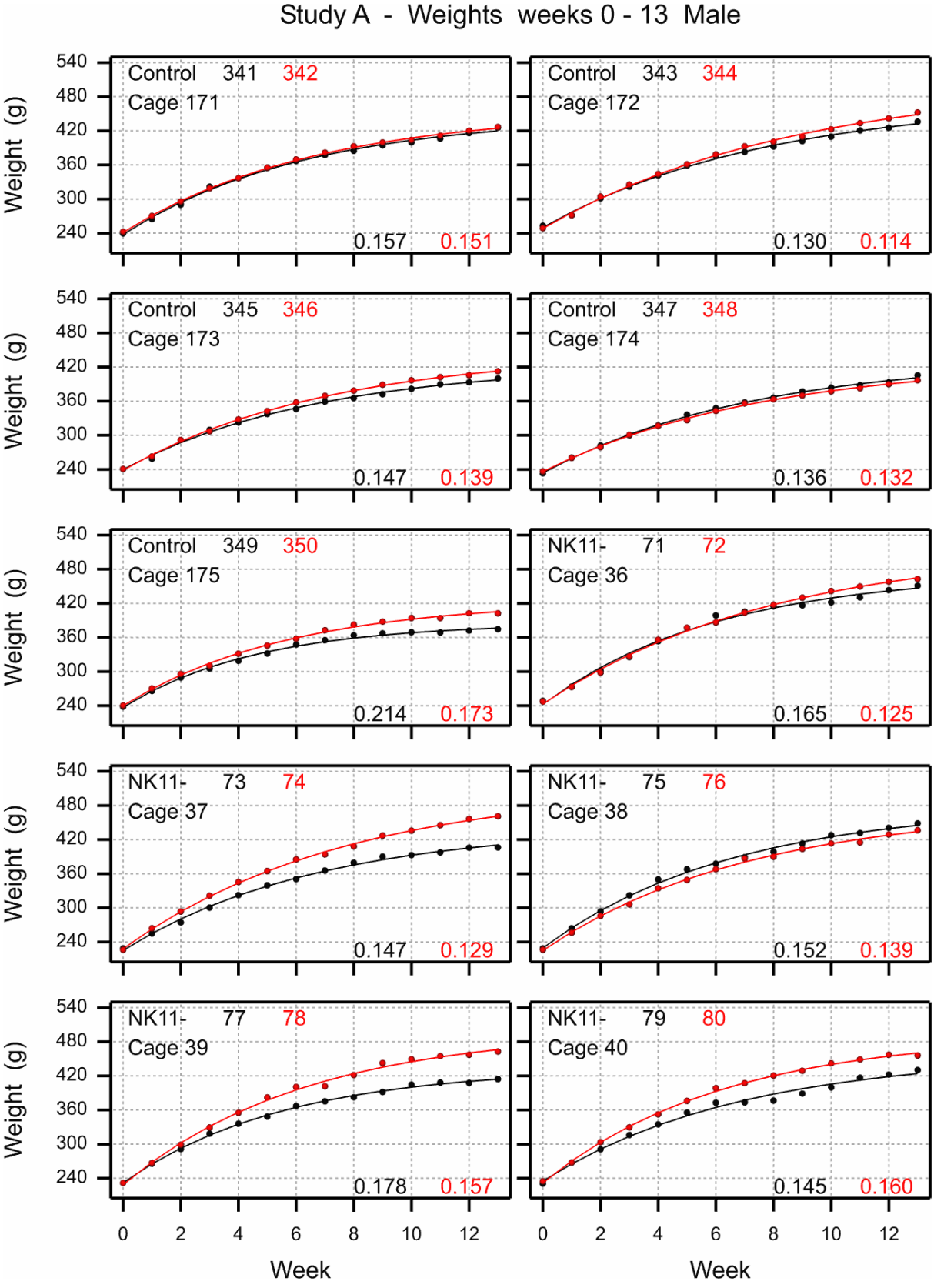

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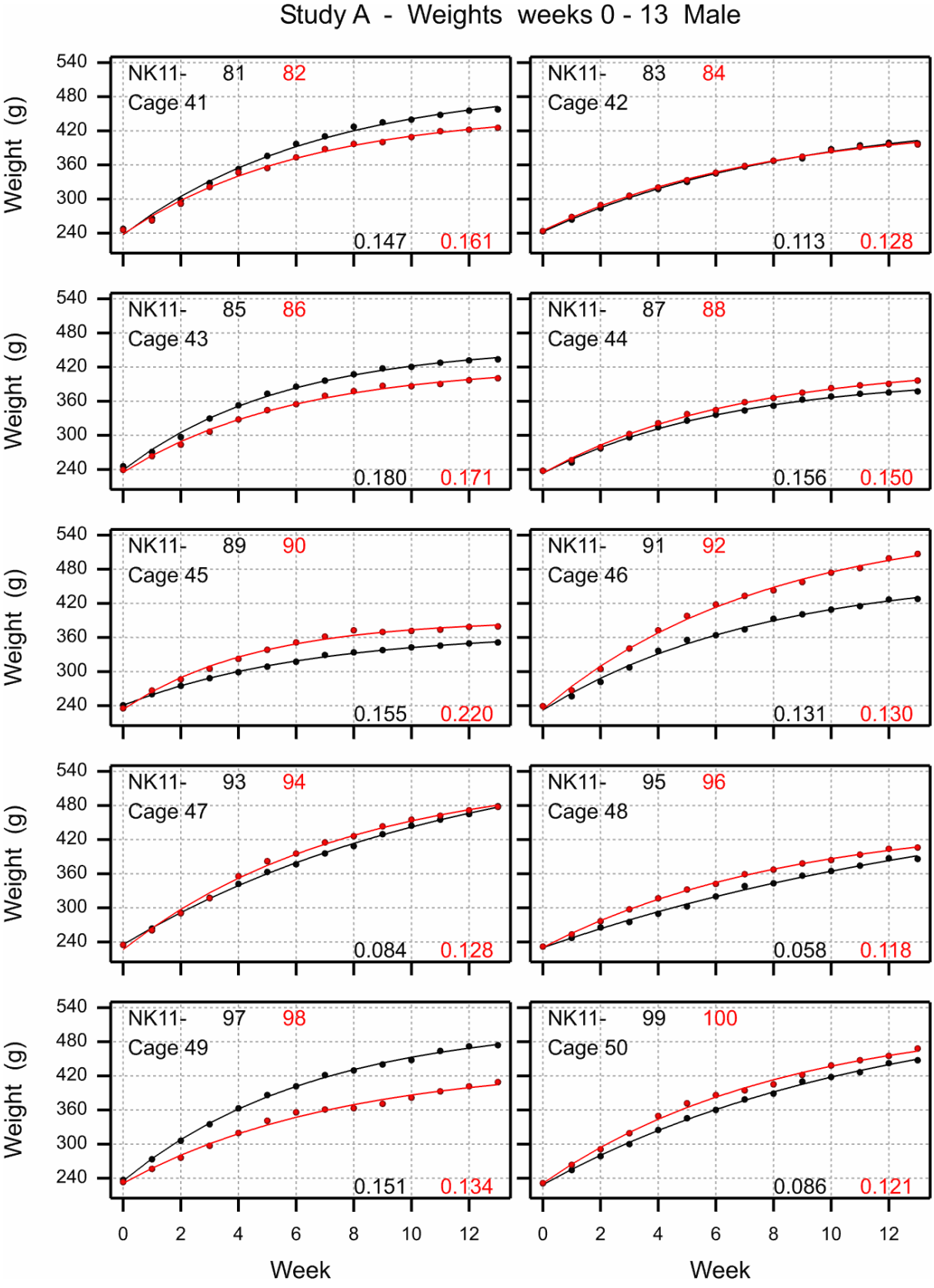

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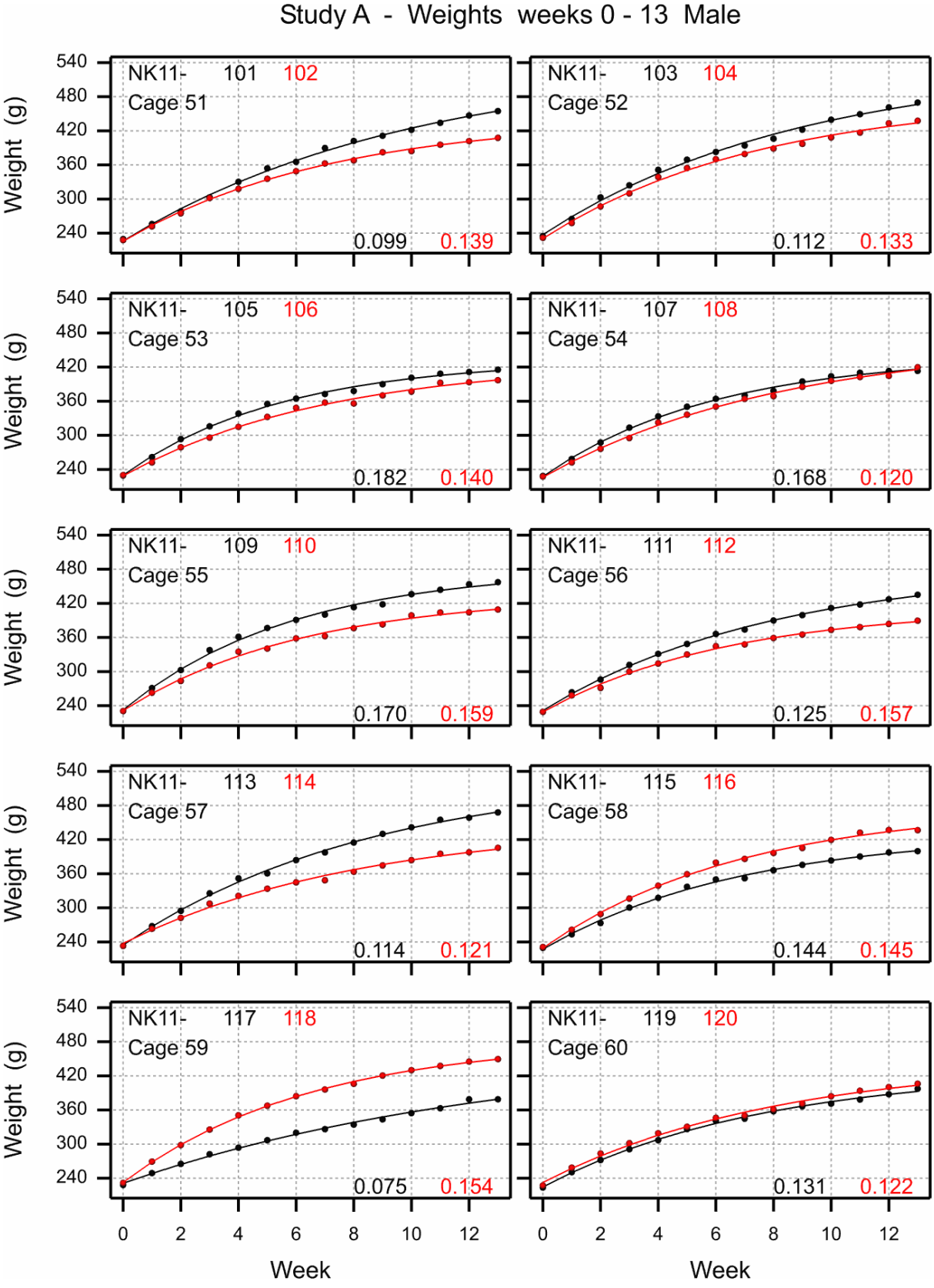

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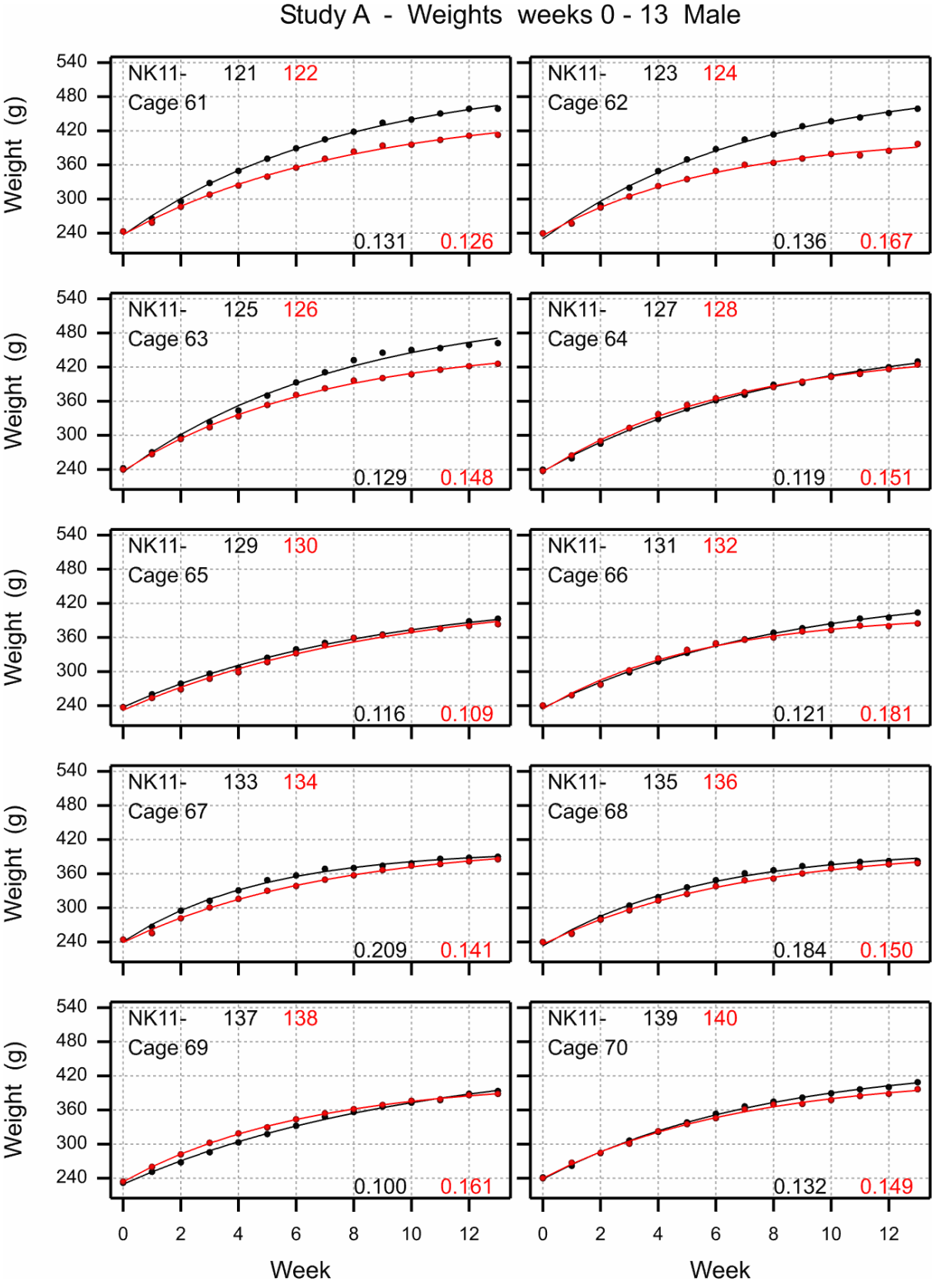

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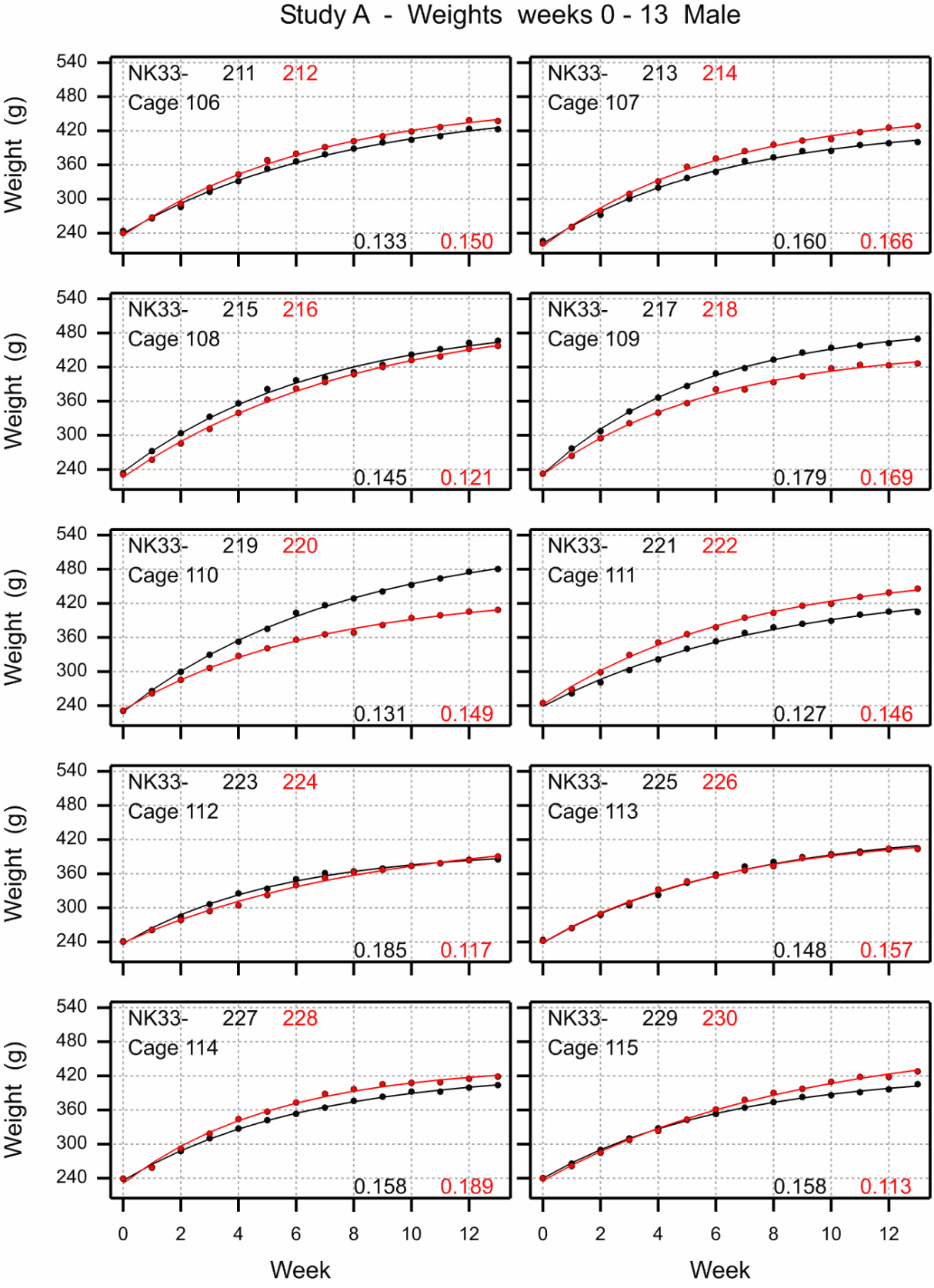

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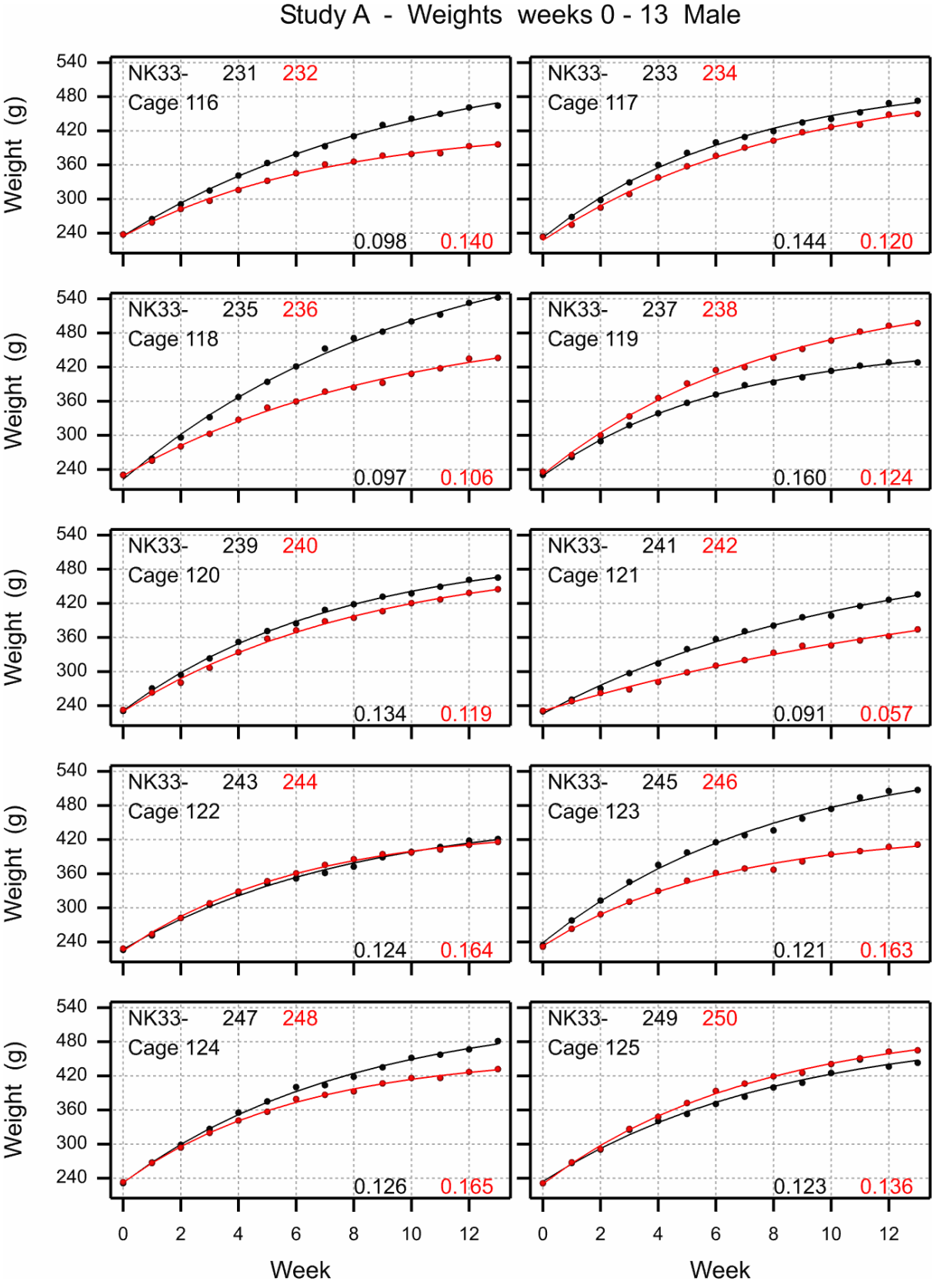

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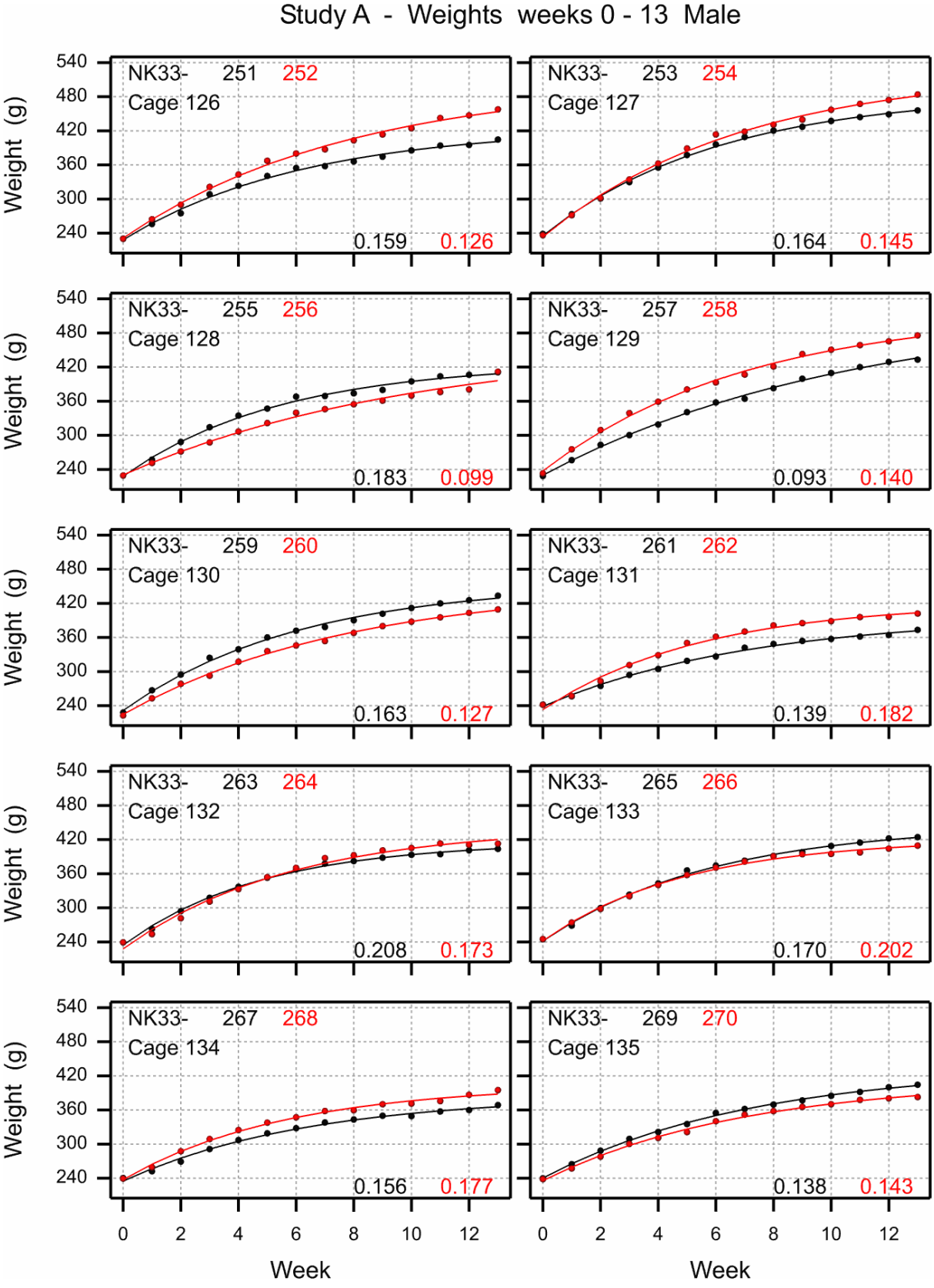

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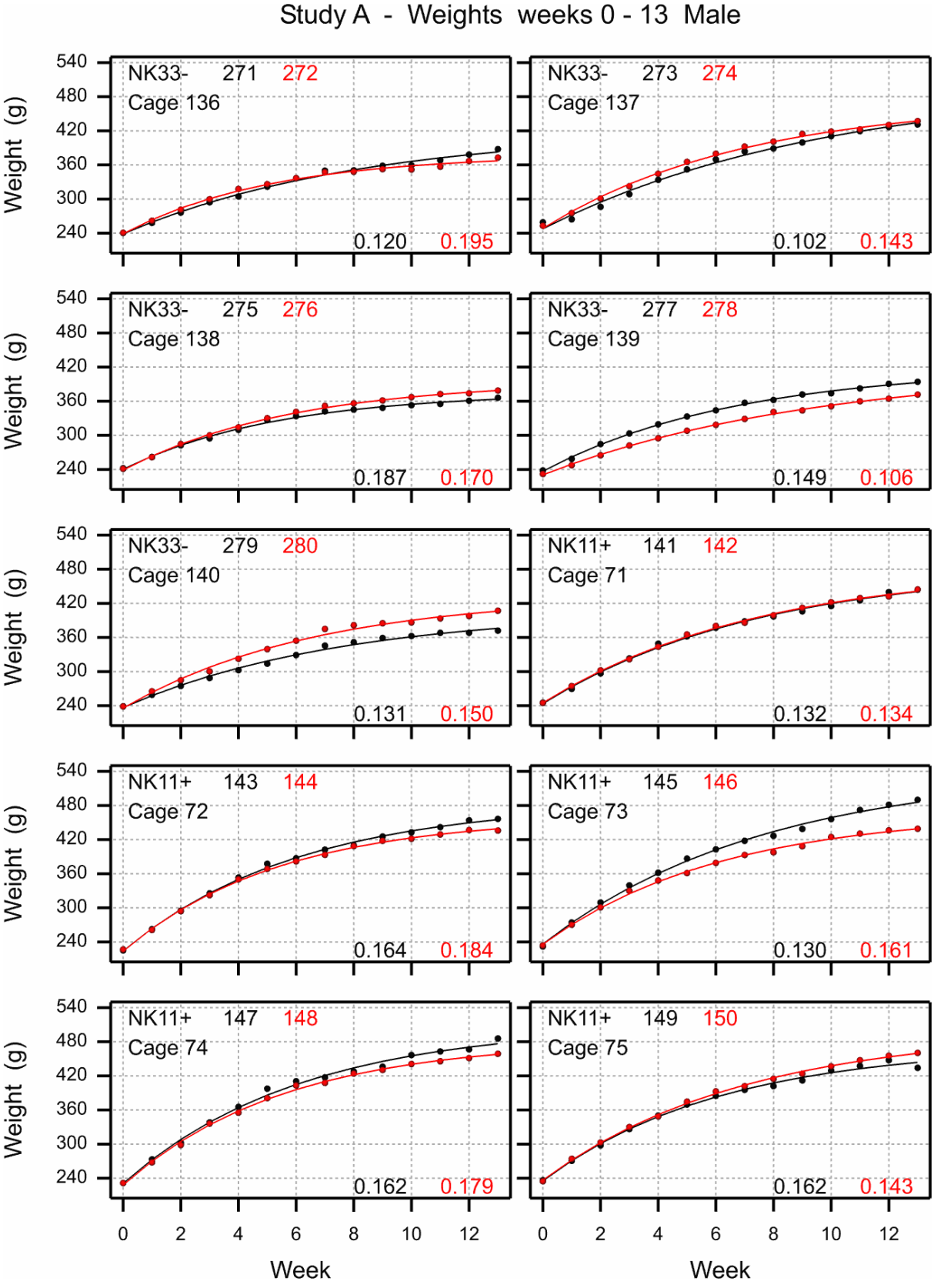

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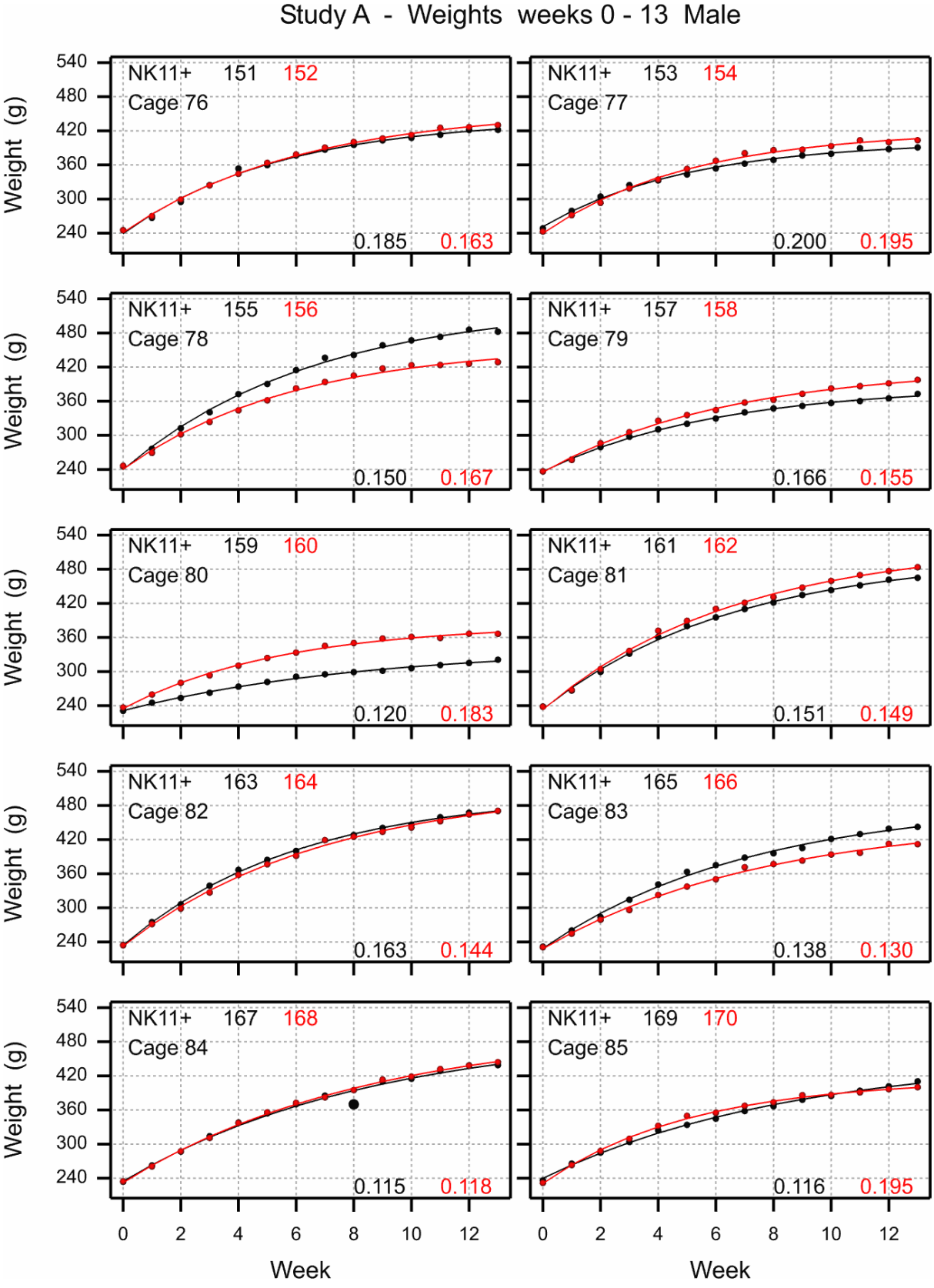

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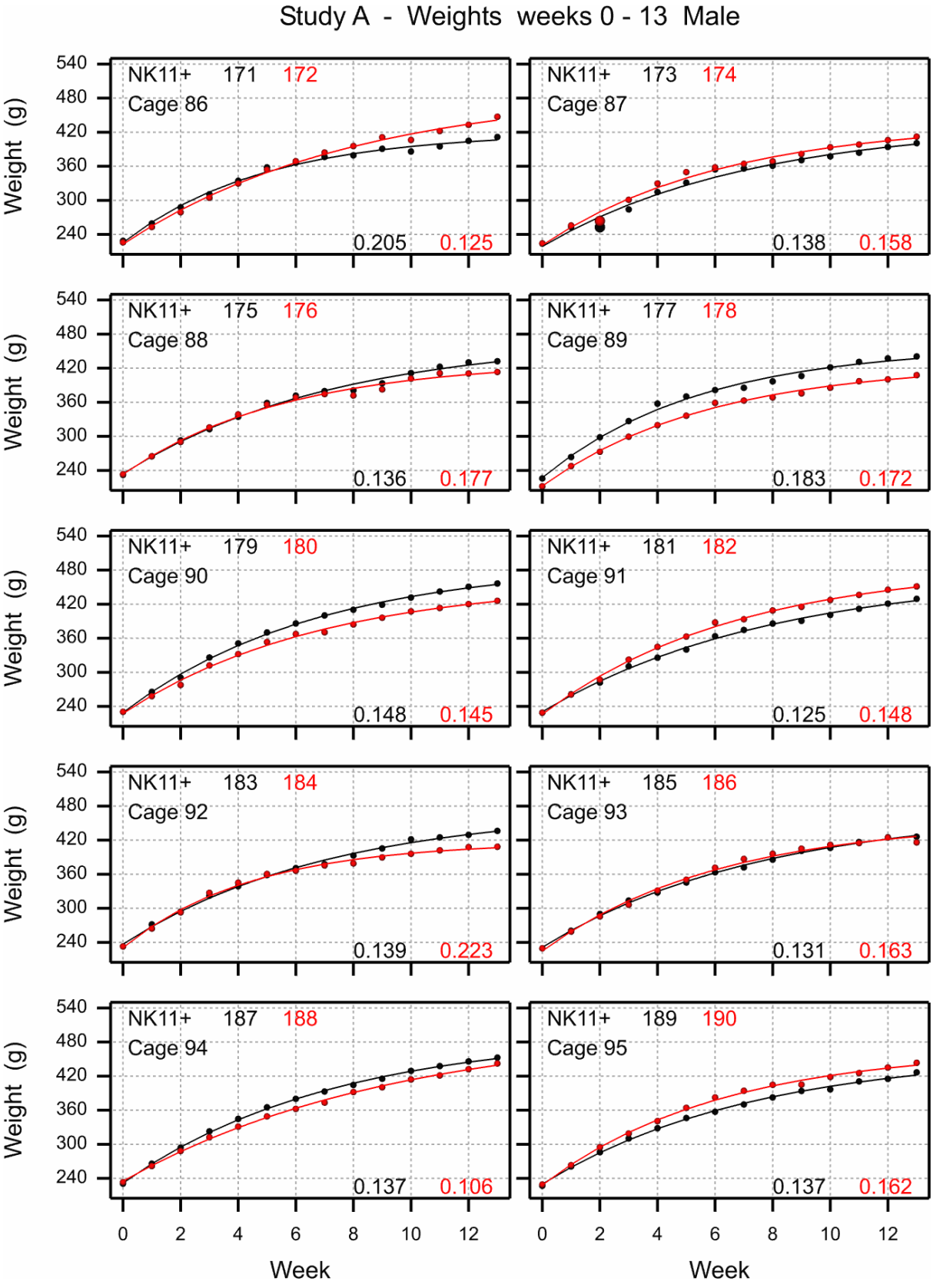
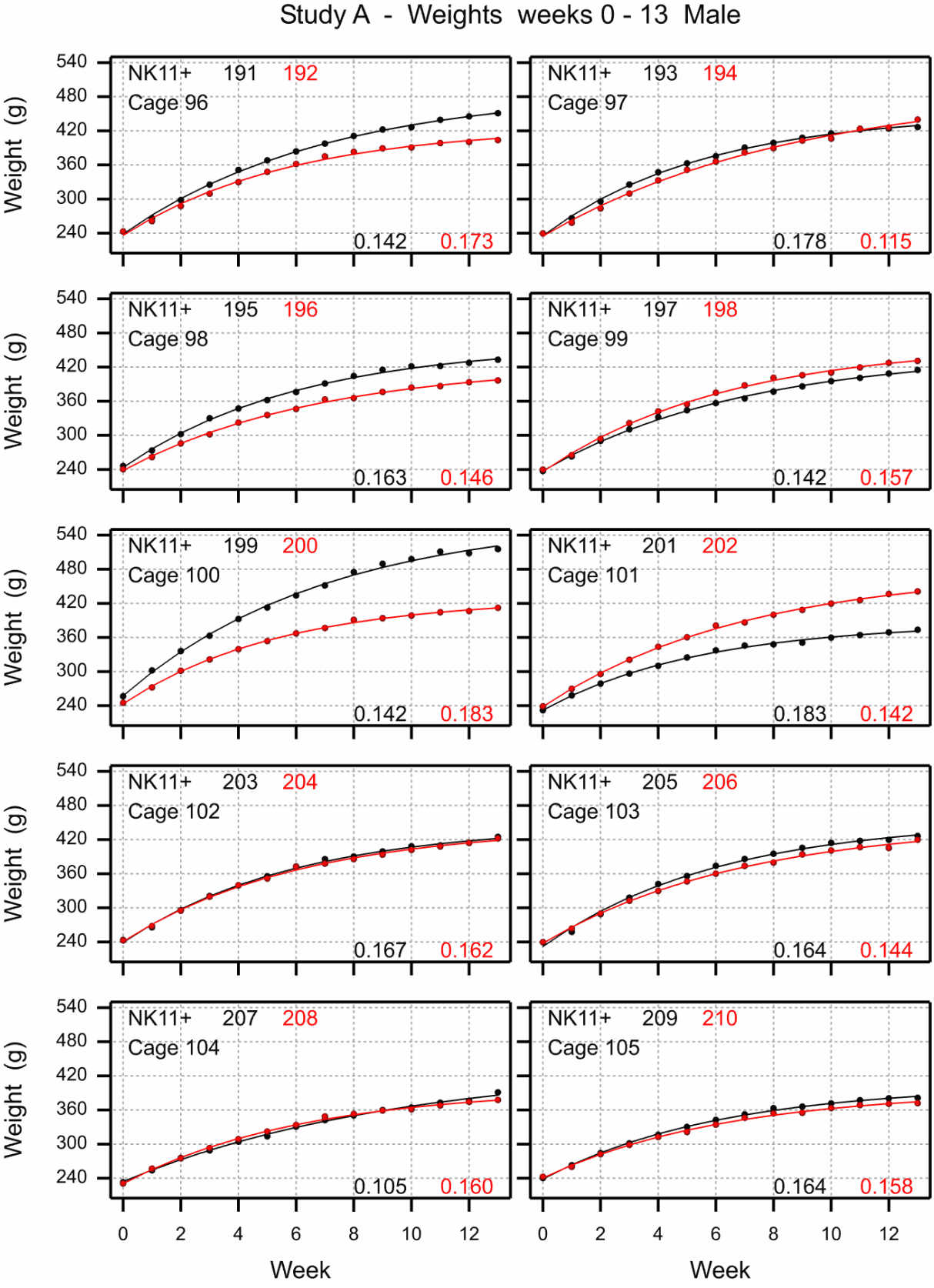


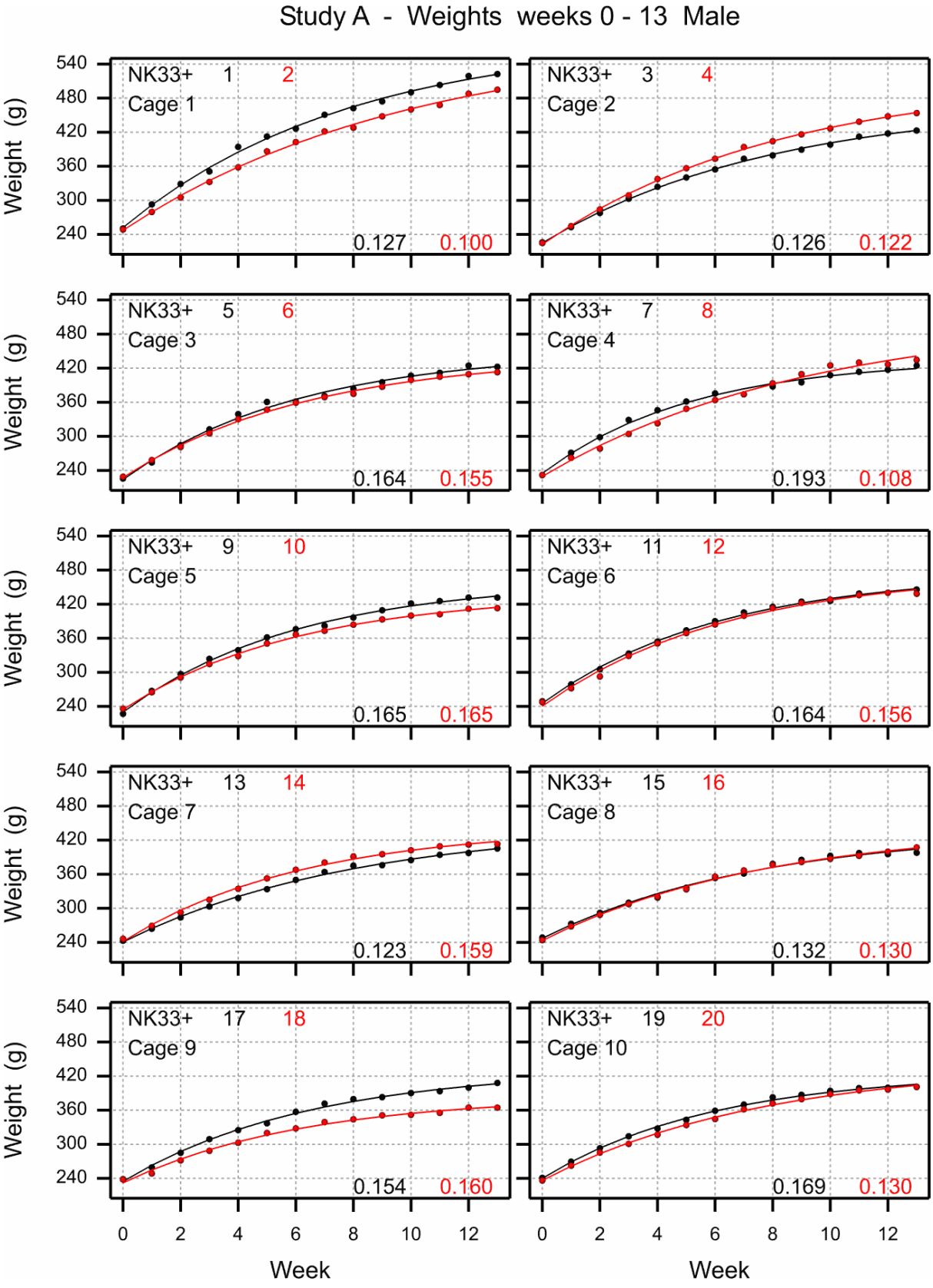
Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph, while the estimated growth rate, i.e. $\gamma = -\log(R)$, is given in the right-bottom corner.



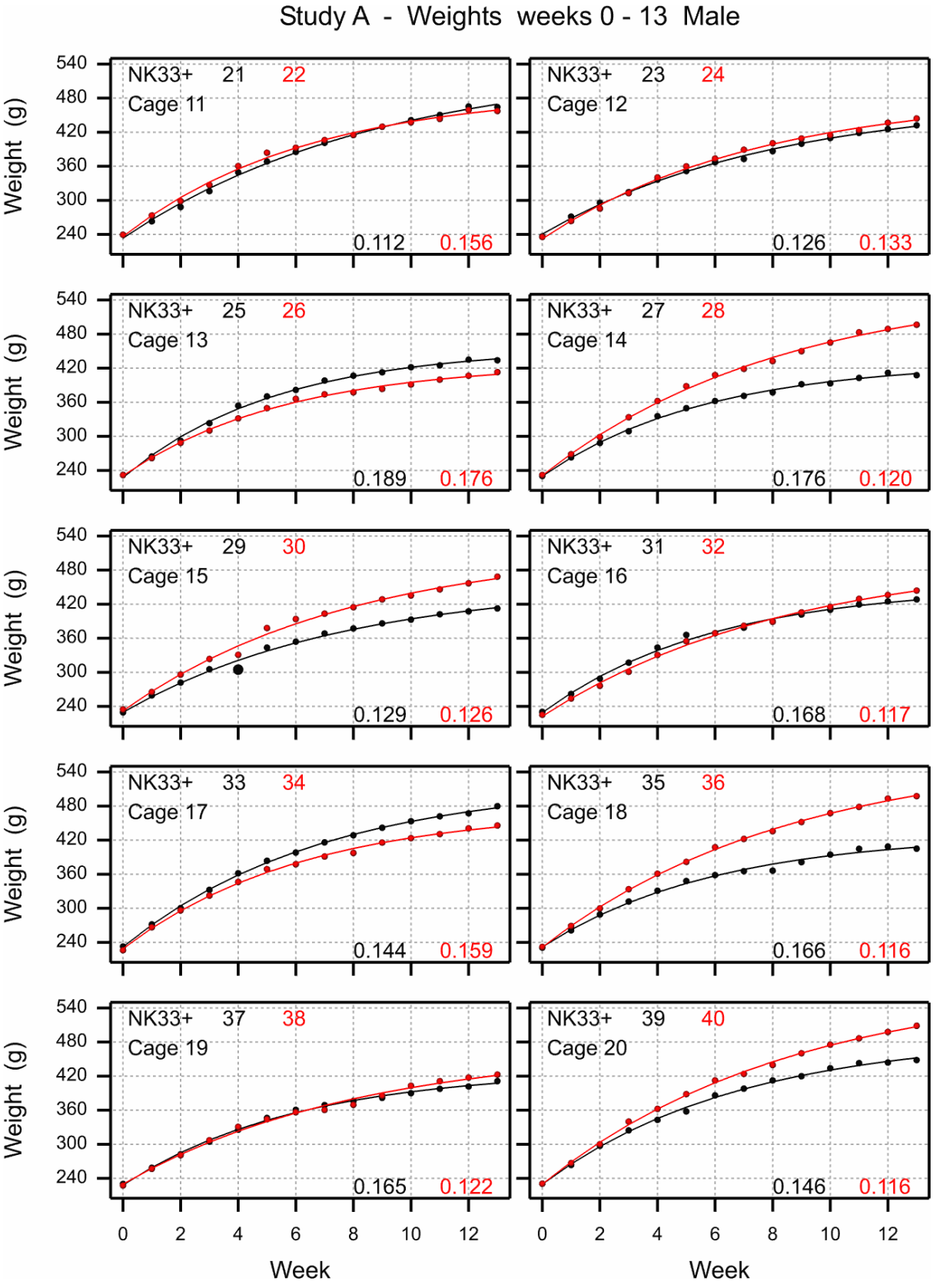
Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph, while the estimated growth rate, i.e. $\gamma = -\log(R)$, is given in the right-bottom corner.



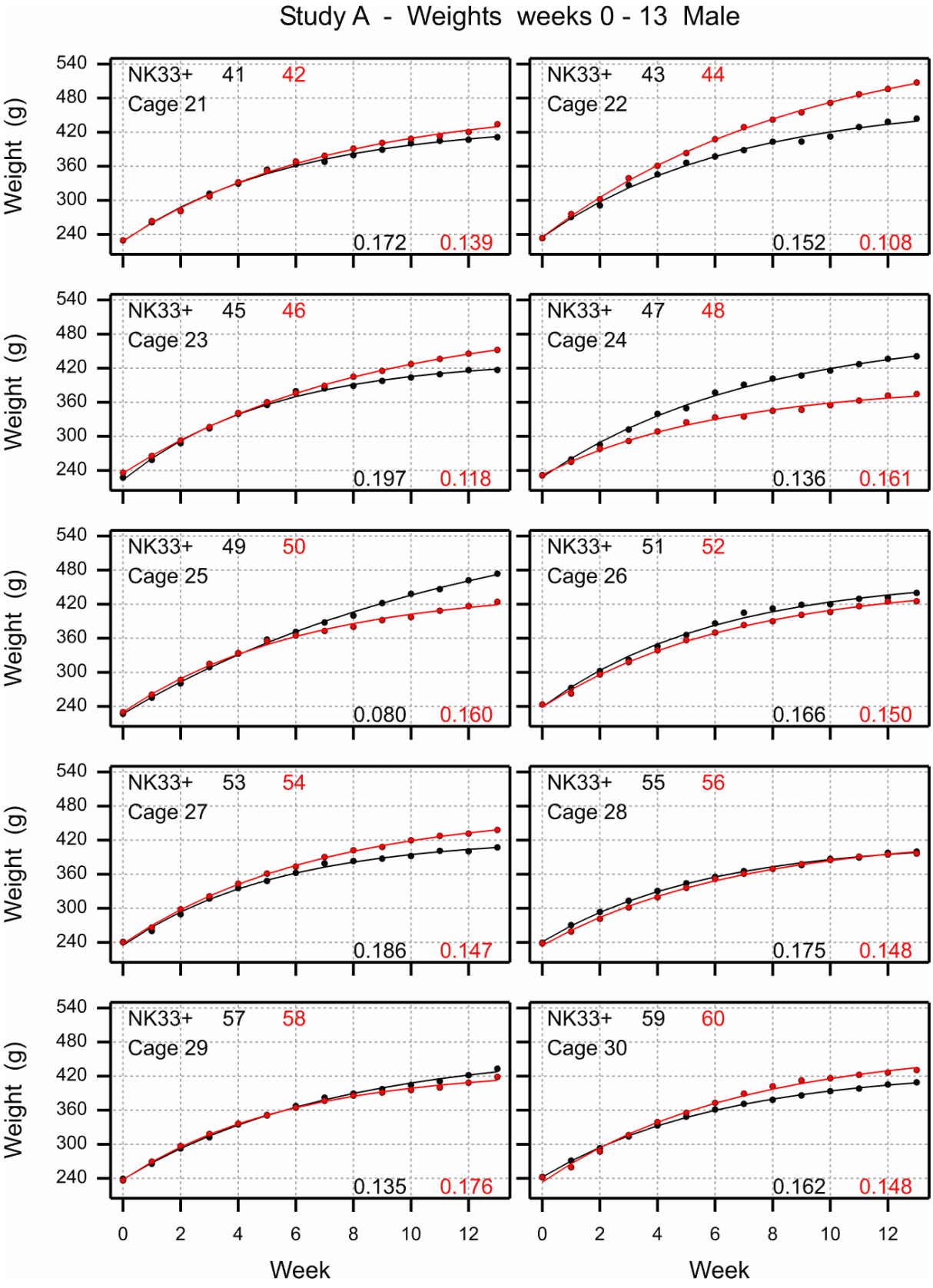
Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph, while the estimated growth rate, i.e. $\gamma = -\log(R)$, is given in the right-bottom corner.



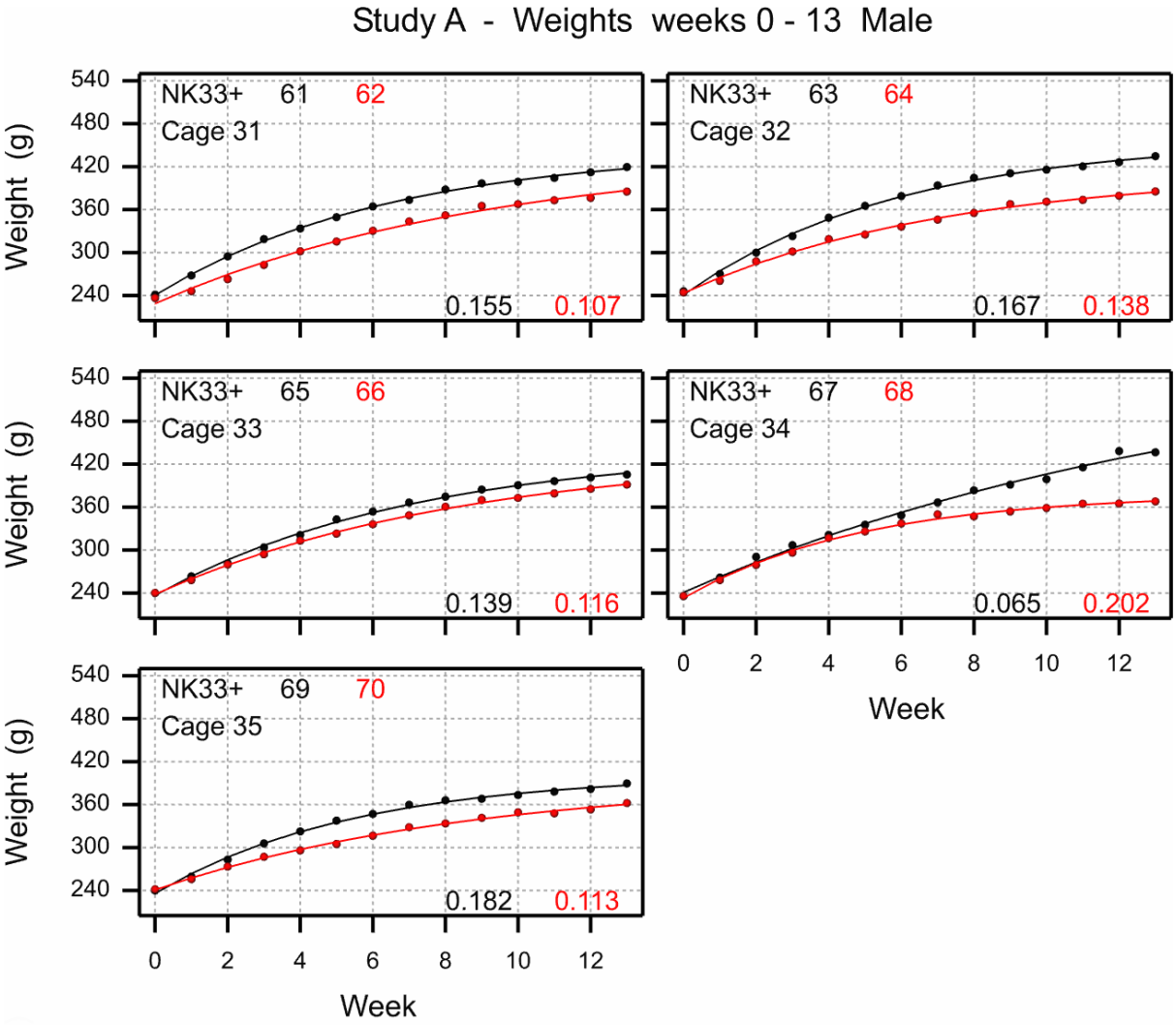
Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph, while the estimated growth rate, i.e. $\gamma = -\log(R)$, is given in the right-bottom corner.



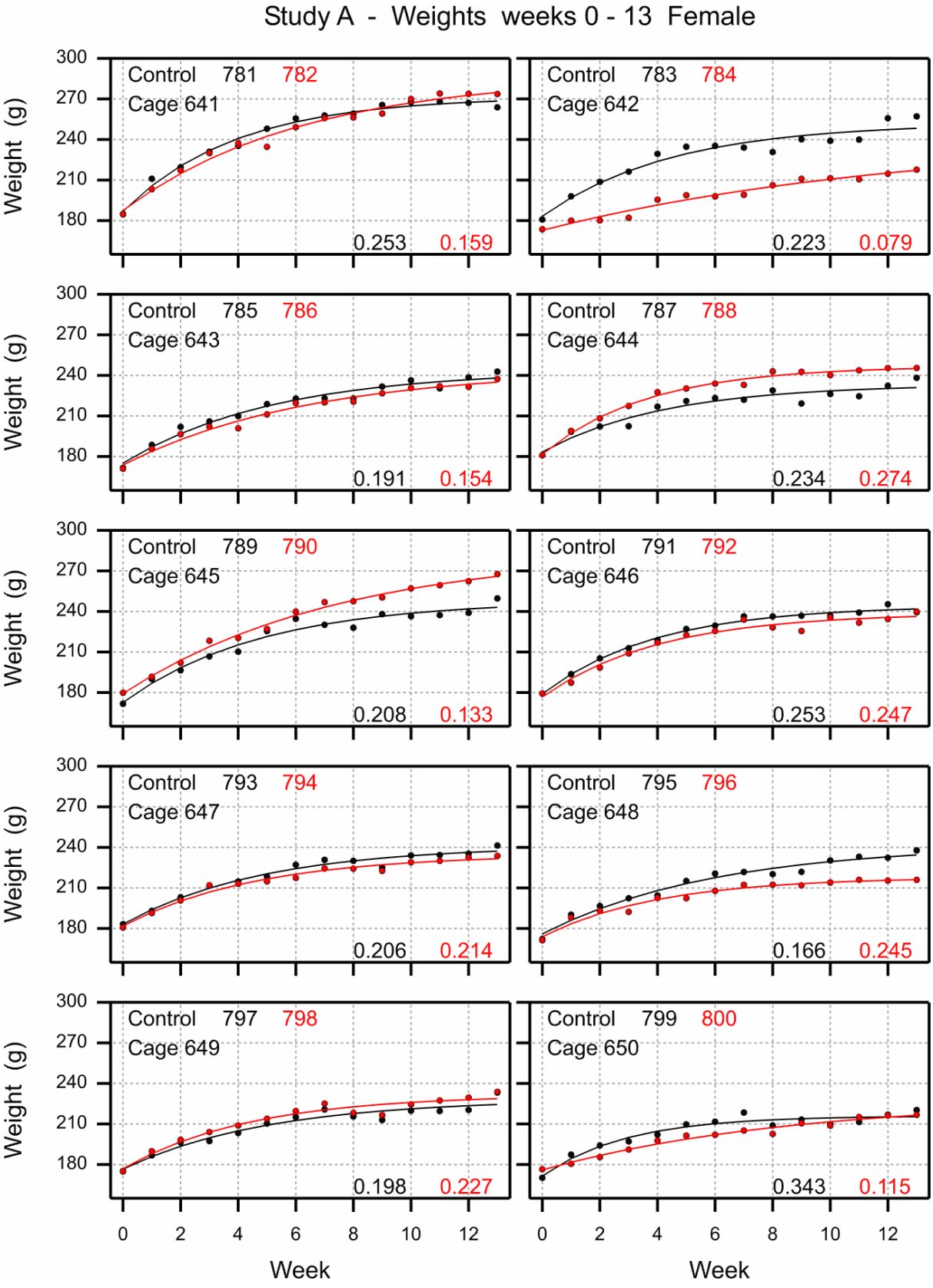
Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph, while the estimated growth rate, i.e. $\gamma = -\log(R)$, is given in the right-bottom corner.



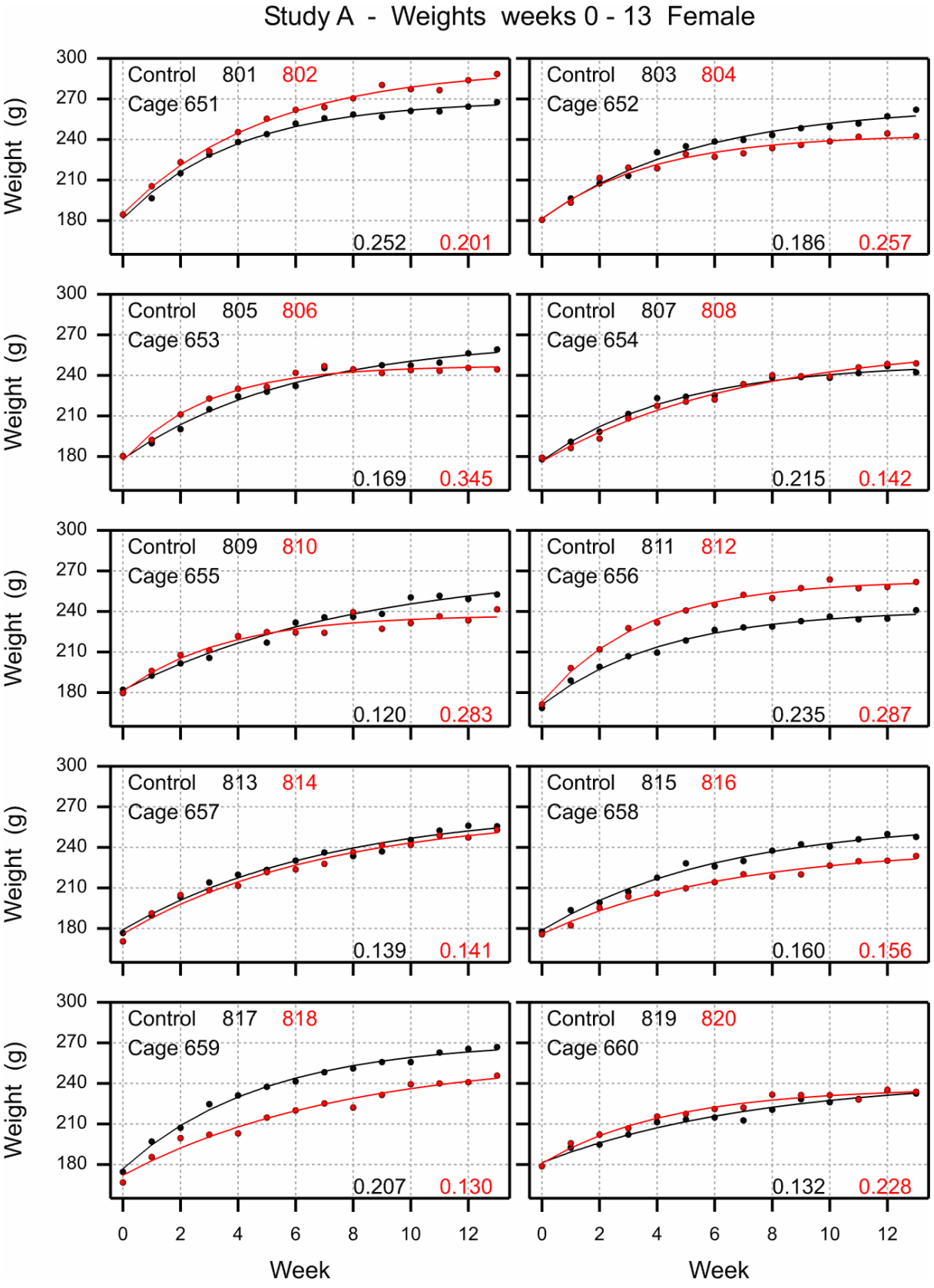
Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph, while the estimated growth rate, i.e. $\gamma = -\log(R)$, is given in the right-bottom corner.



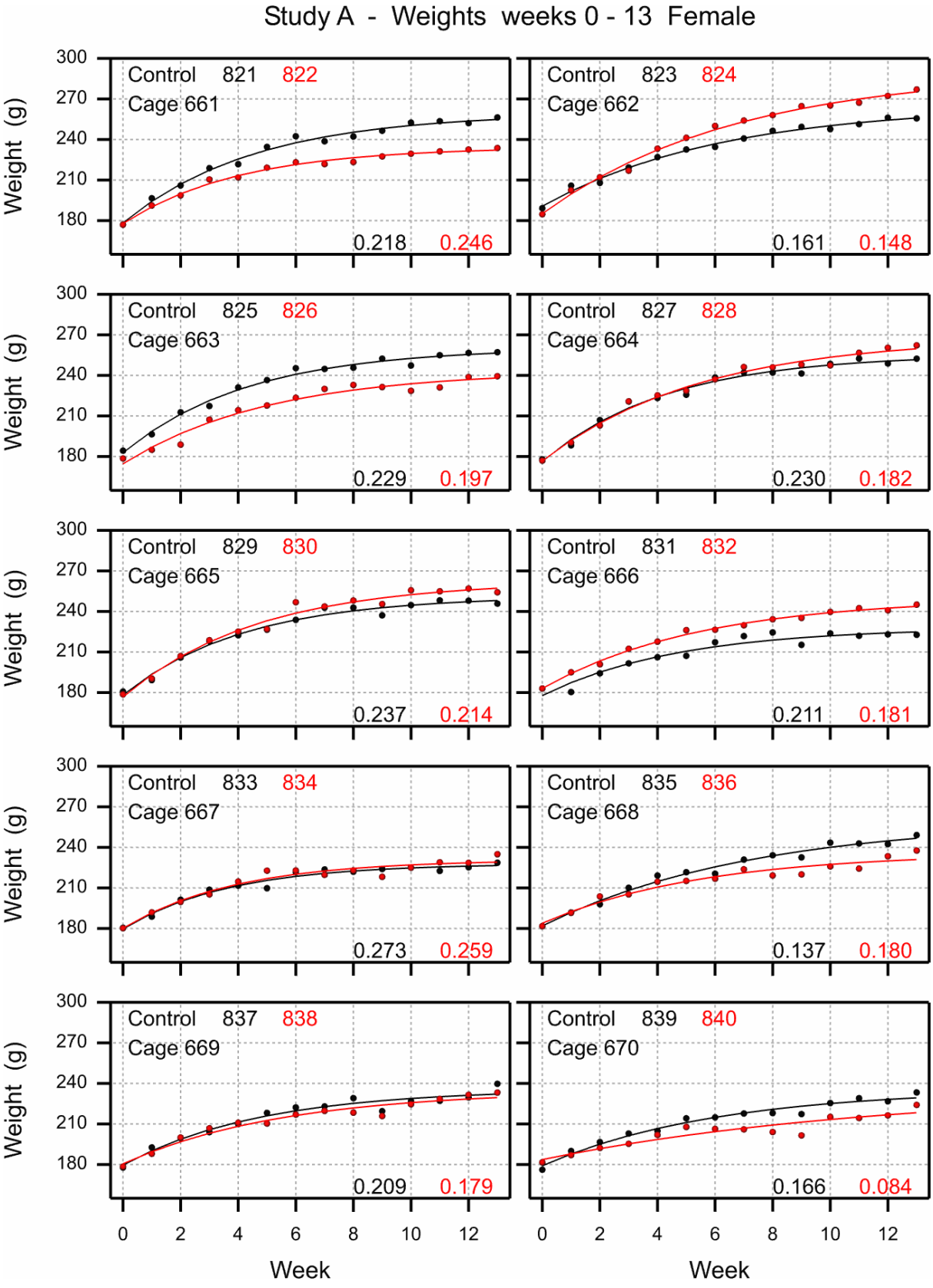
Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph, while the estimated growth rate, i.e. $\gamma = -\log(R)$, is given in the right-bottom corner.



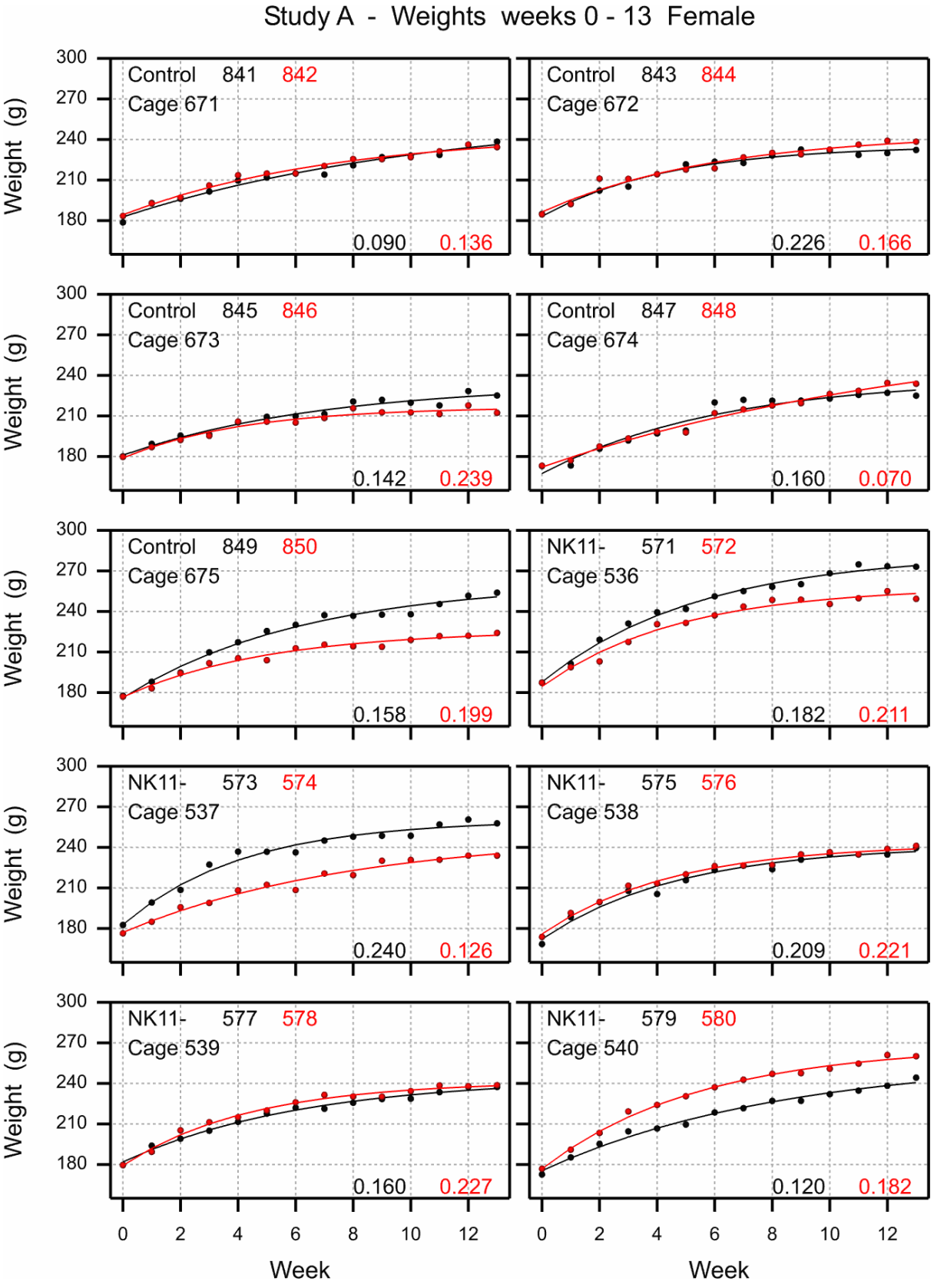
Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph, while the estimated growth rate, i.e. $\gamma = -\log(R)$, is given in the right-bottom corner.



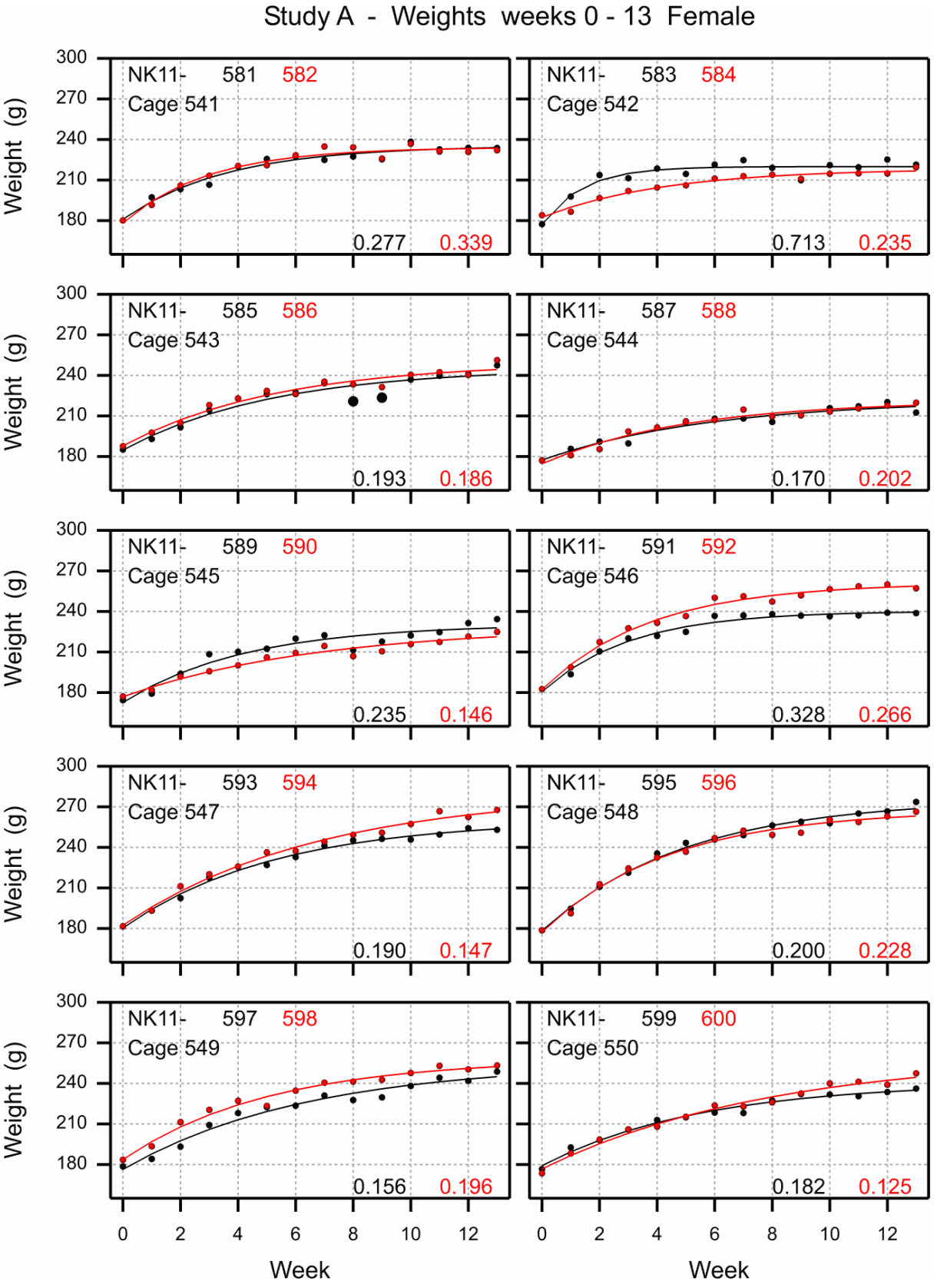
Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph, while the estimated growth rate, i.e. $\gamma = -\log(R)$, is given in the right-bottom corner.



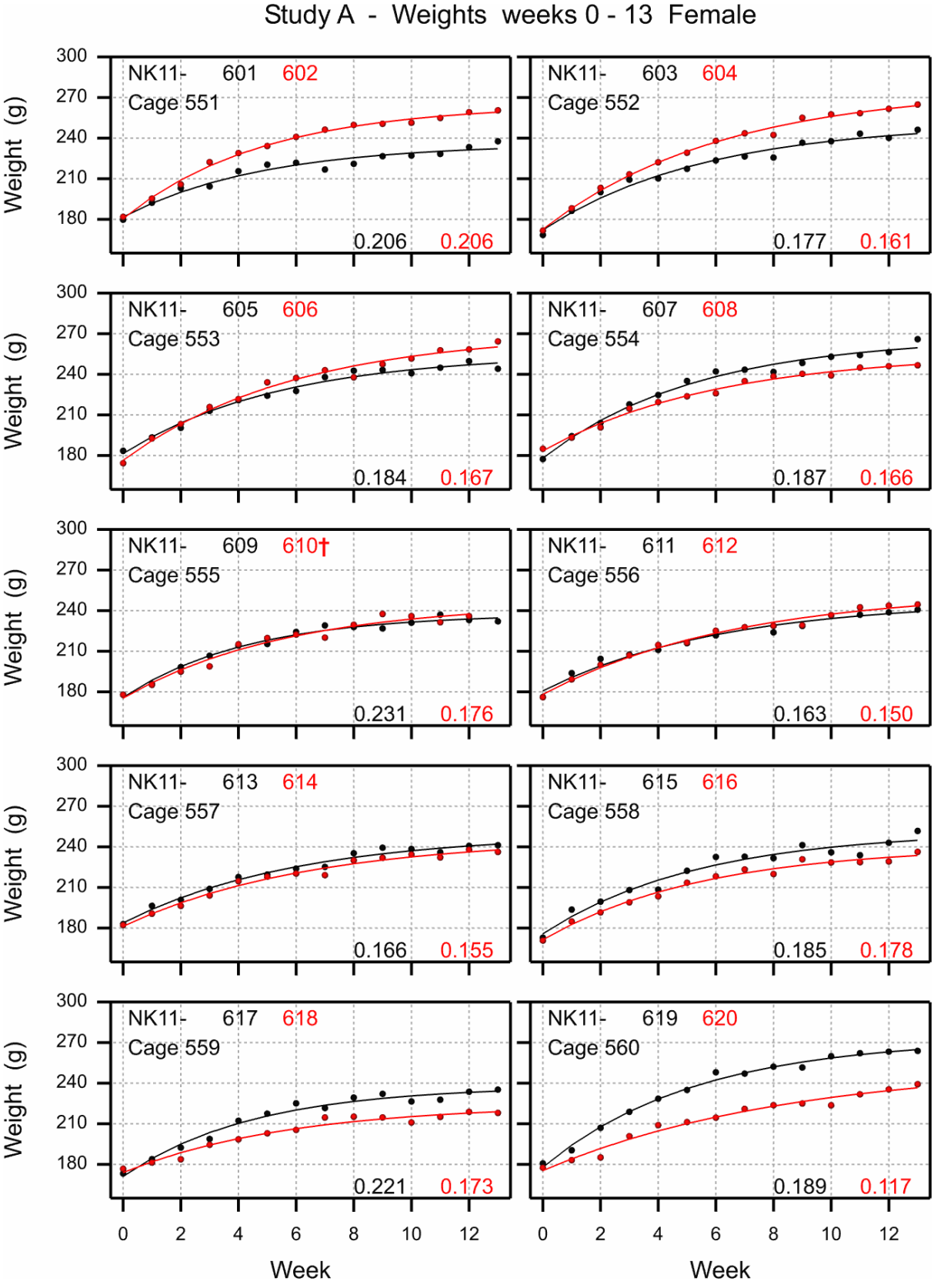
Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph, while the estimated growth rate, i.e. $\gamma = -\log(R)$, is given in the right-bottom corner.



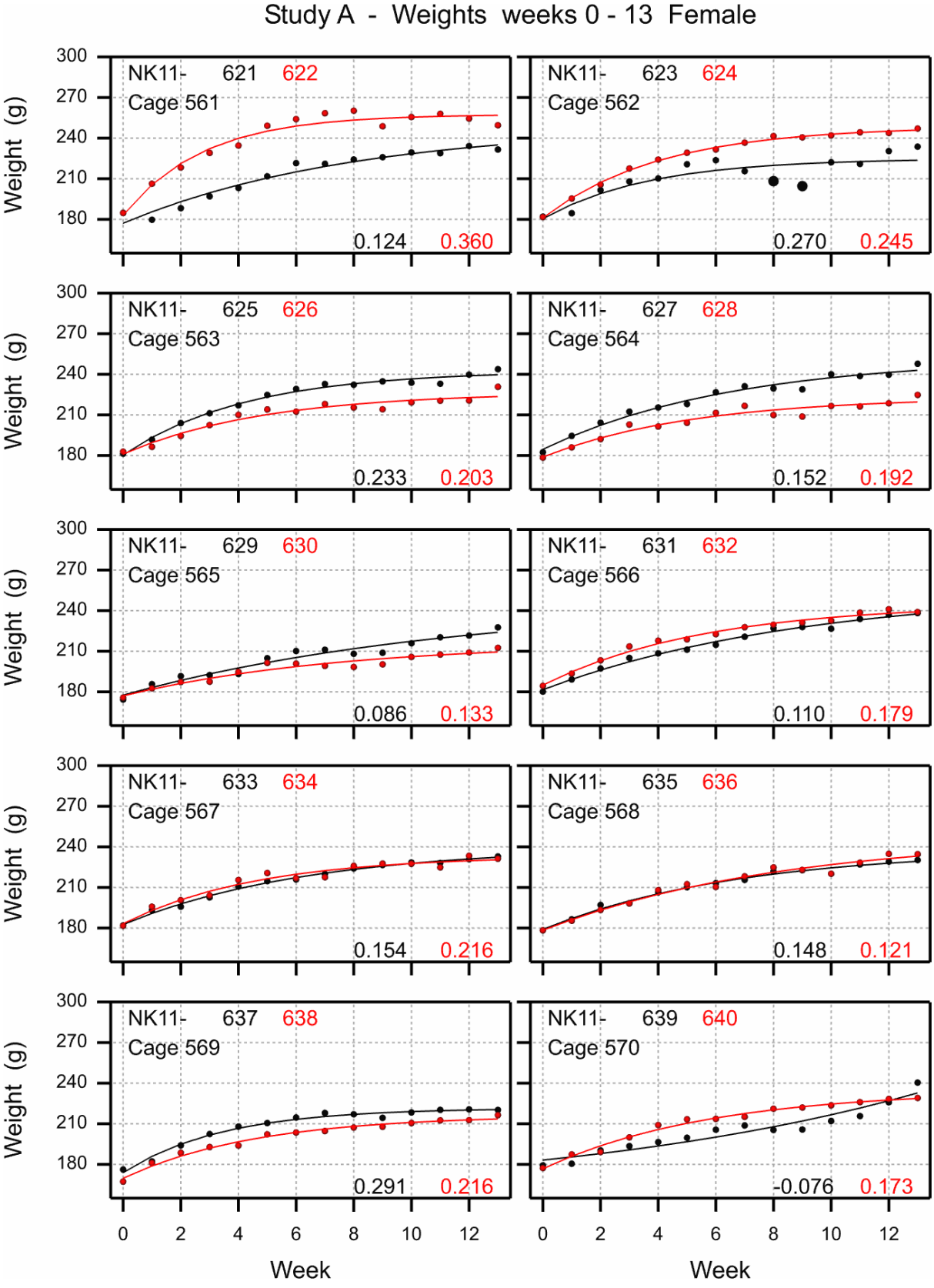
Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph, while the estimated growth rate, i.e. $\gamma = -\log(R)$, is given in the right-bottom corner.



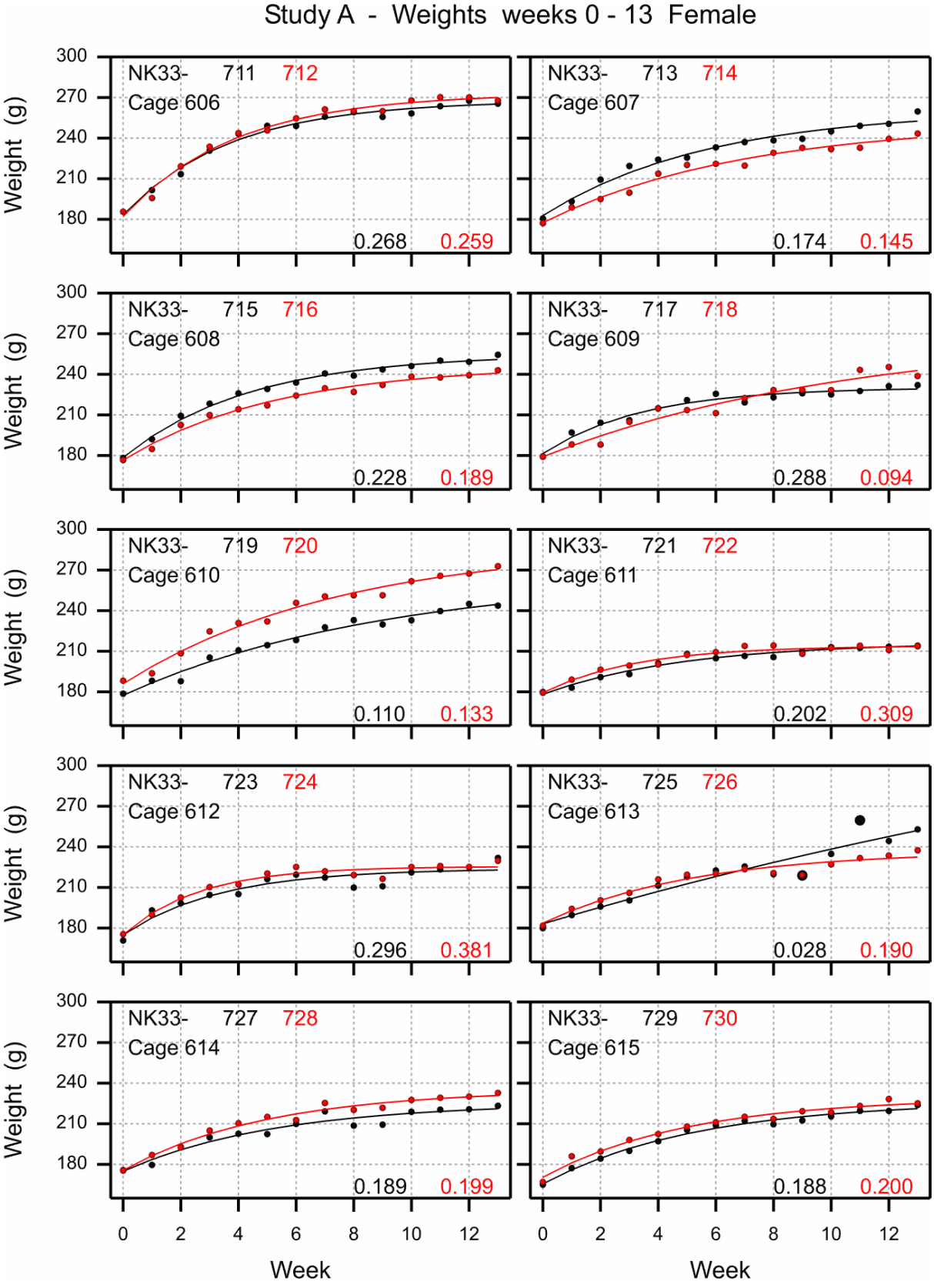
Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph, while the estimated growth rate, i.e. $\gamma = -\log(R)$, is given in the right-bottom corner.



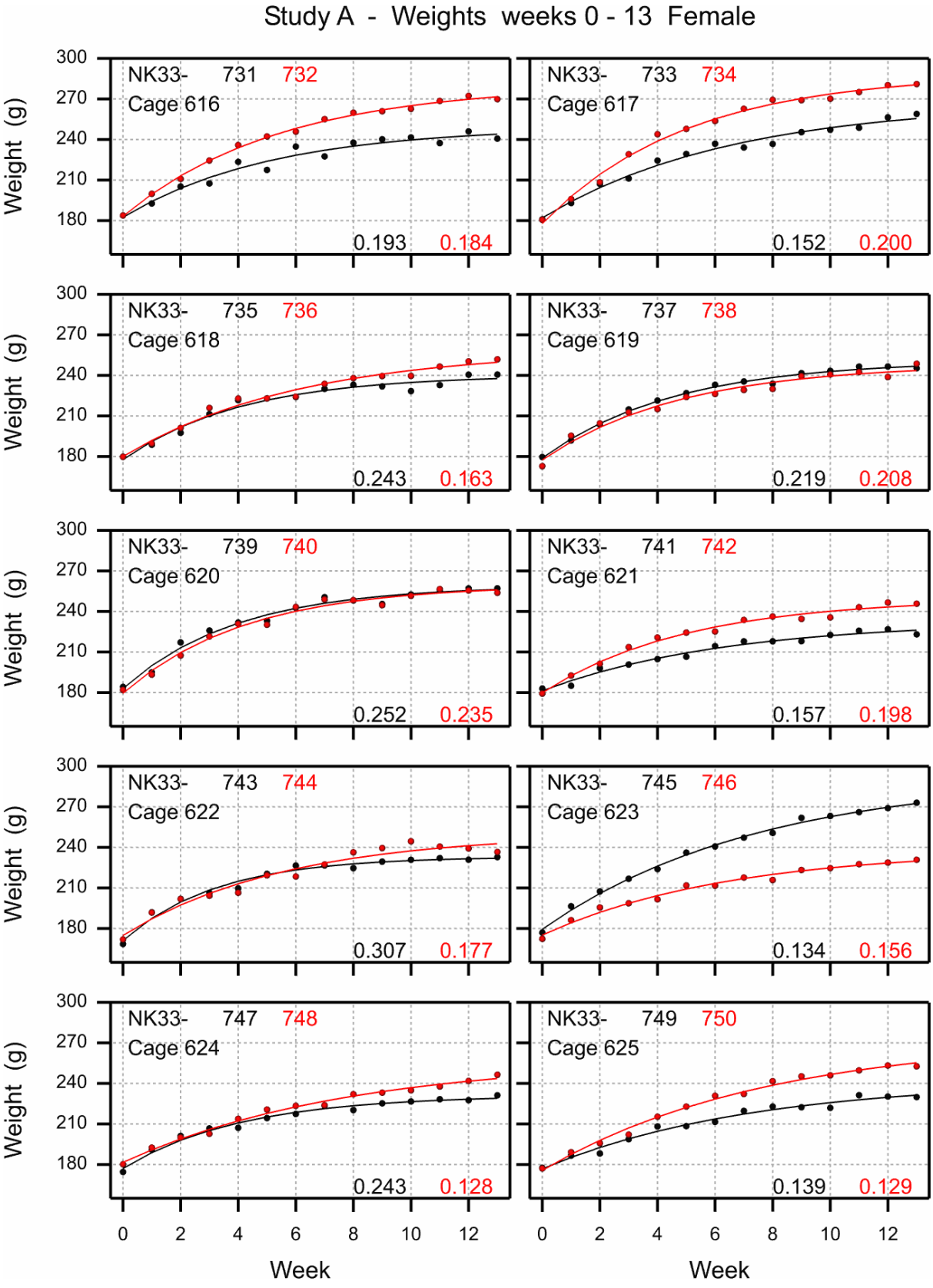
Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph, while the estimated growth rate, i.e. $\gamma = -\log(R)$, is given in the right-bottom corner.



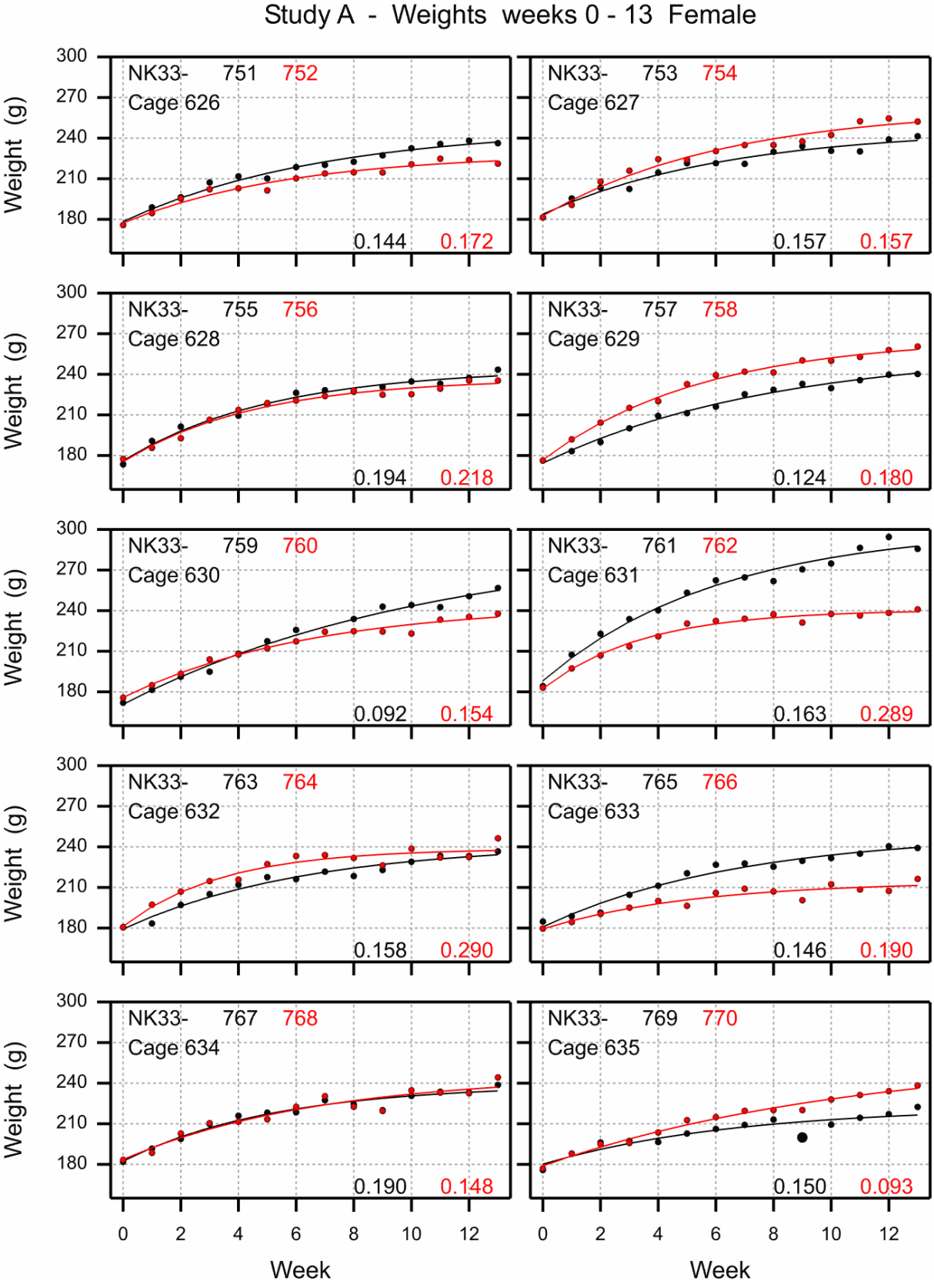
Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph, while the estimated growth rate, i.e. $\gamma = -\log(R)$, is given in the right-bottom corner.



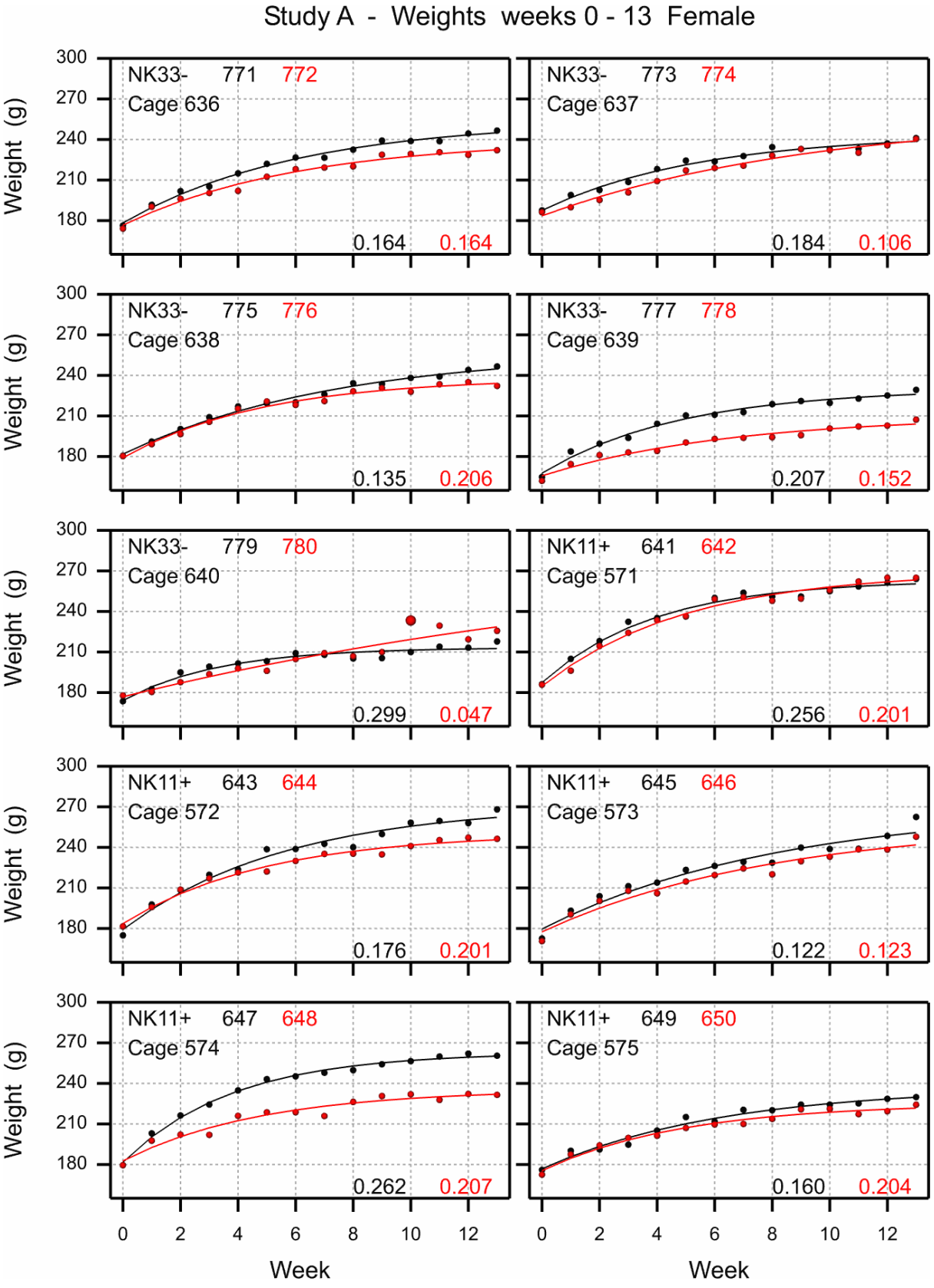
Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph, while the estimated growth rate, i.e. $\gamma = -\log(R)$, is given in the right-bottom corner.



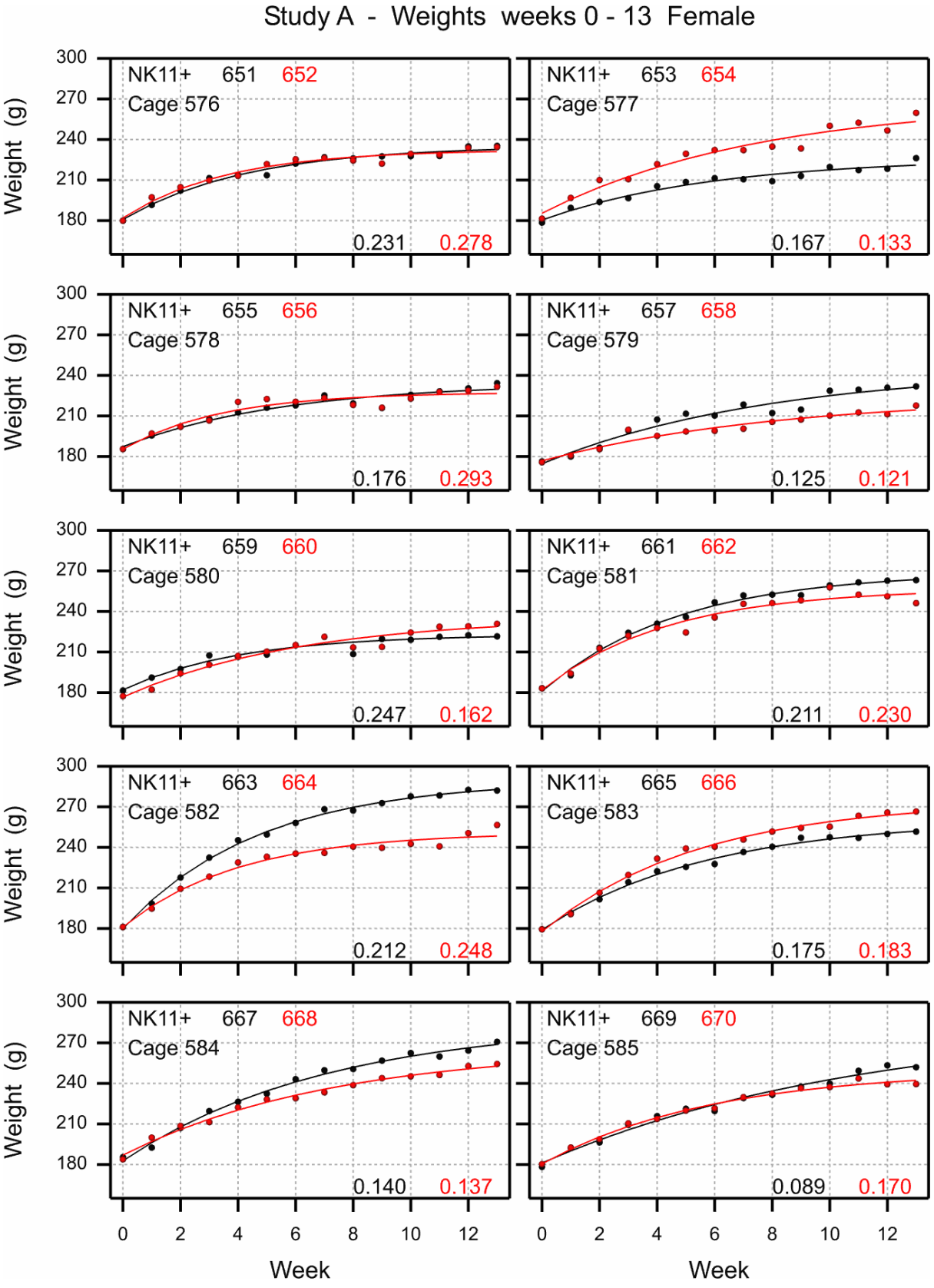
Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph, while the estimated growth rate, i.e. $\gamma = -\log(R)$, is given in the right-bottom corner.



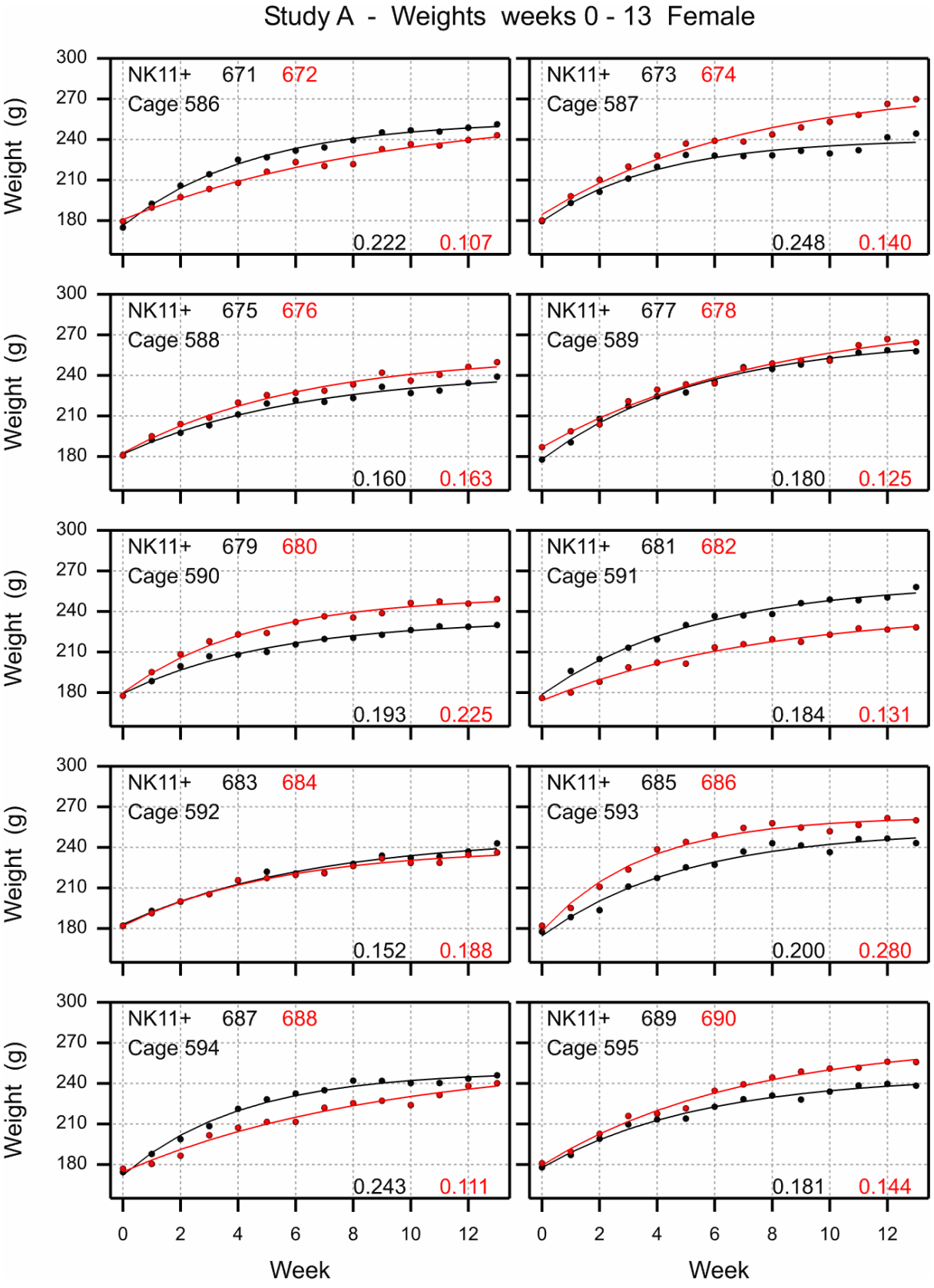
Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph, while the estimated growth rate, i.e. $\gamma = -\log(R)$, is given in the right-bottom corner.



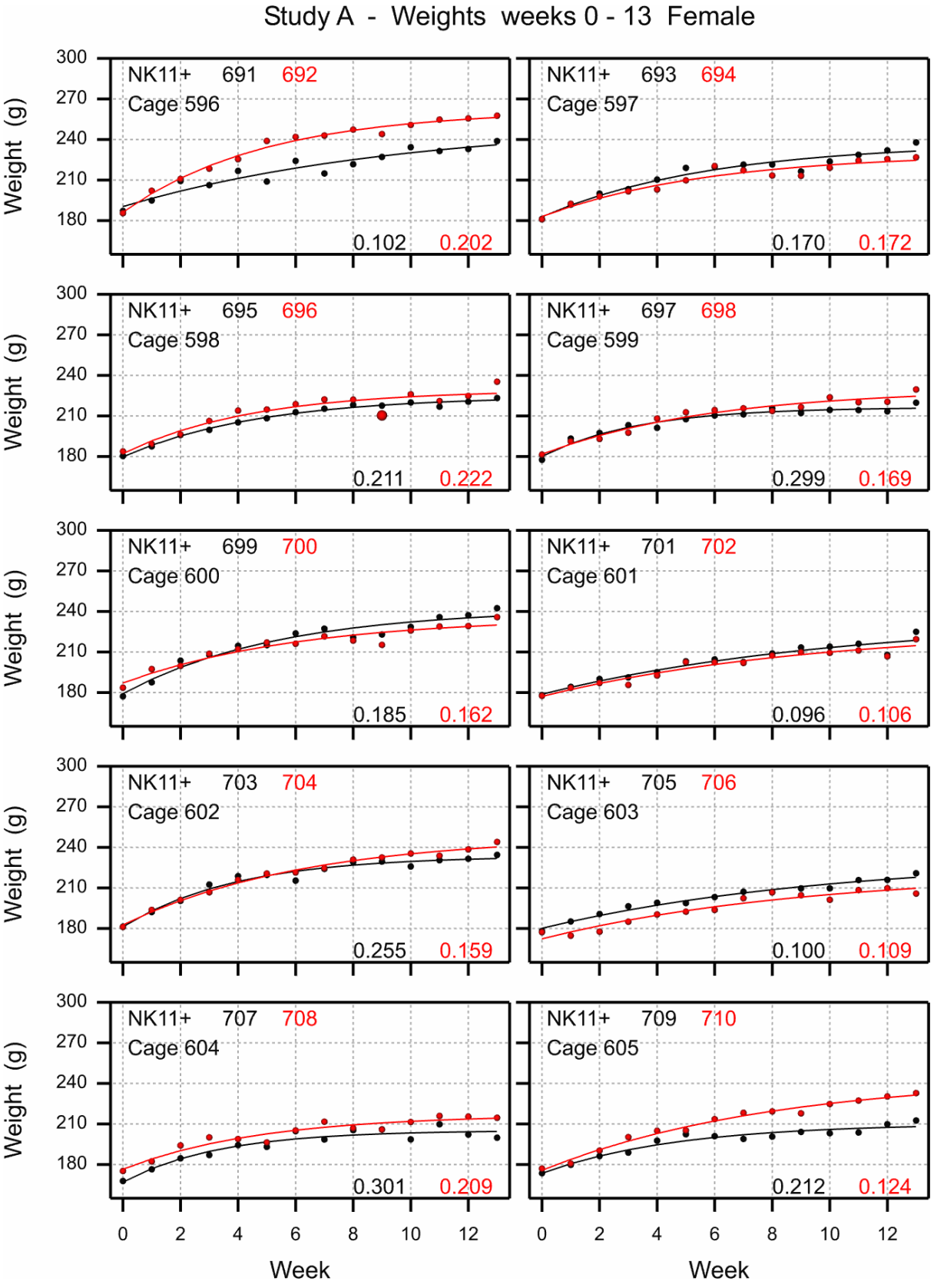
Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph, while the estimated growth rate, i.e. $\gamma = -\log(R)$, is given in the right-bottom corner.



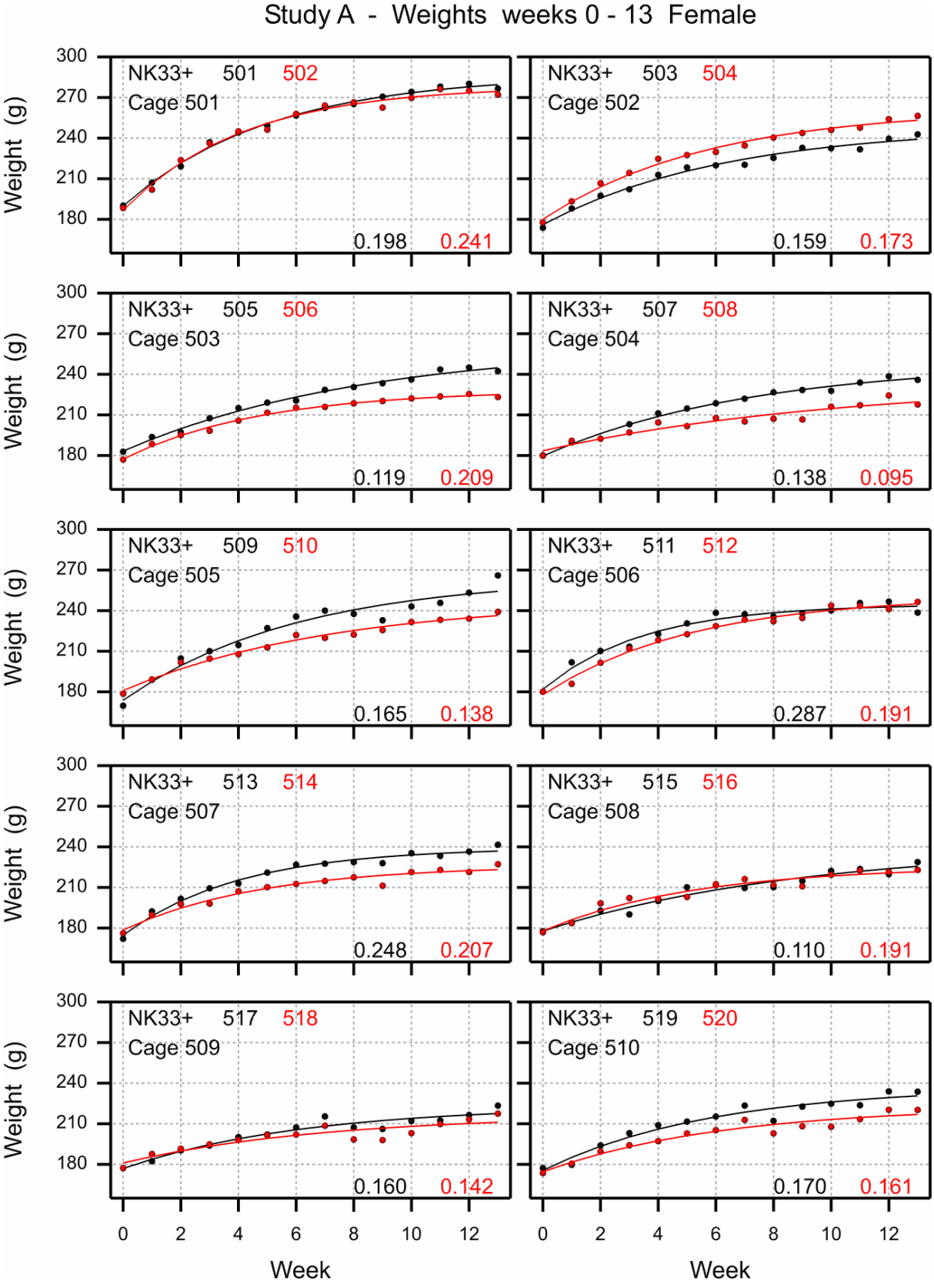
Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph, while the estimated growth rate, i.e. $\gamma = -\log(R)$, is given in the right-bottom corner.



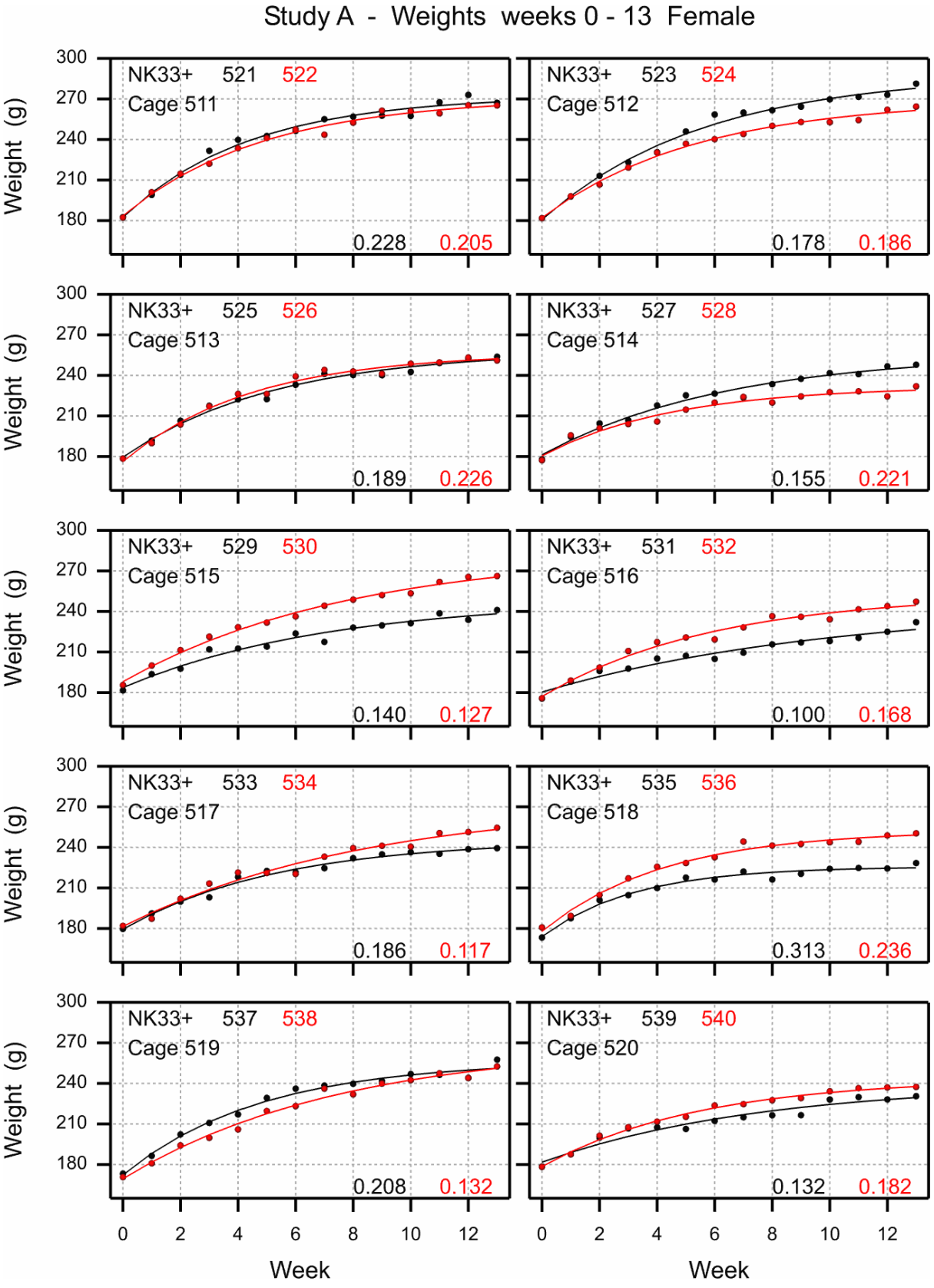
Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph, while the estimated growth rate, i.e. $\gamma = -\log(R)$, is given in the right-bottom corner.



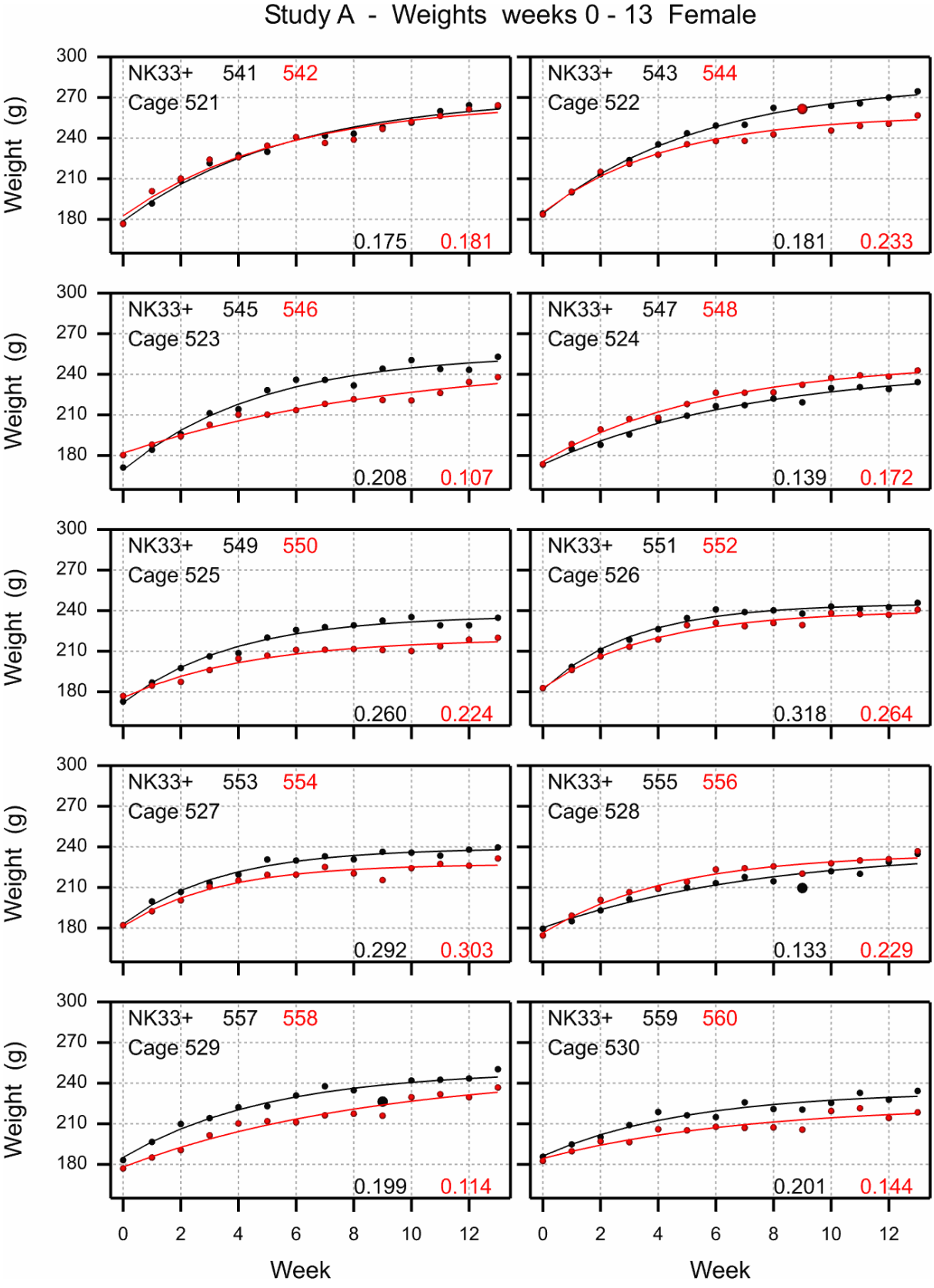
Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph, while the estimated growth rate, i.e. $\gamma = -\log(R)$, is given in the right-bottom corner.



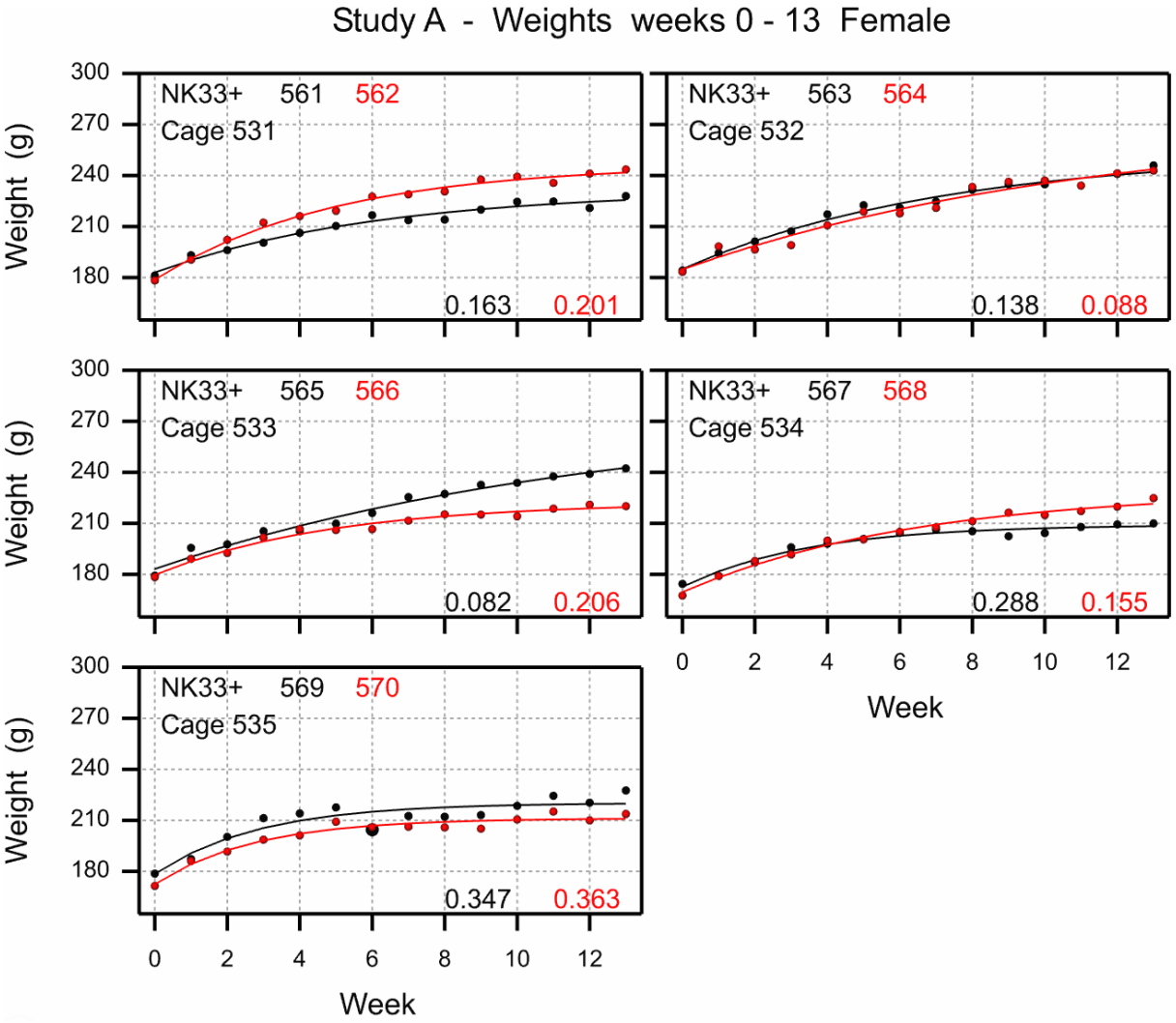
Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph, while the estimated growth rate, i.e. $\gamma = -\log(R)$, is given in the right-bottom corner.



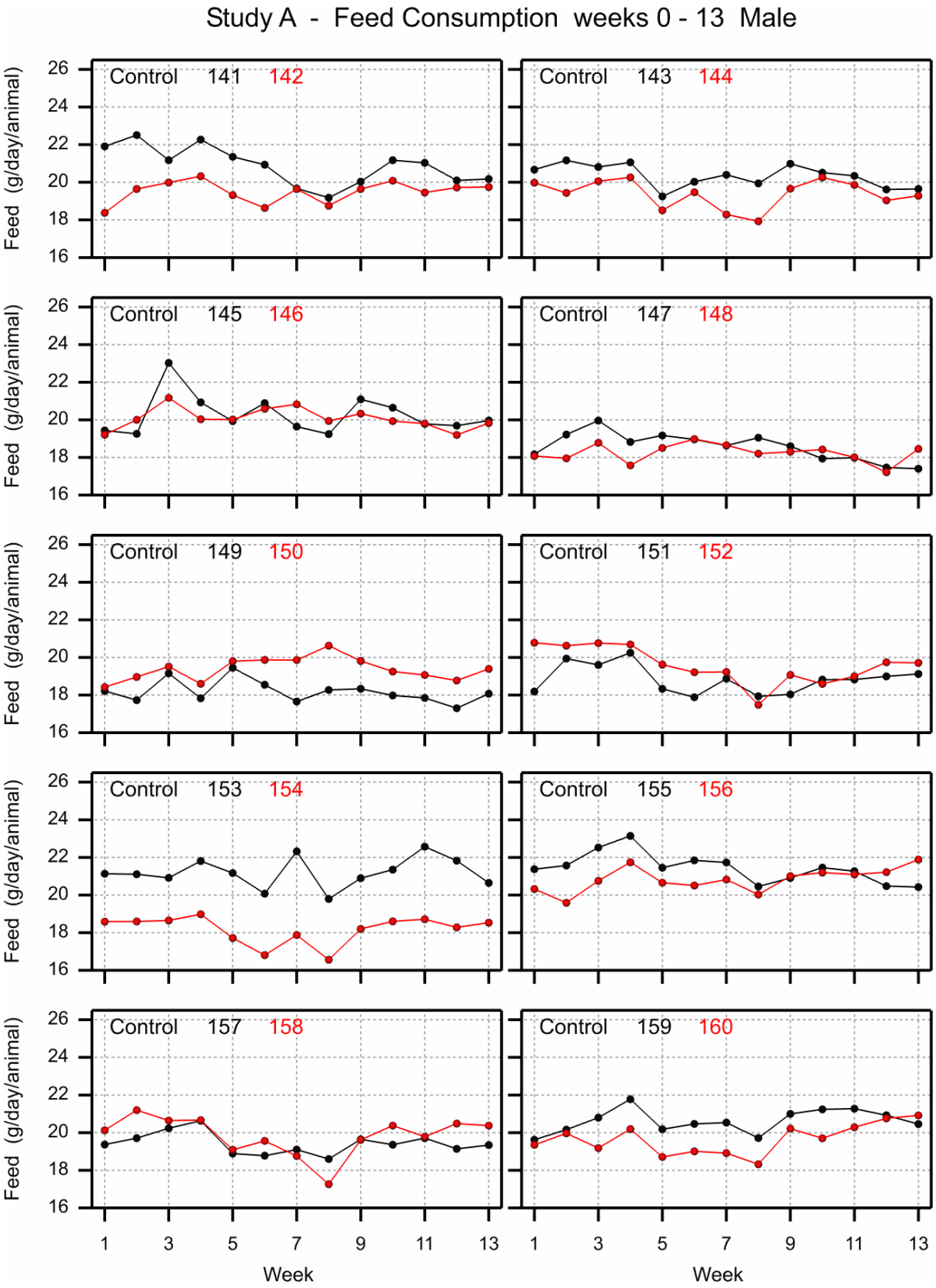
Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph, while the estimated growth rate, i.e. $\gamma = -\log(R)$, is given in the right-bottom corner.



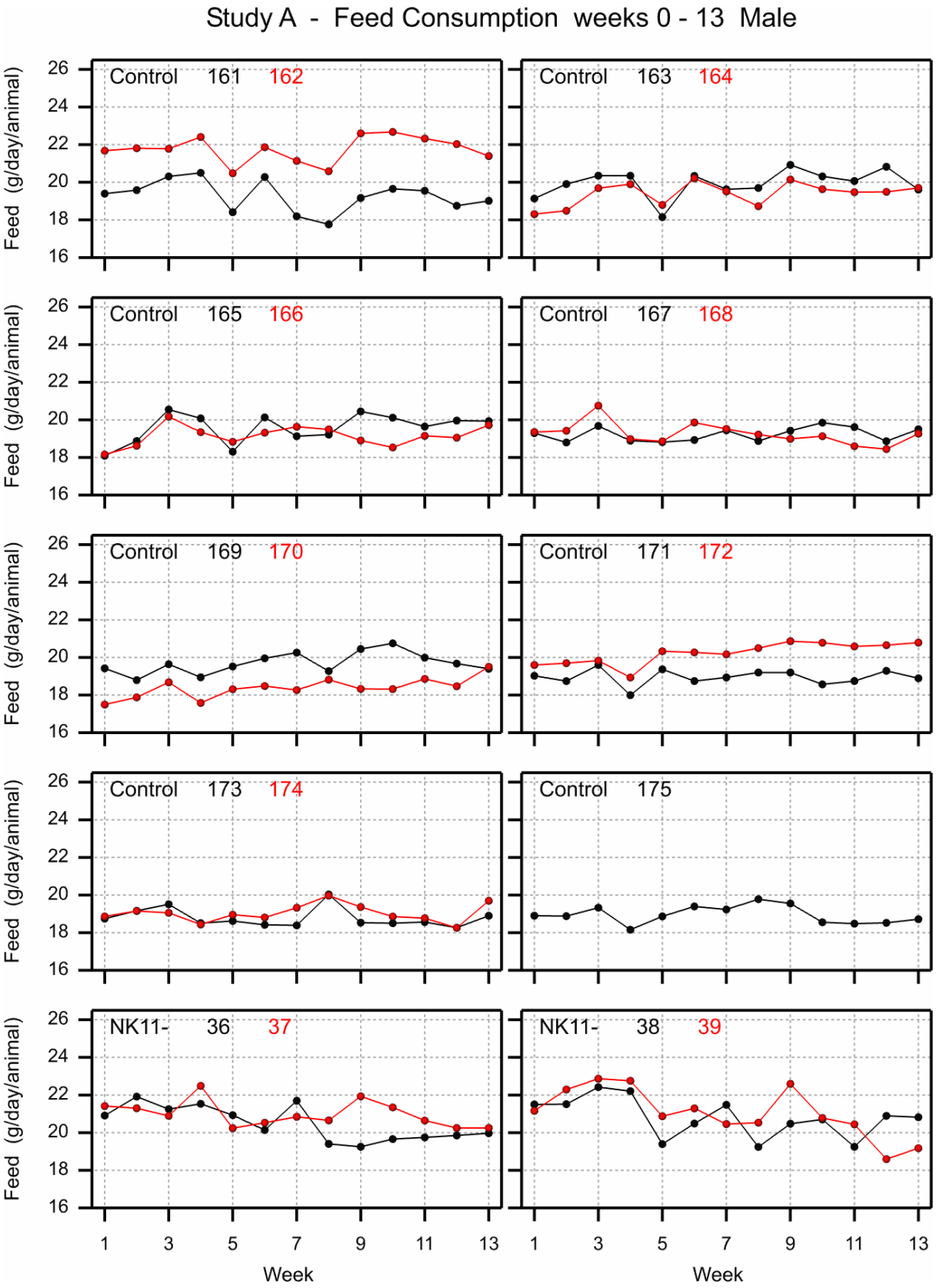
Appendix 2. Feed consumption per cage

The feed group and cage numbers are given in the left top corner of the graph.



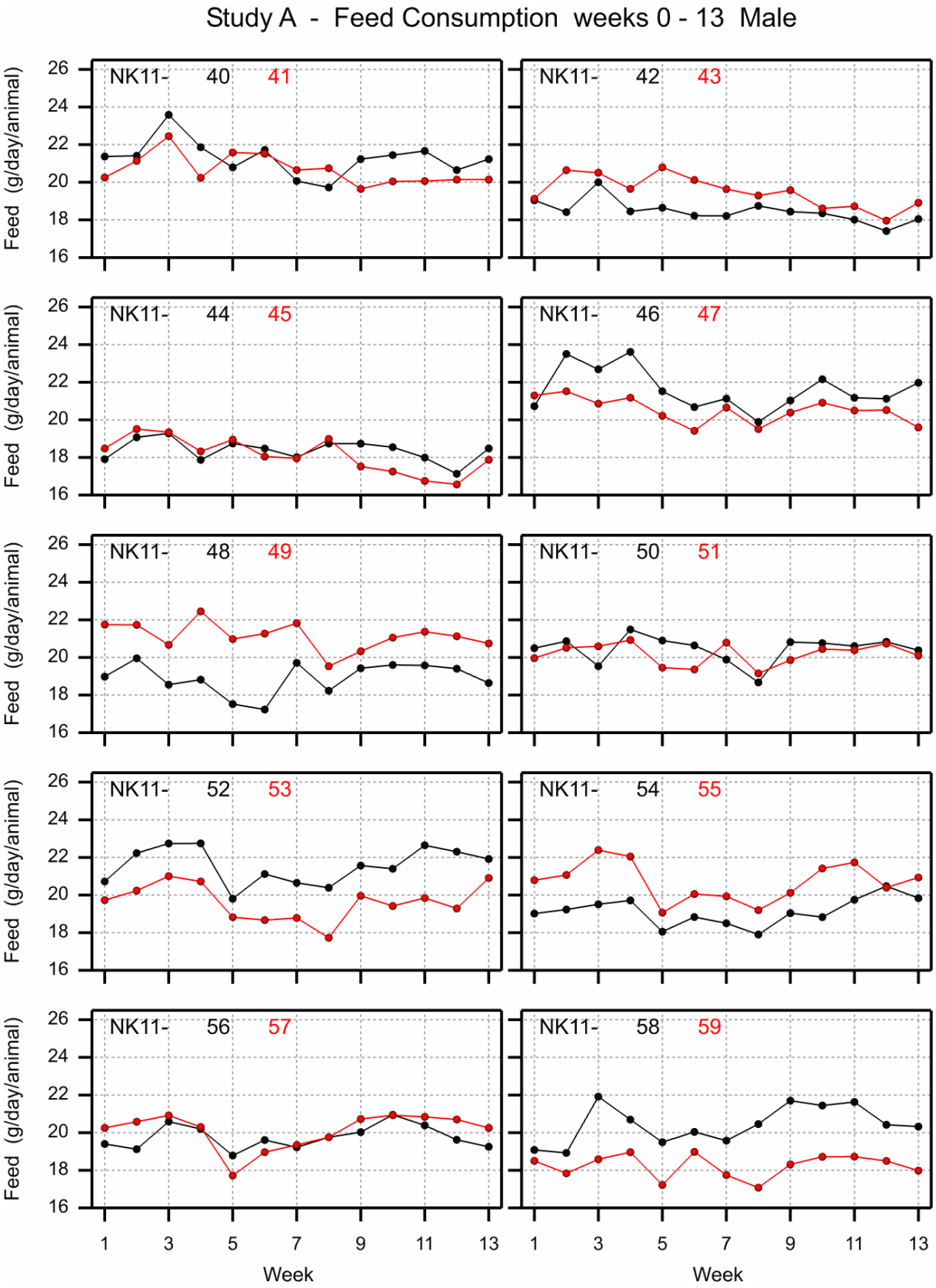
Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph.



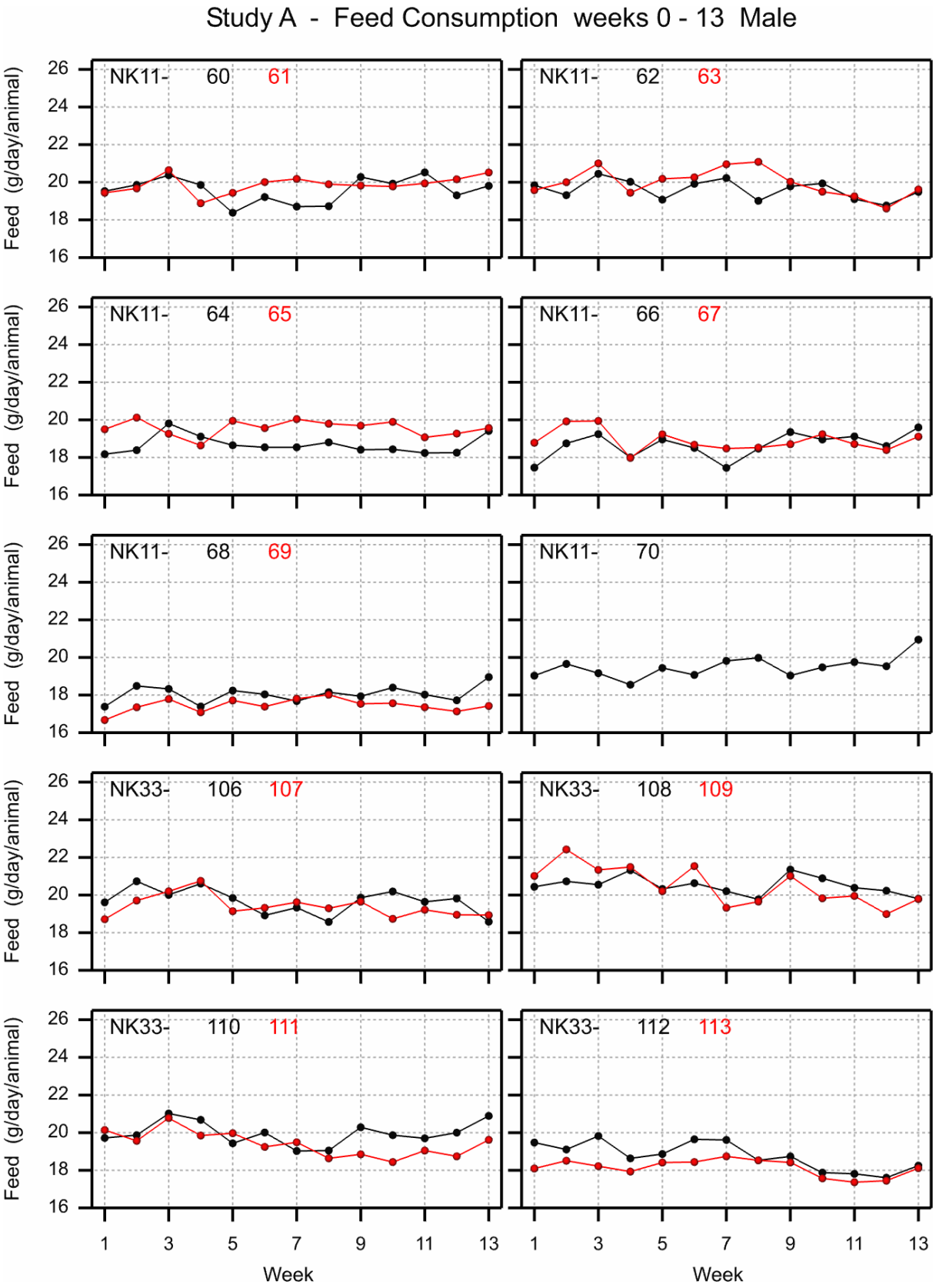
Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph.



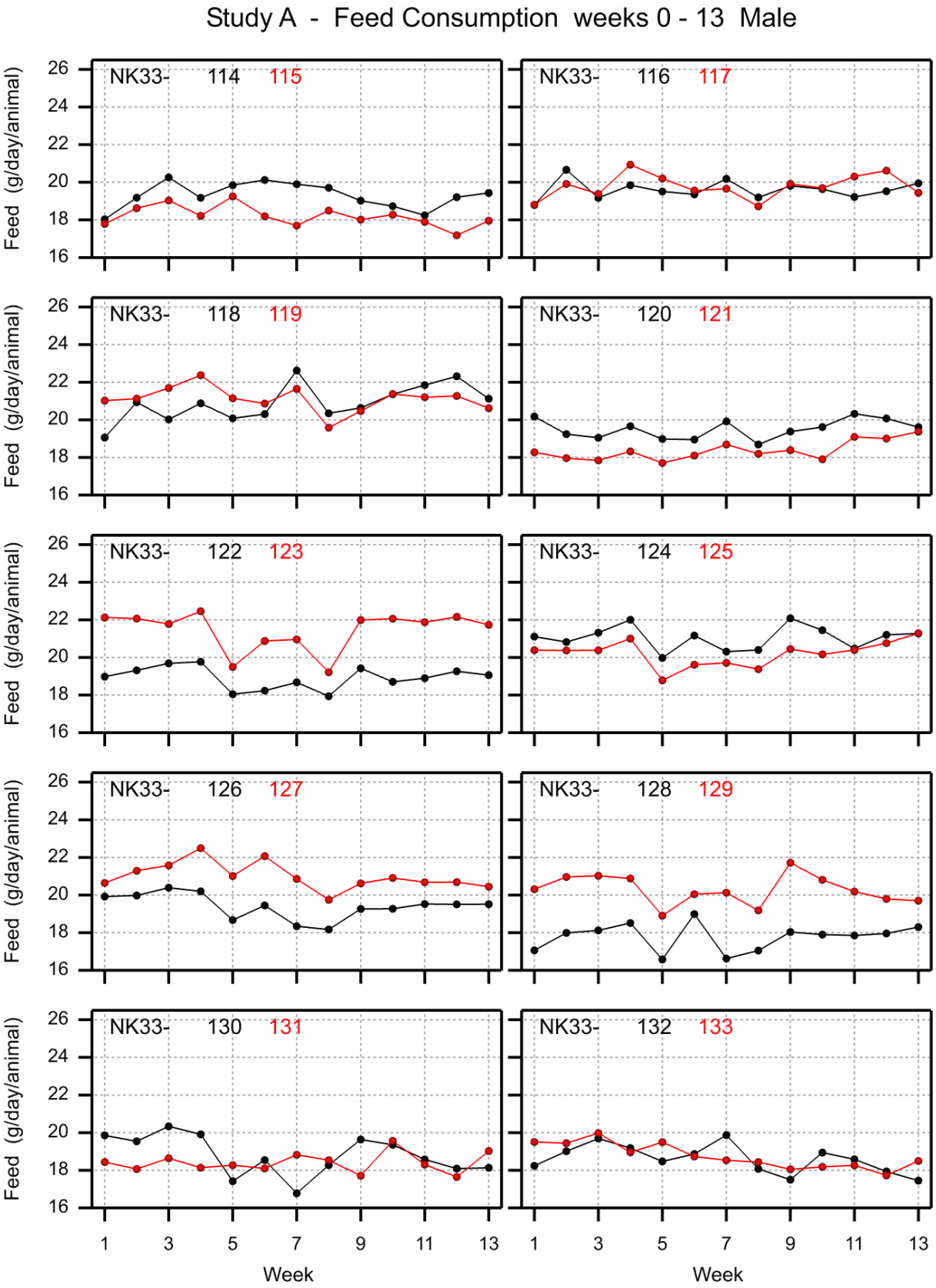
Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph.



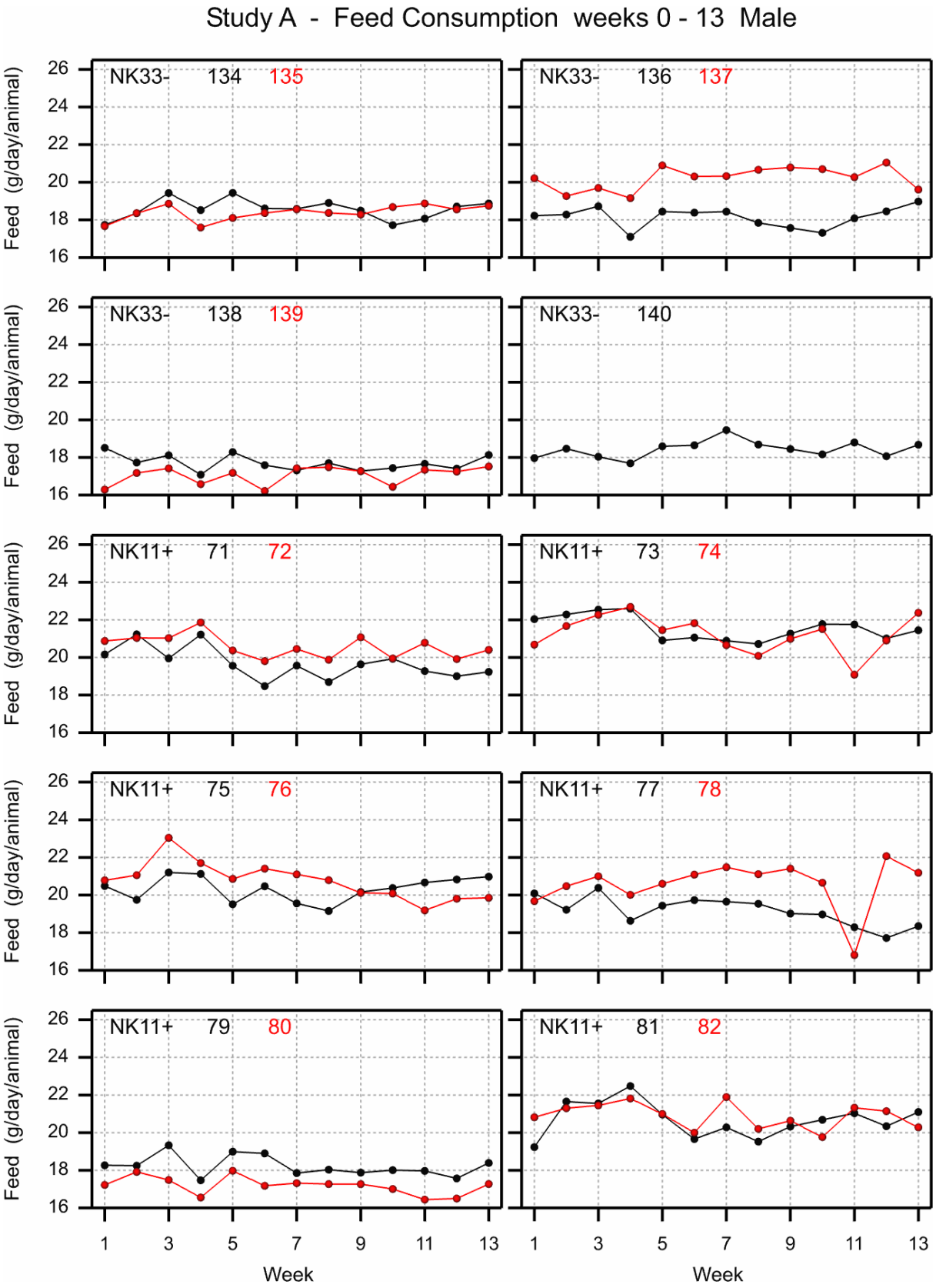
Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph.



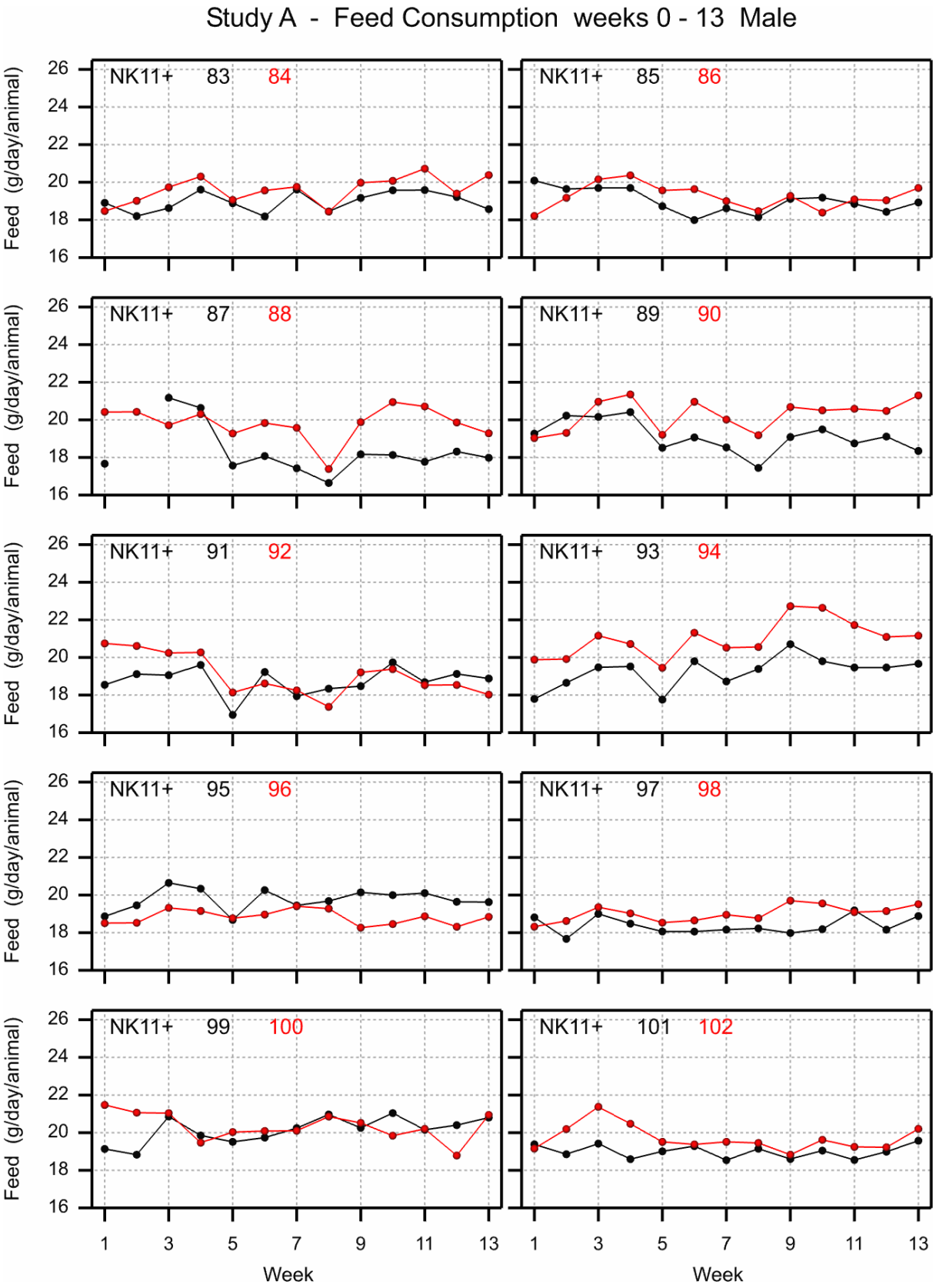
Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph.



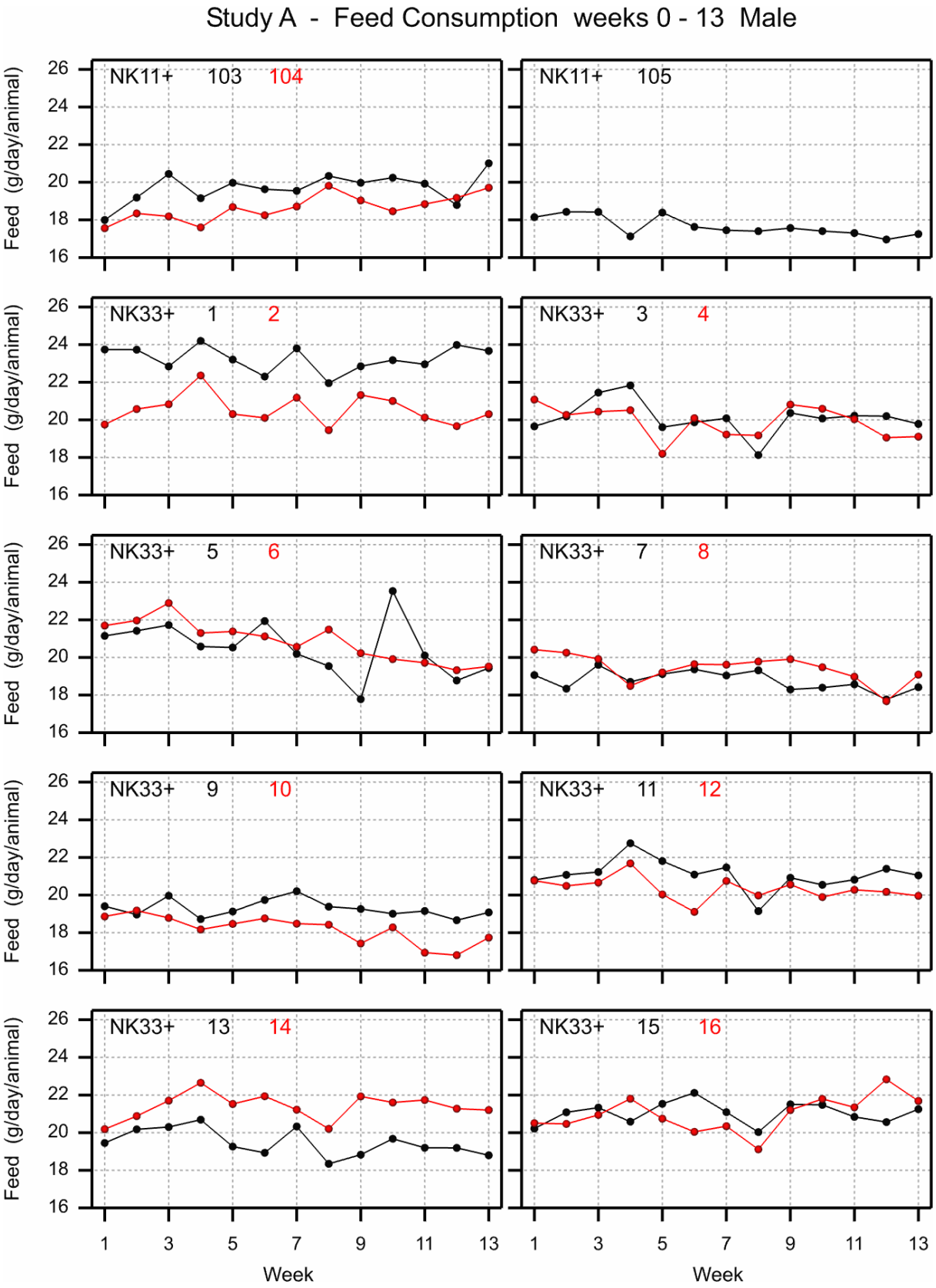
Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph.



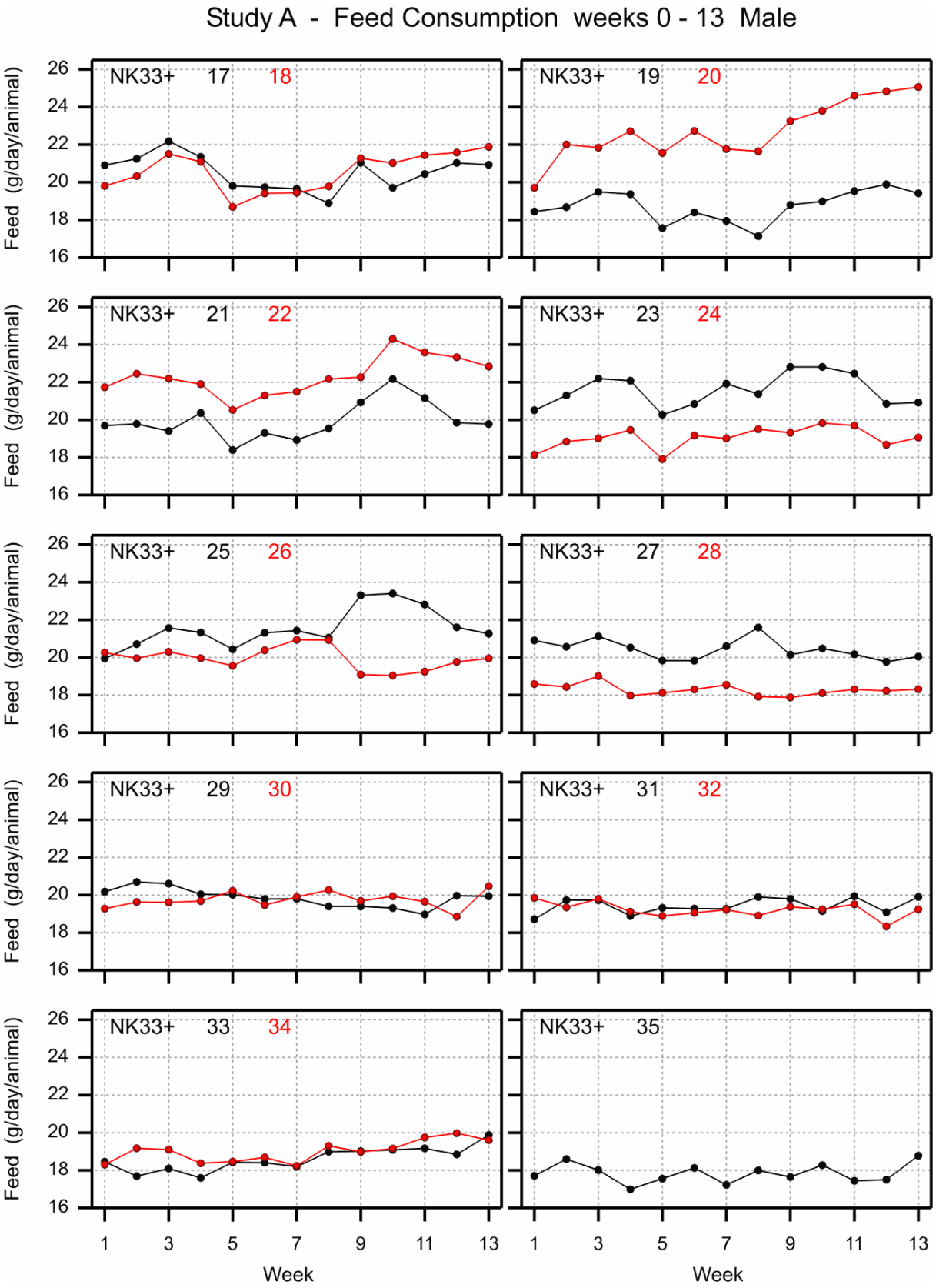
Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph.



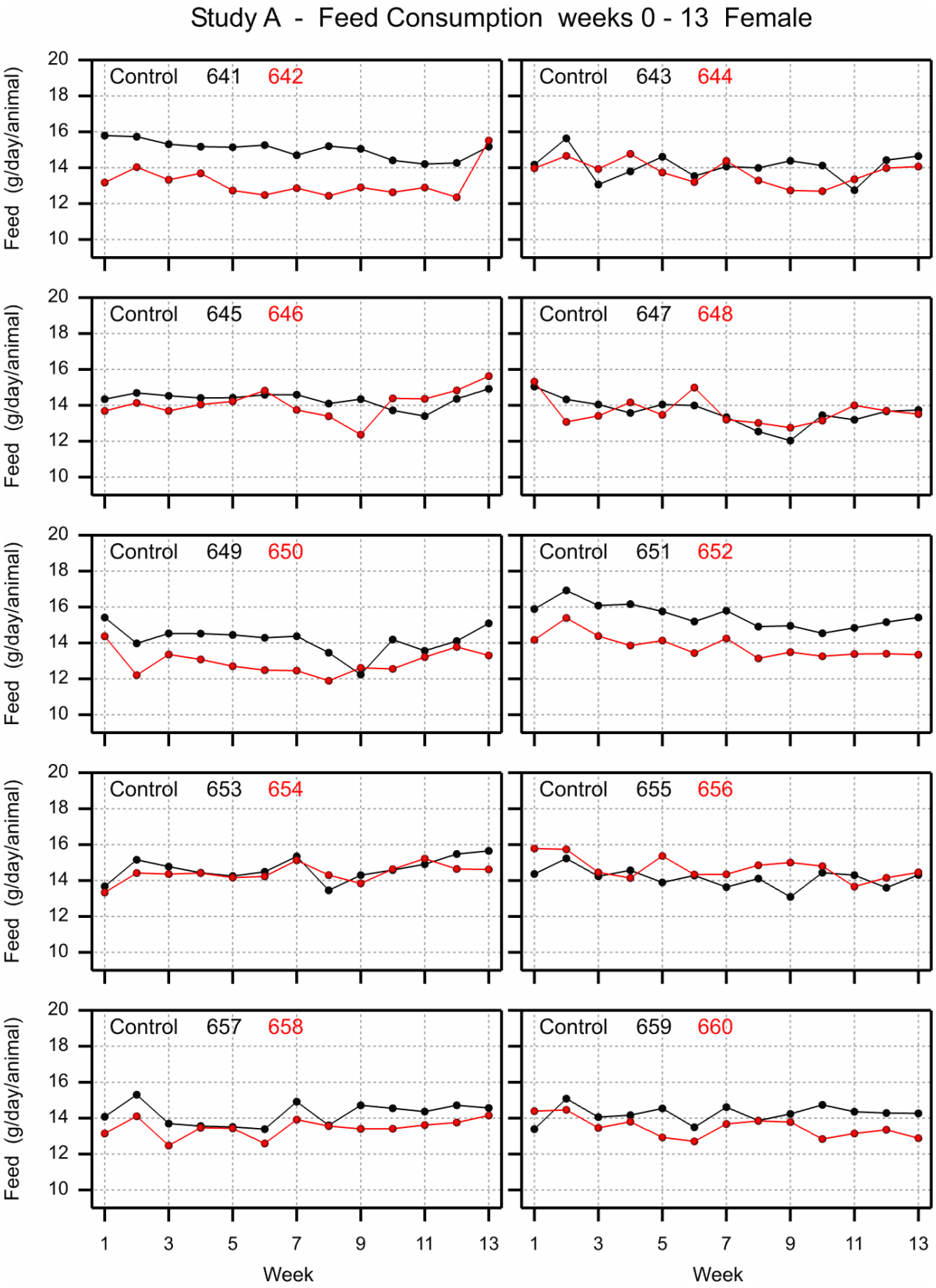
Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph.



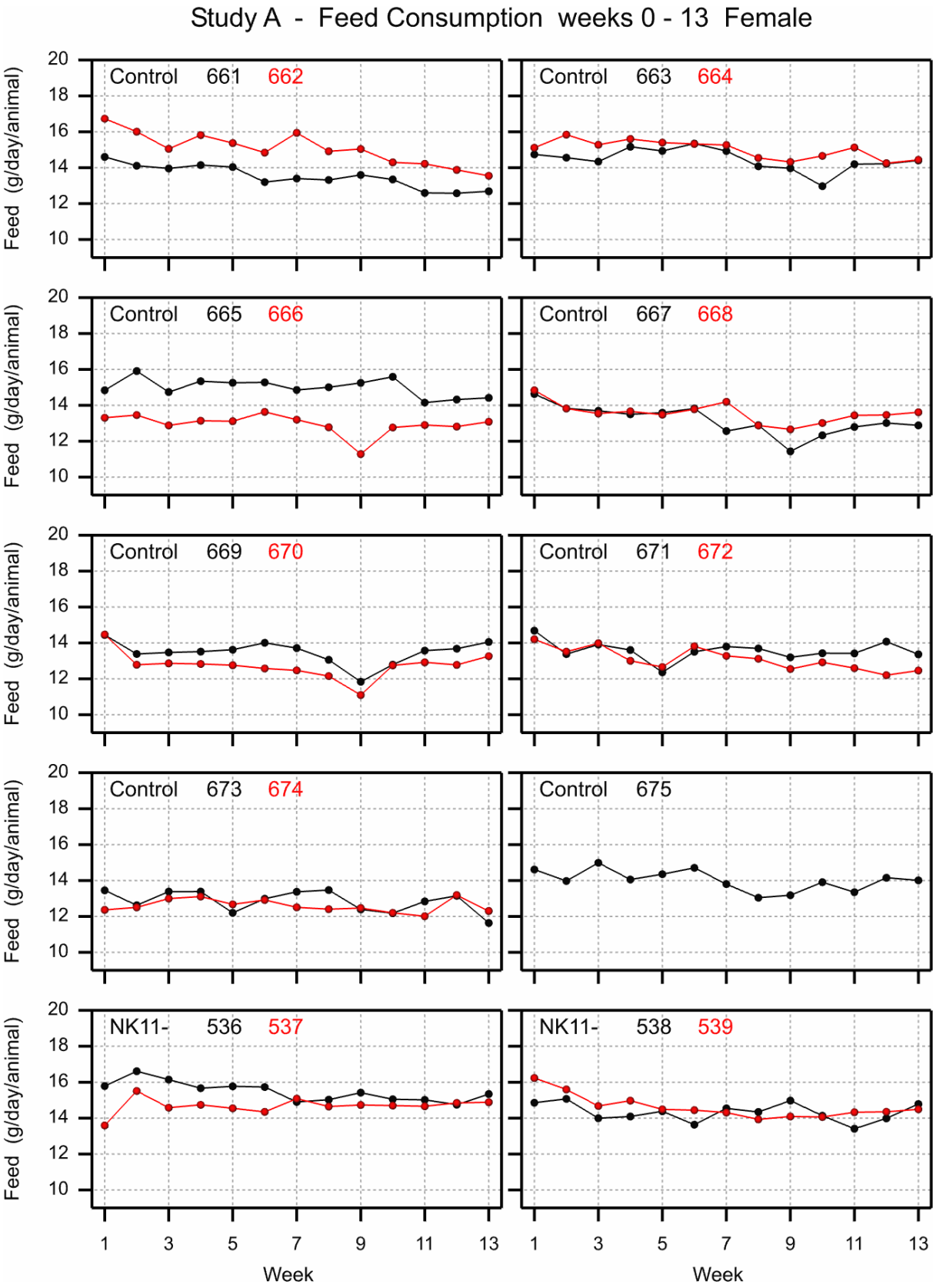
Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph.



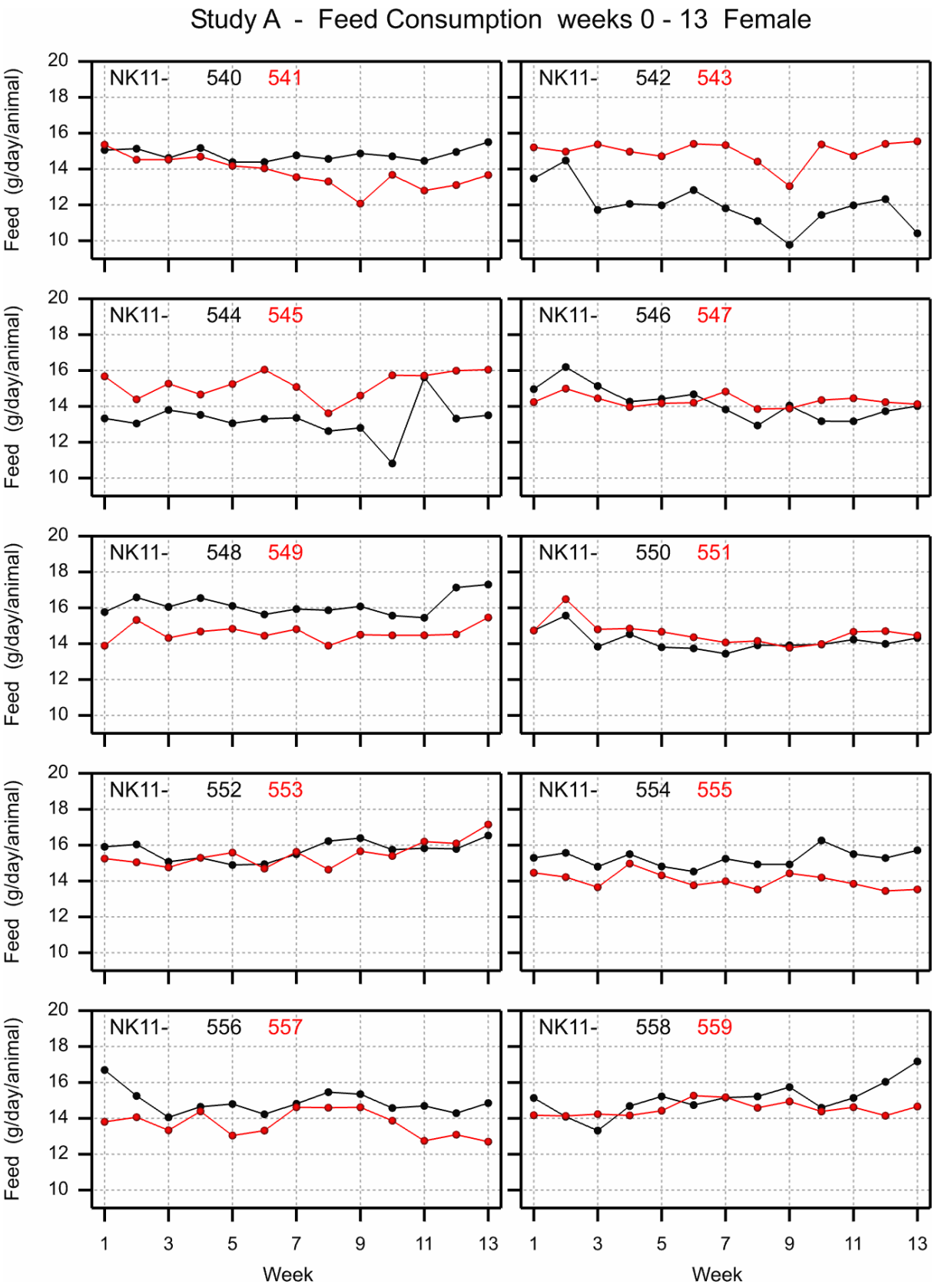
Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph.



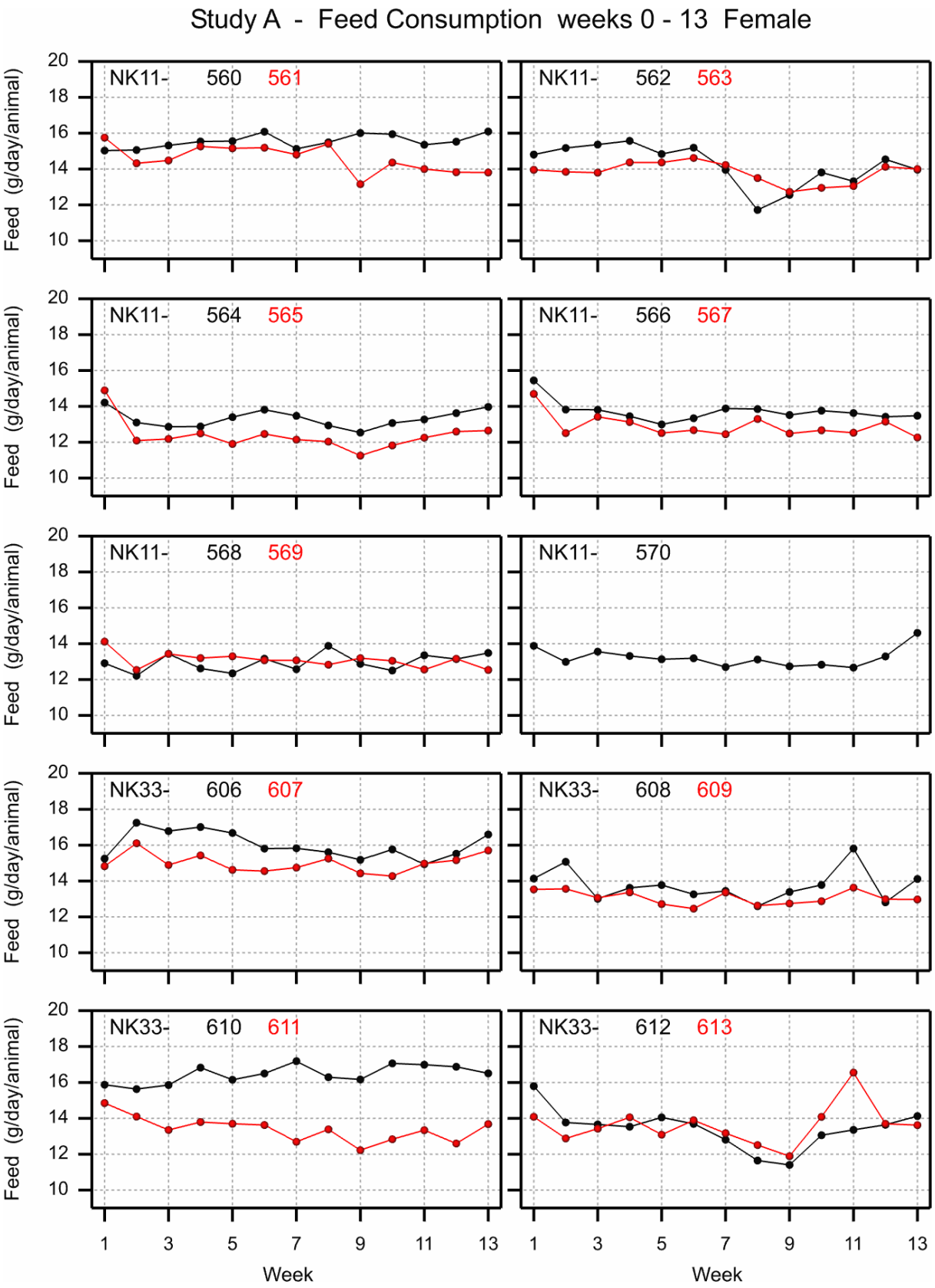
Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph.



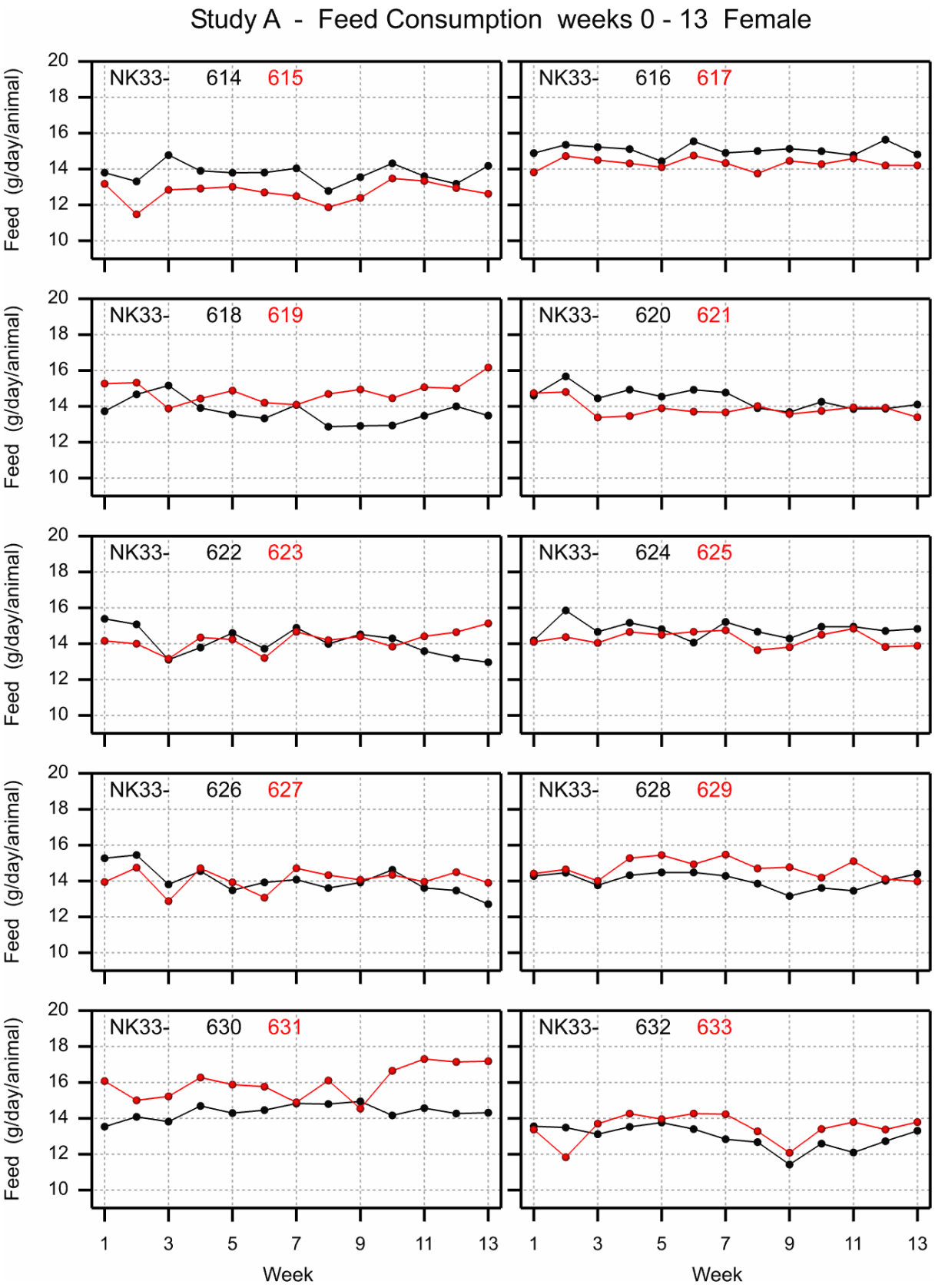
Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph.



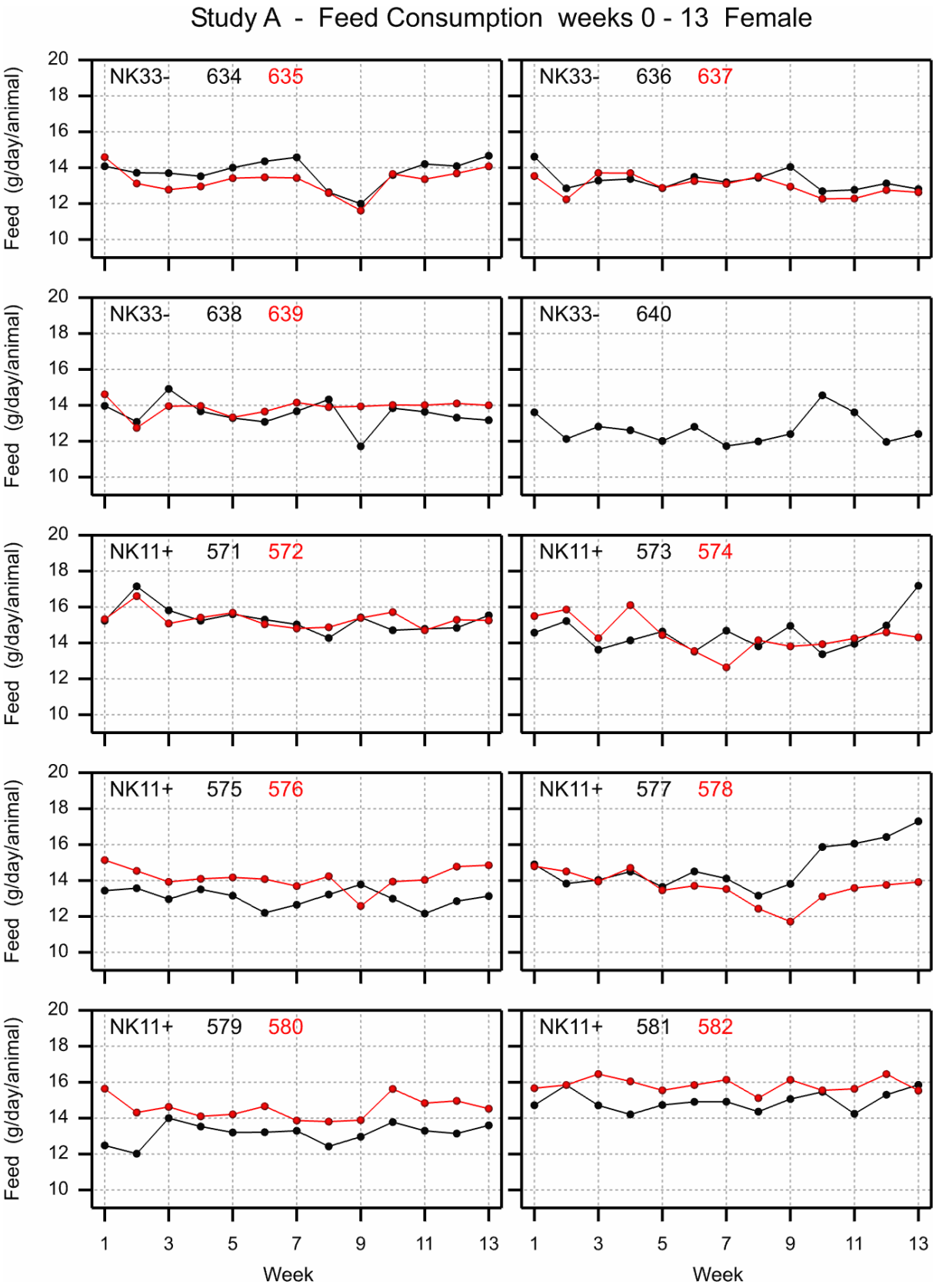
Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph.



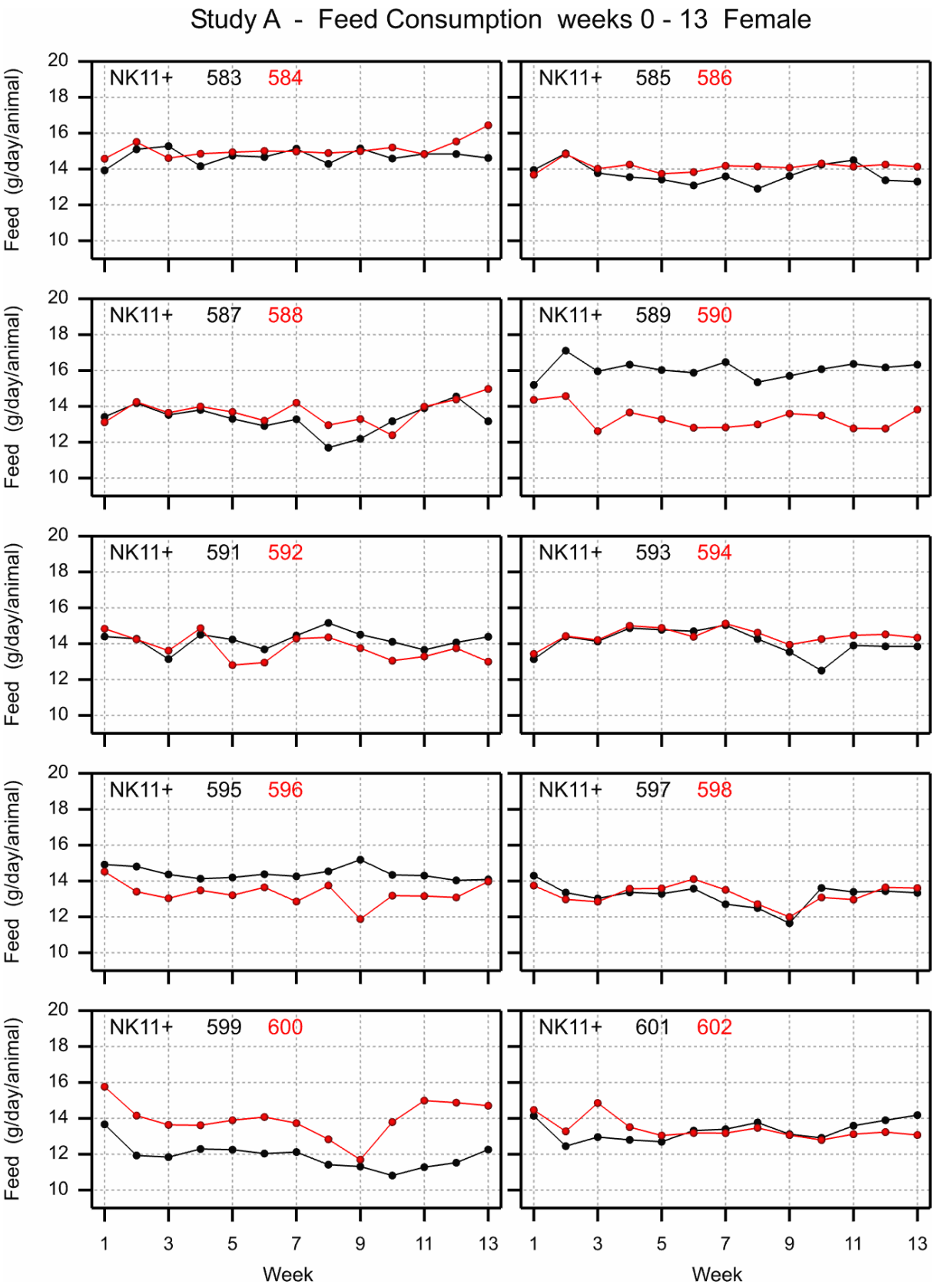
Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph.



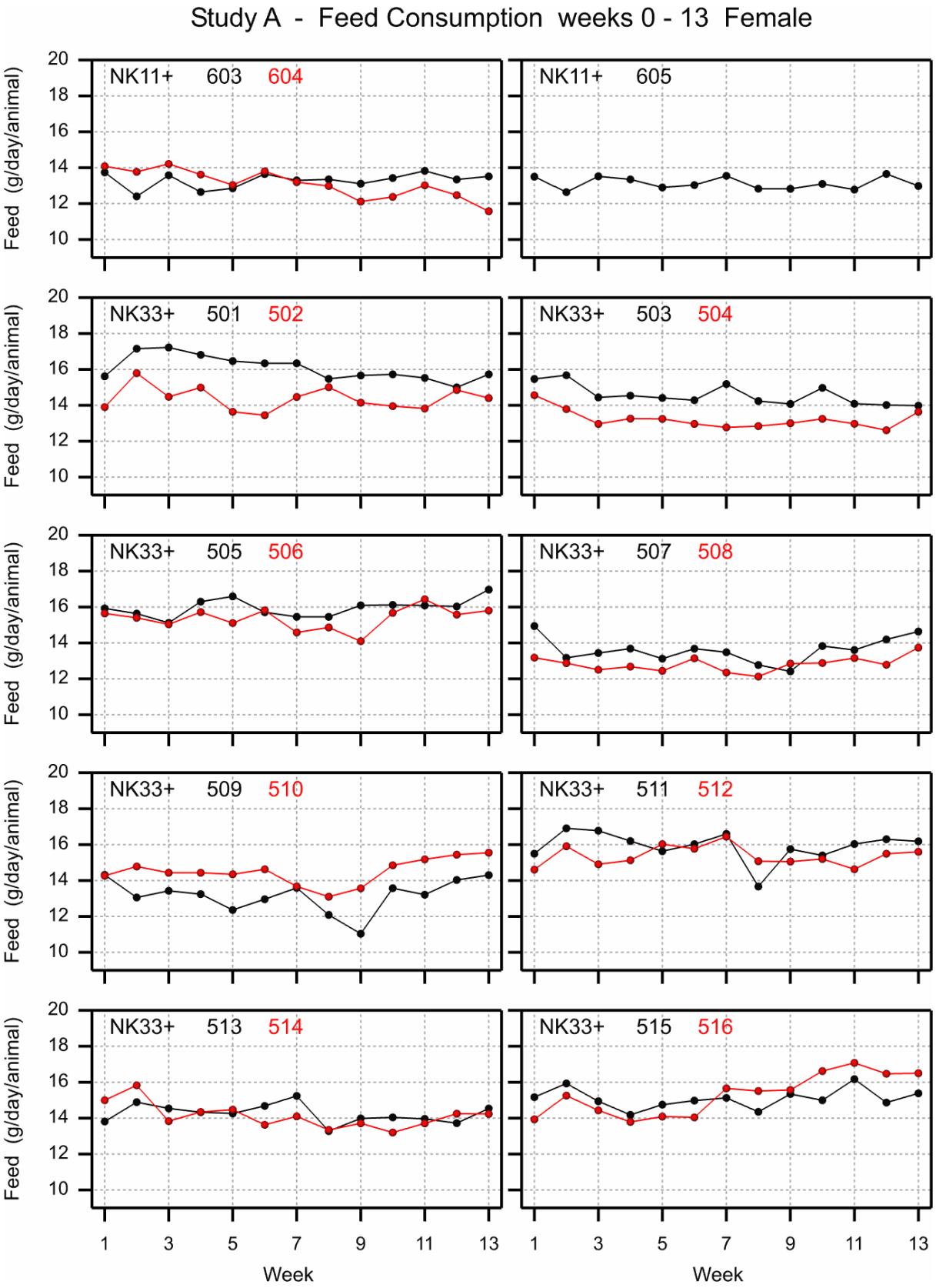
Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph.



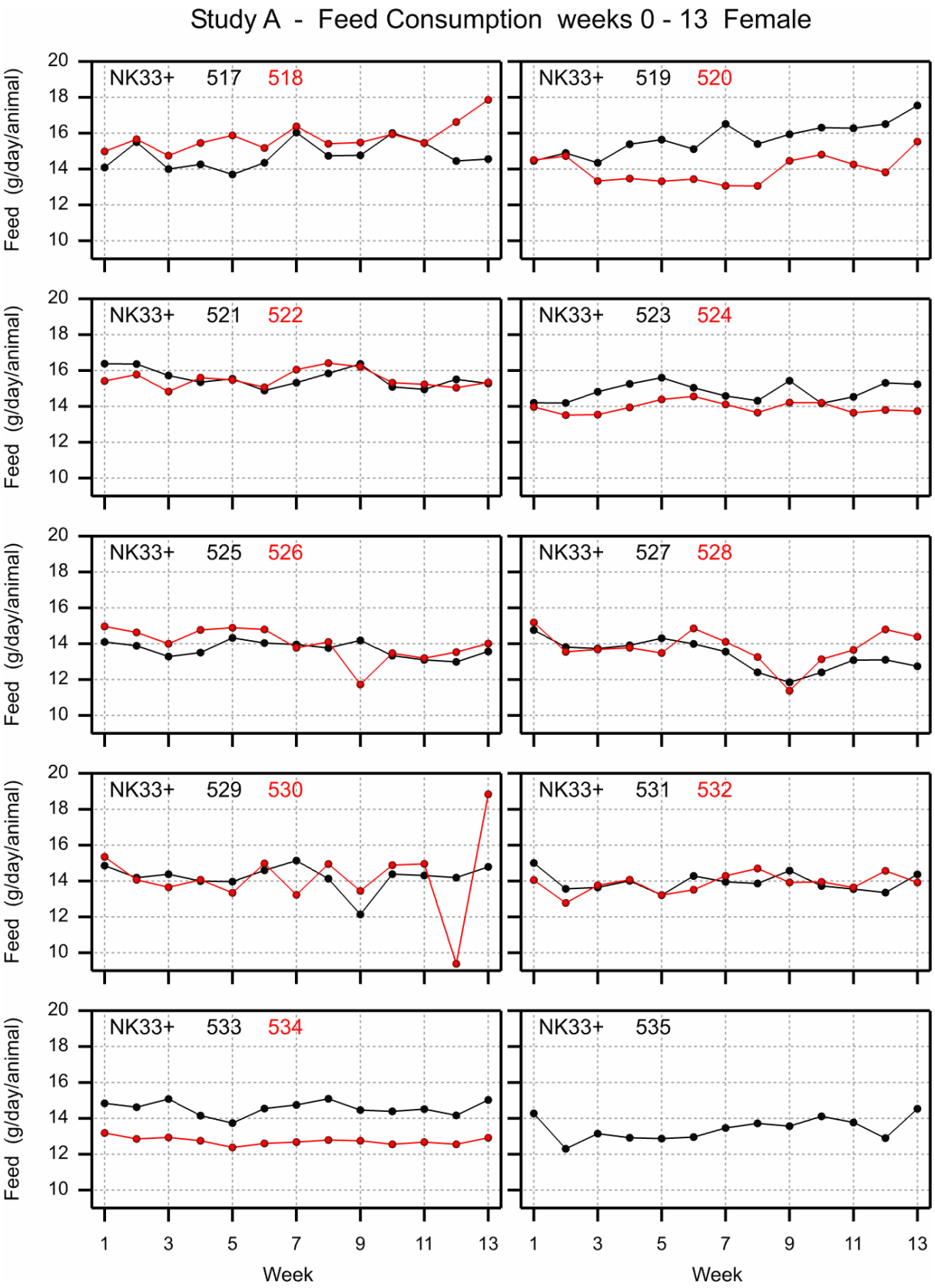
Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph.



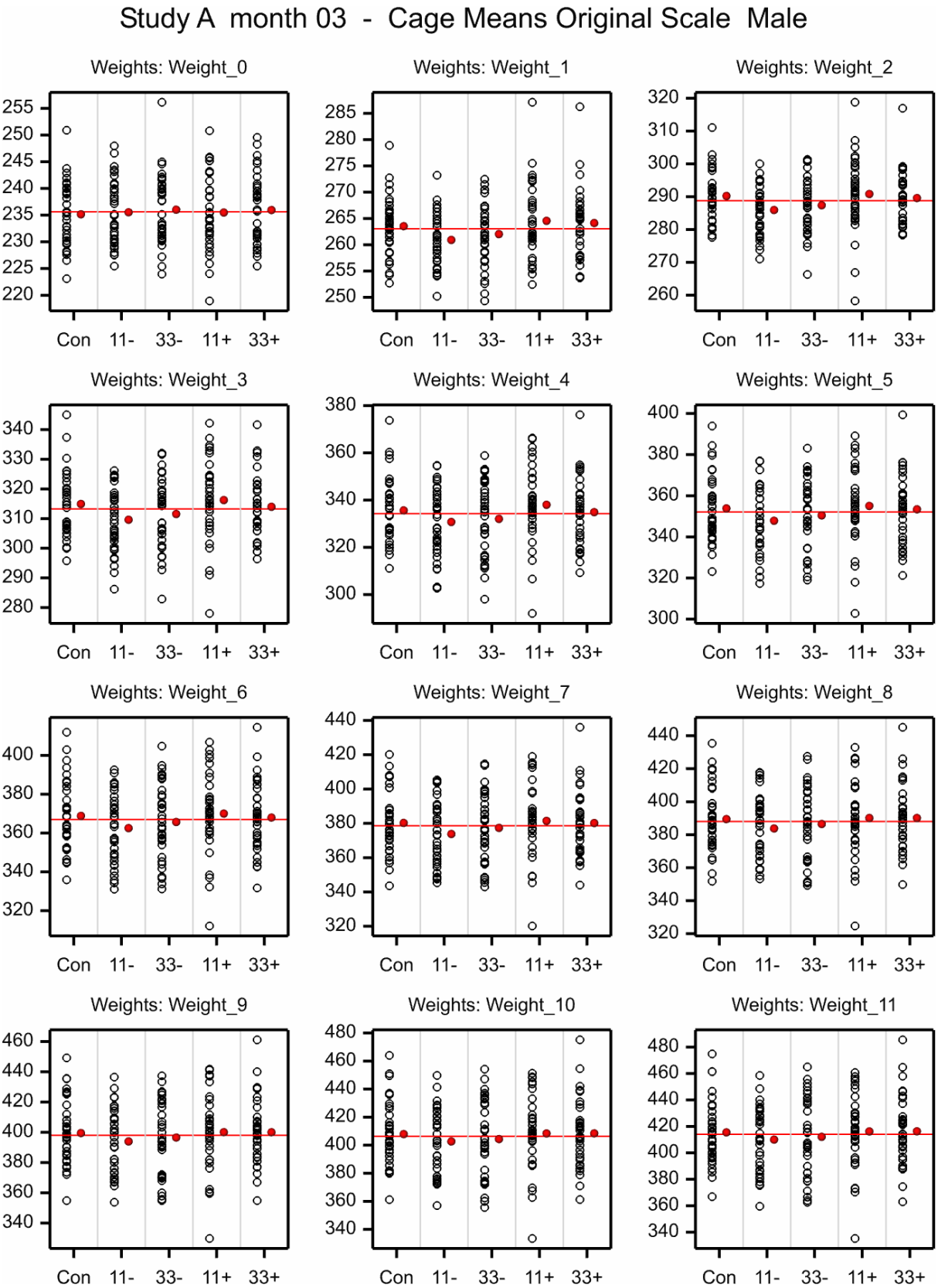
Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph.



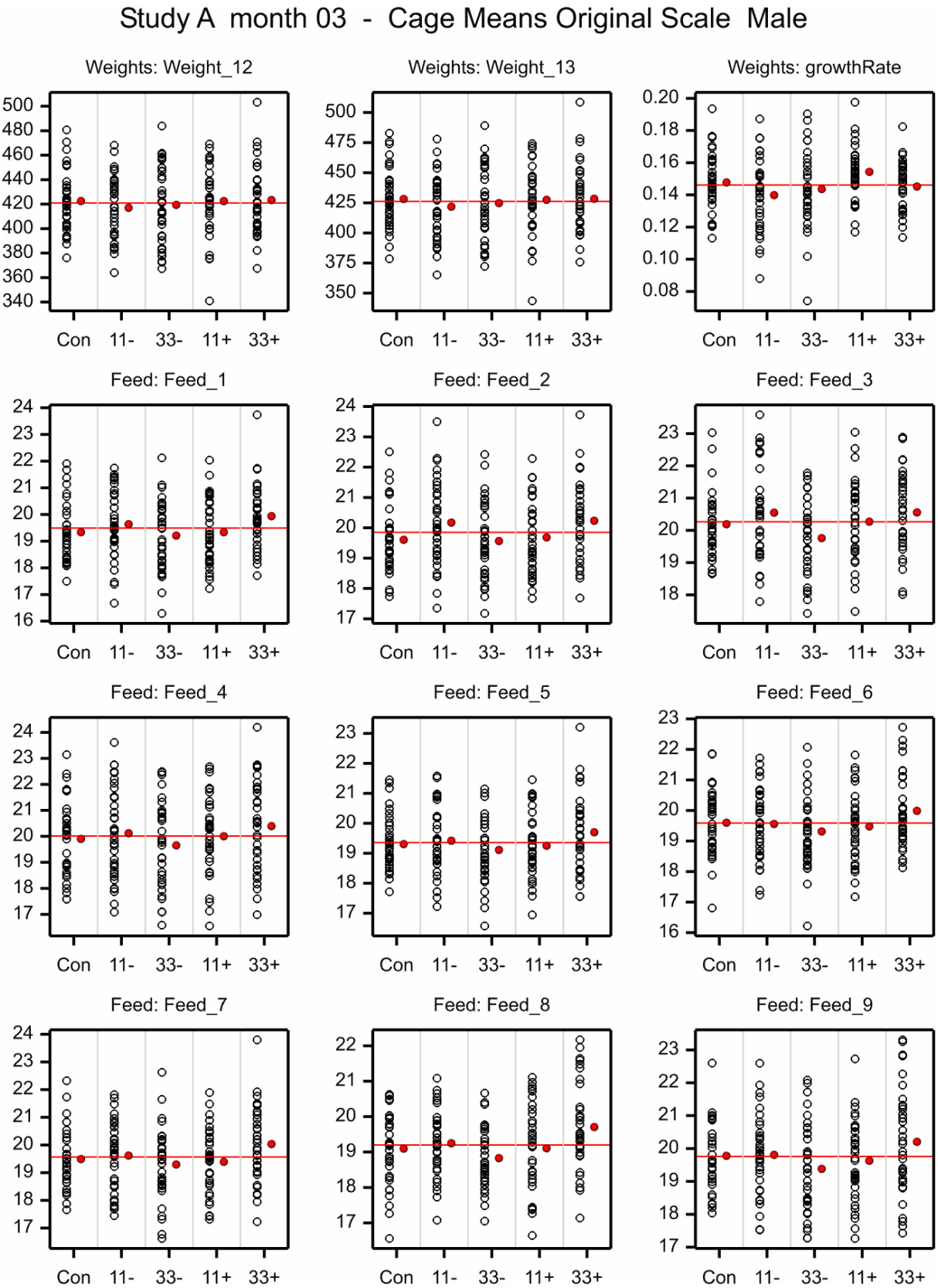
Appendix 3. Graphs of cage means on the original scale

Red symbols denote means for feeding groups while the red line denotes the overall mean.



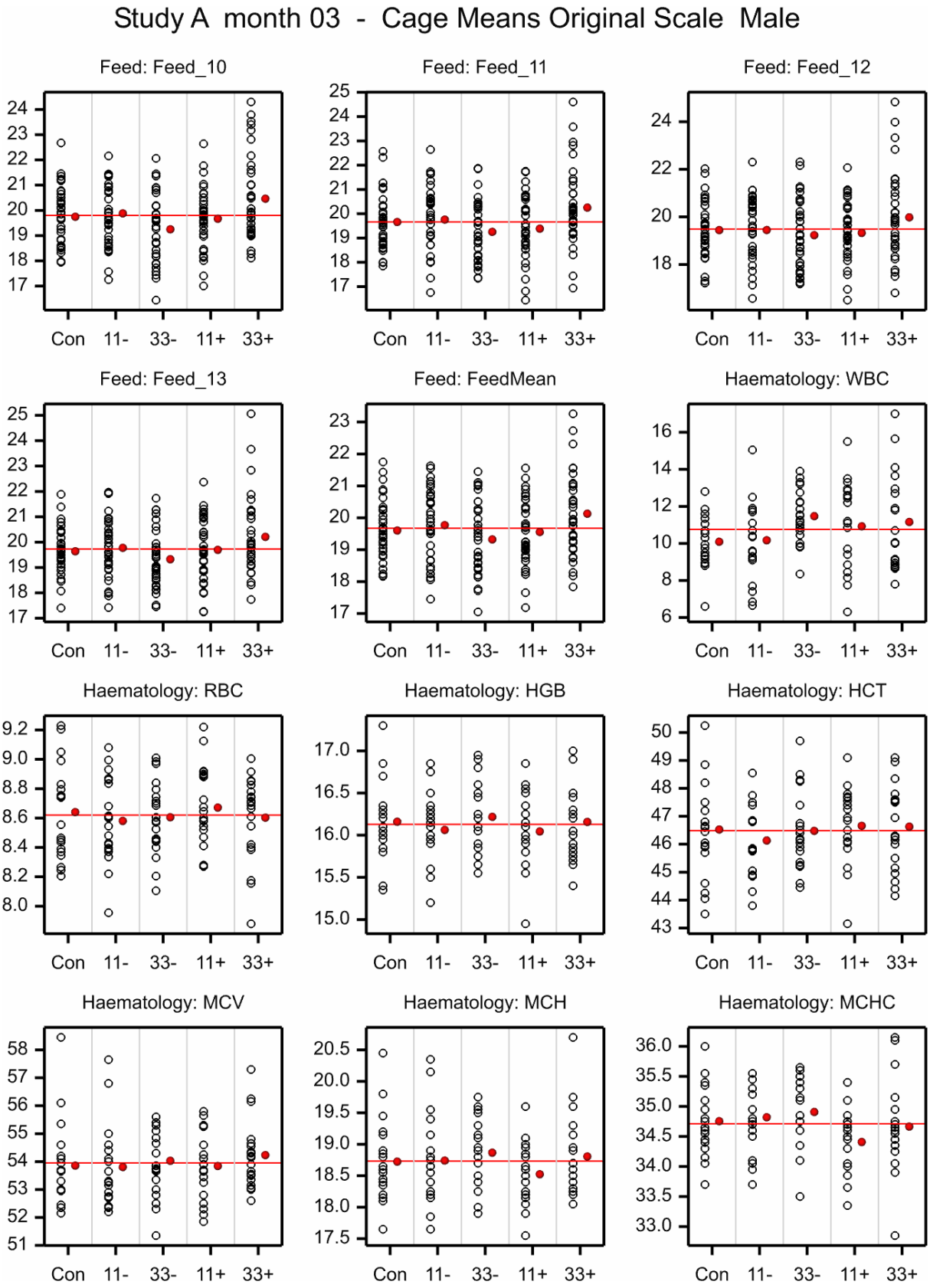
Appendix 3. Graphs of cage means on the original scale (continued)

Red symbols denote means for feeding groups while the red line denotes the overall mean.



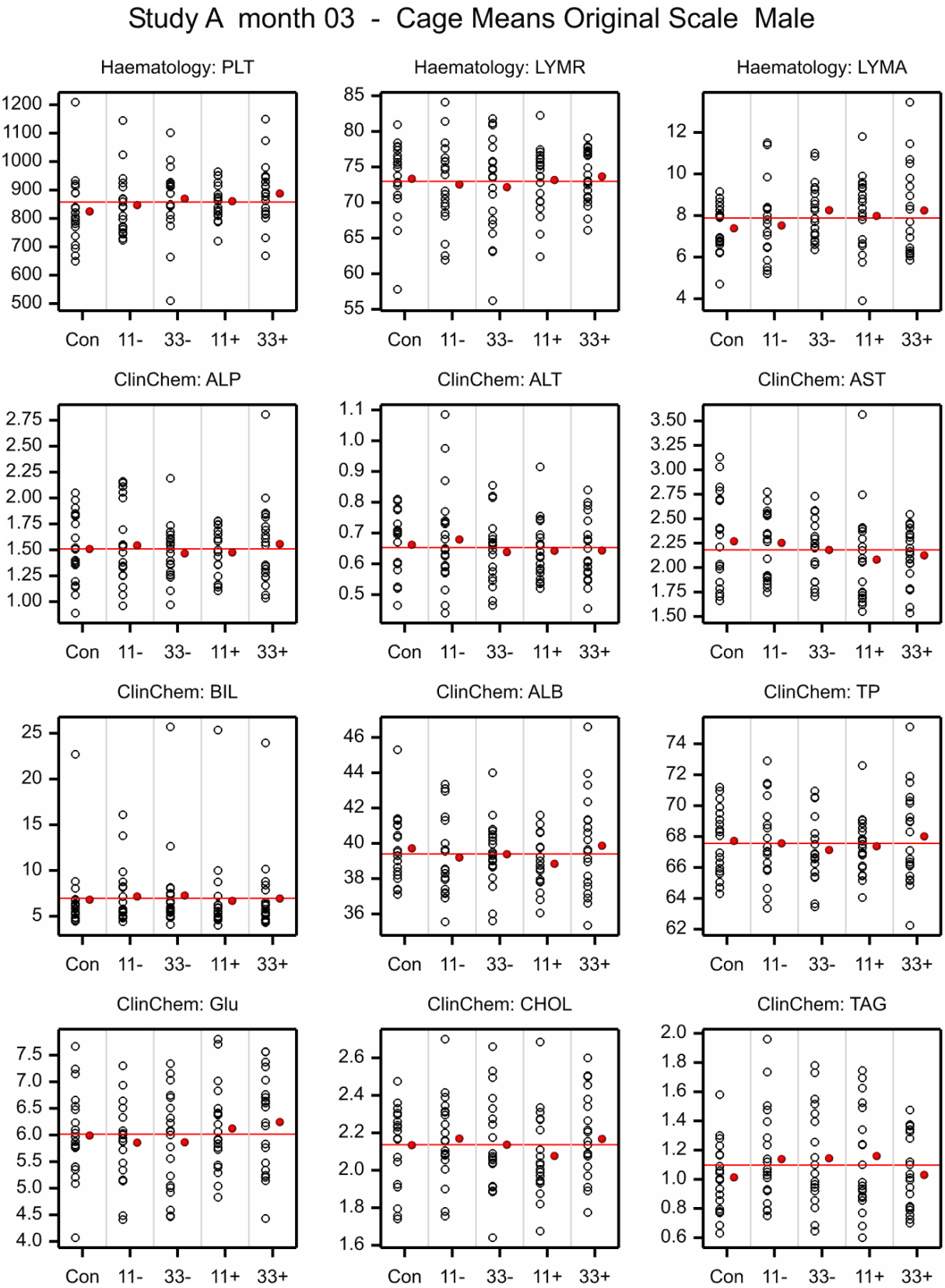
Appendix 3. Graphs of cage means on the original scale (continued)

Red symbols denote means for feeding groups while the red line denotes the overall mean.



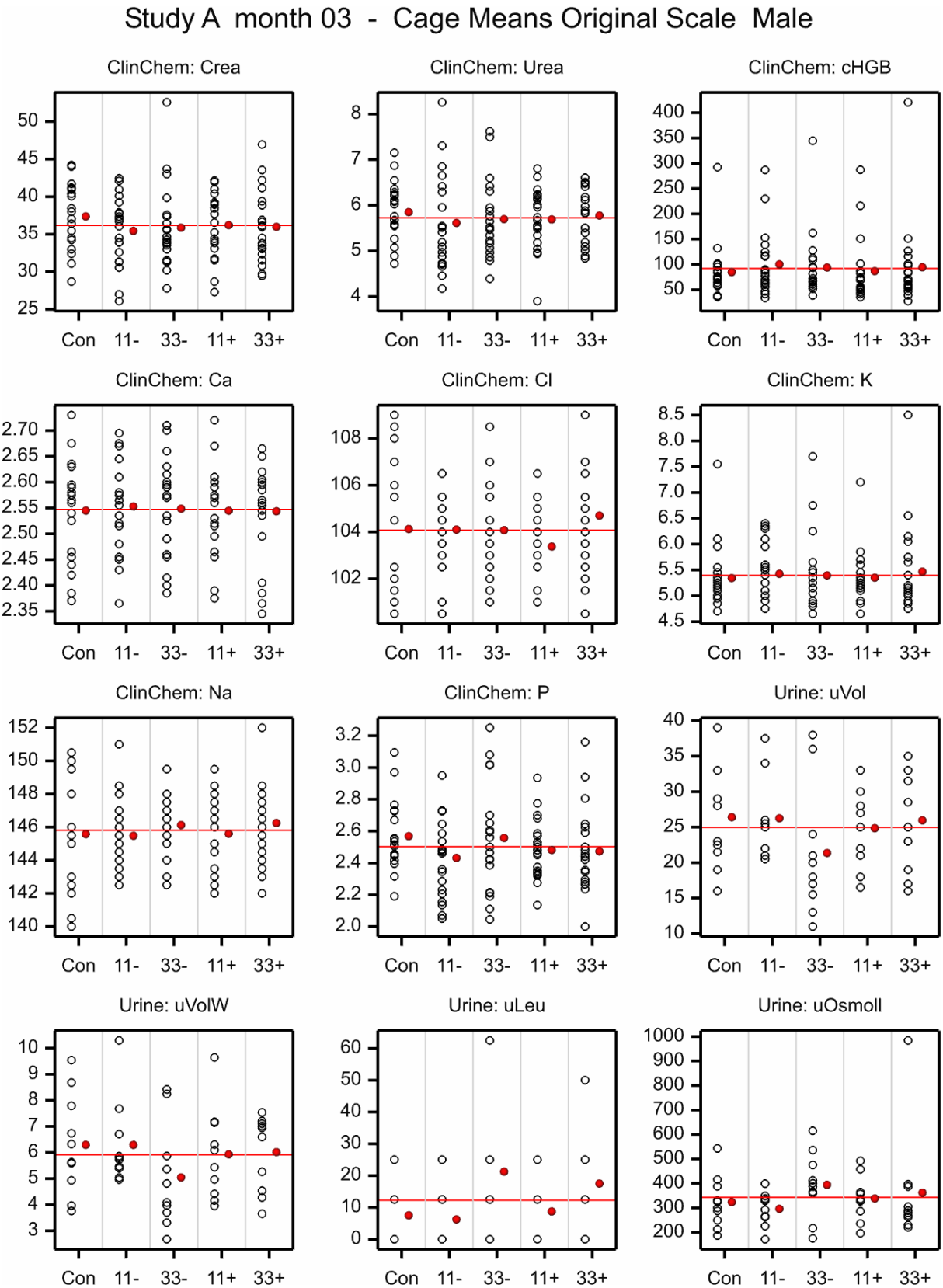
Appendix 3. Graphs of cage means on the original scale (continued)

Red symbols denote means for feeding groups while the red line denotes the overall mean.



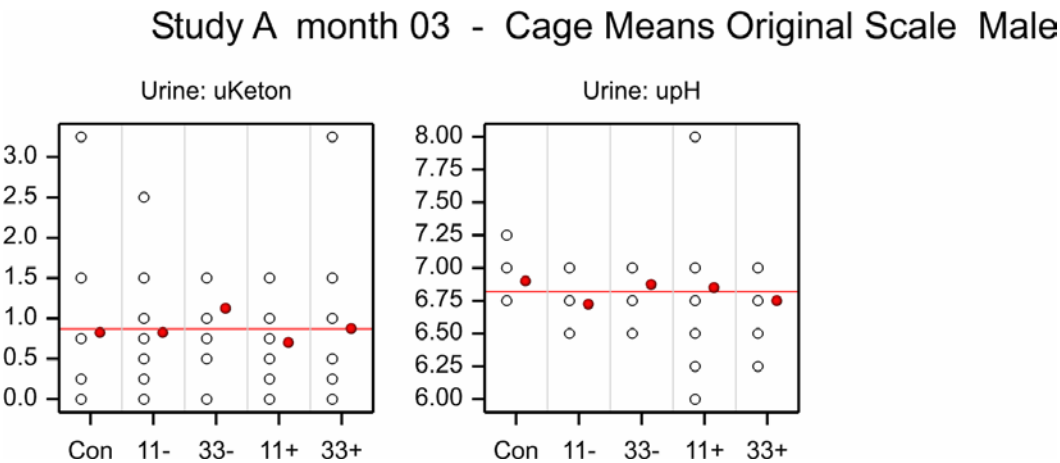
Appendix 3. Graphs of cage means on the original scale (continued)

Red symbols denote means for feeding groups while the red line denotes the overall mean.



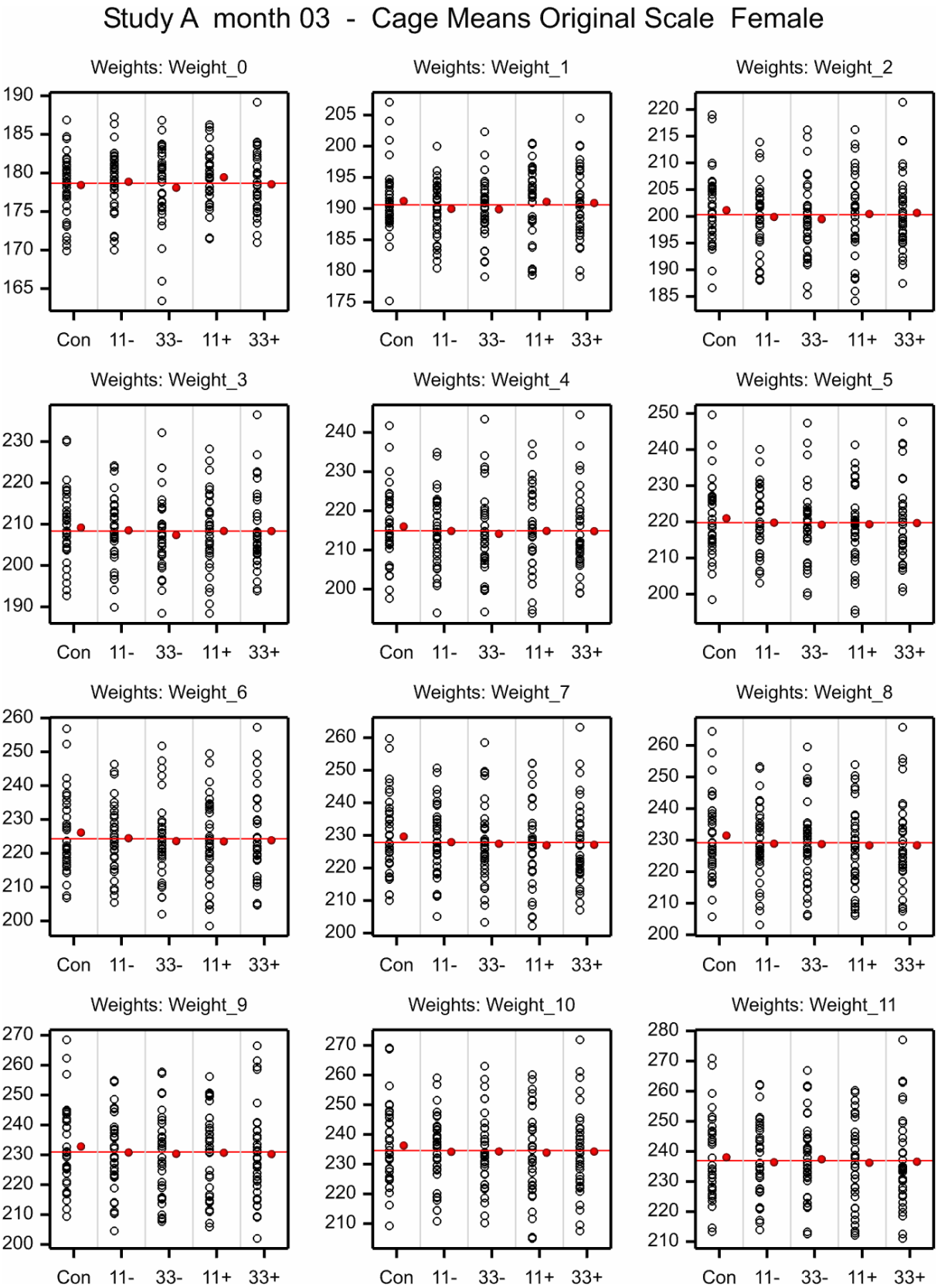
Appendix 3. Graphs of cage means on the original scale (continued)

Red symbols denote means for feeding groups while the red line denotes the overall mean.



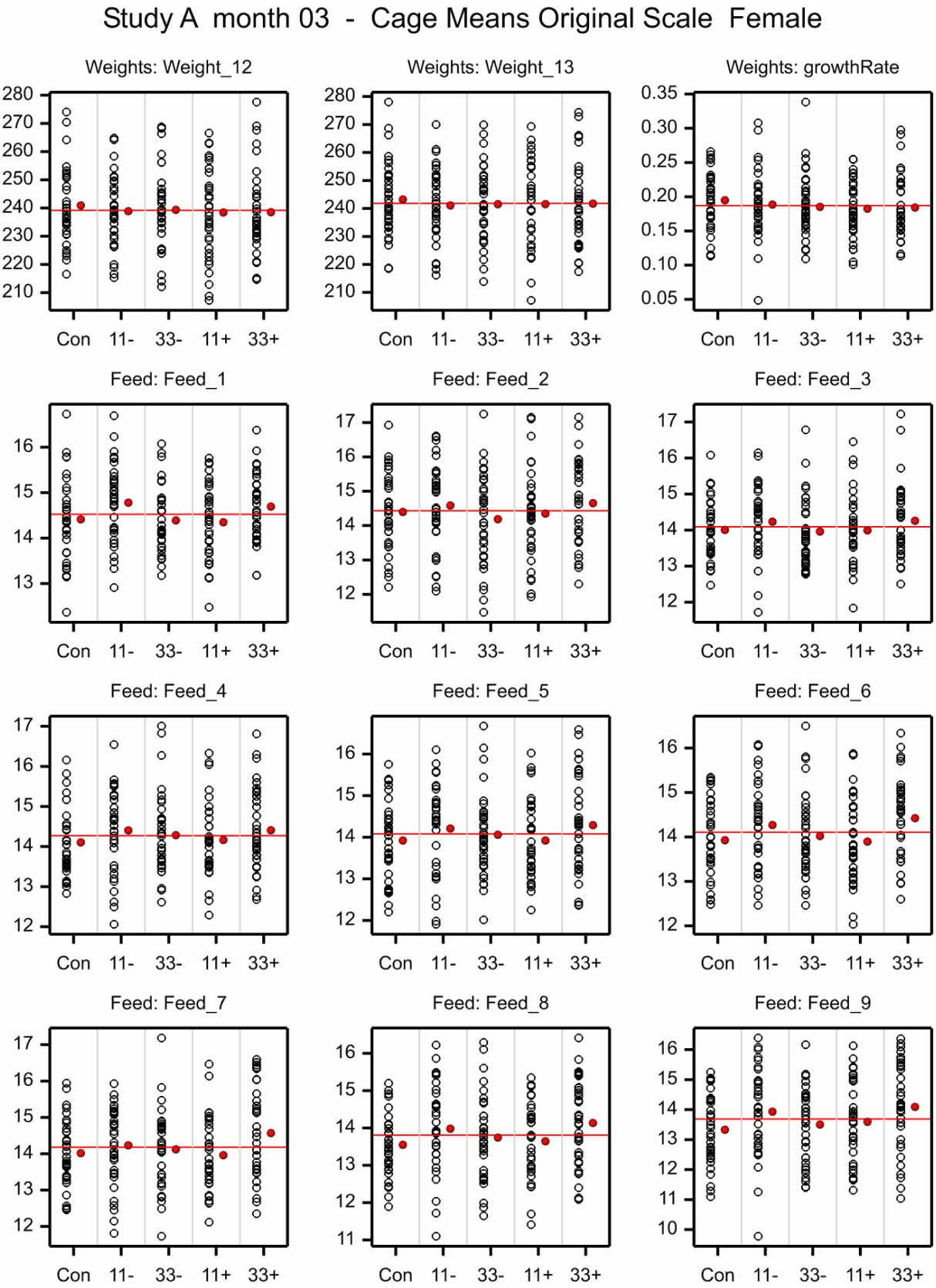
Appendix 3. Graphs of cage means on the original scale (continued)

Red symbols denote means for feeding groups while the red line denotes the overall mean.



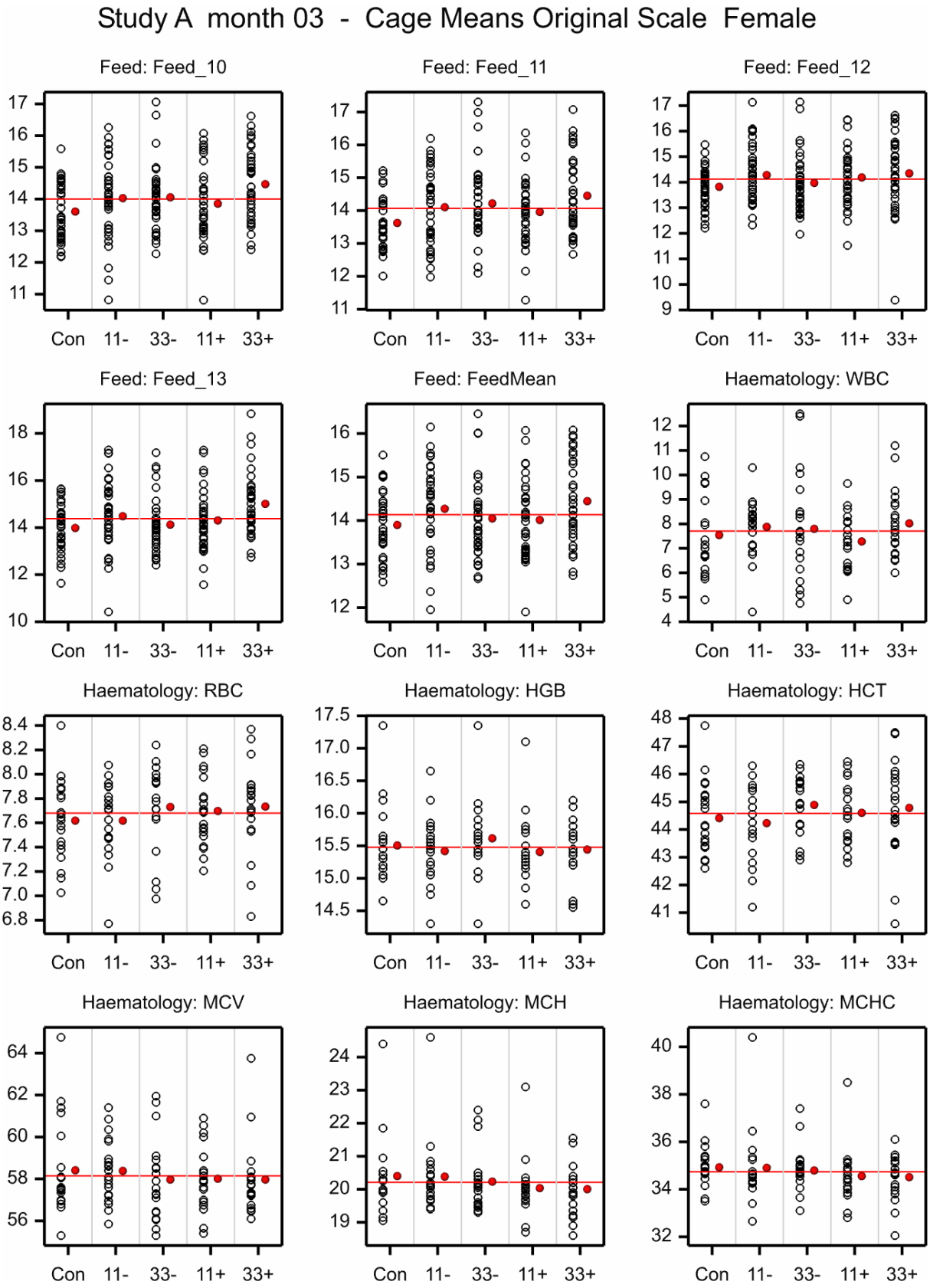
Appendix 3. Graphs of cage means on the original scale (continued)

Red symbols denote means for feeding groups while the red line denotes the overall mean.



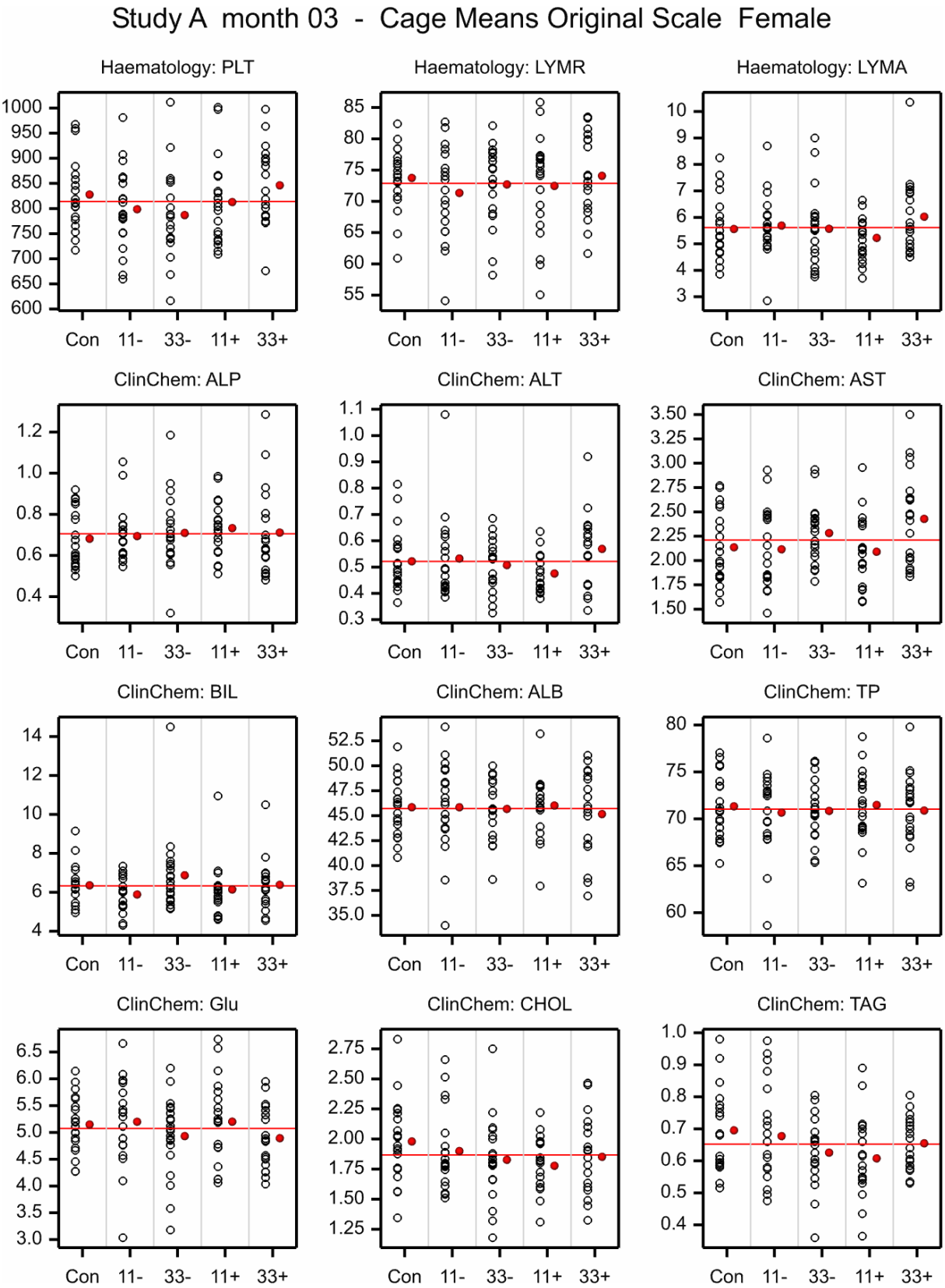
Appendix 3. Graphs of cage means on the original scale (continued)

Red symbols denote means for feeding groups while the red line denotes the overall mean.



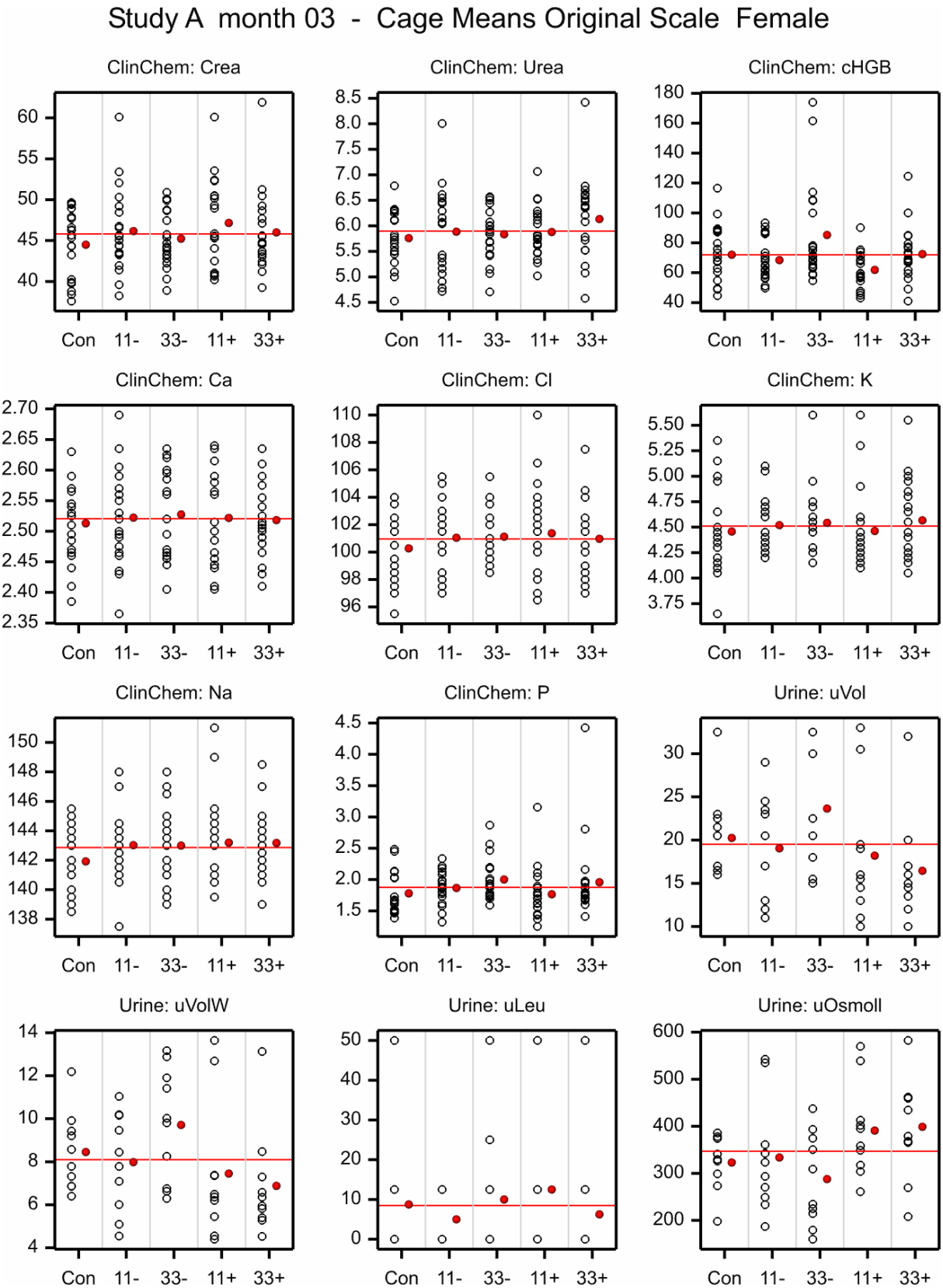
Appendix 3. Graphs of cage means on the original scale (continued)

Red symbols denote means for feeding groups while the red line denotes the overall mean.



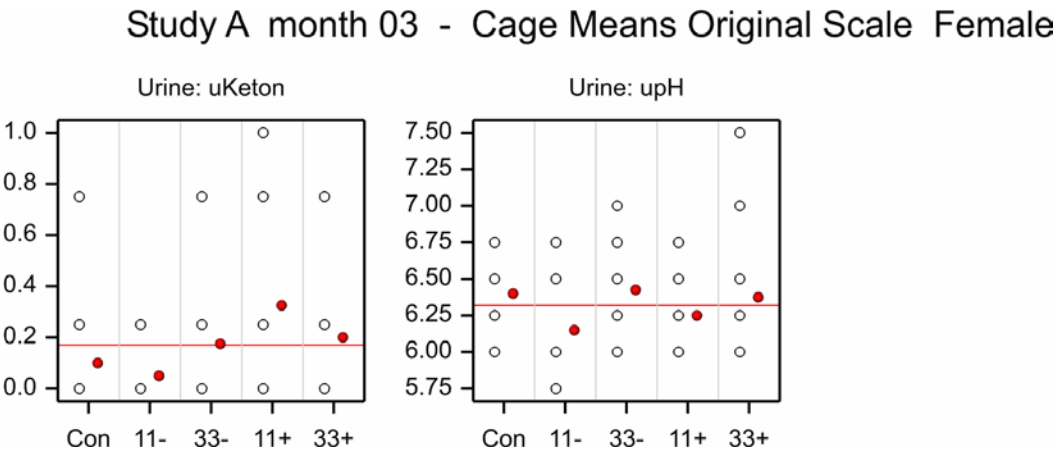
Appendix 3. Graphs of cage means on the original scale (continued)

Red symbols denote means for feeding groups while the red line denotes the overall mean.



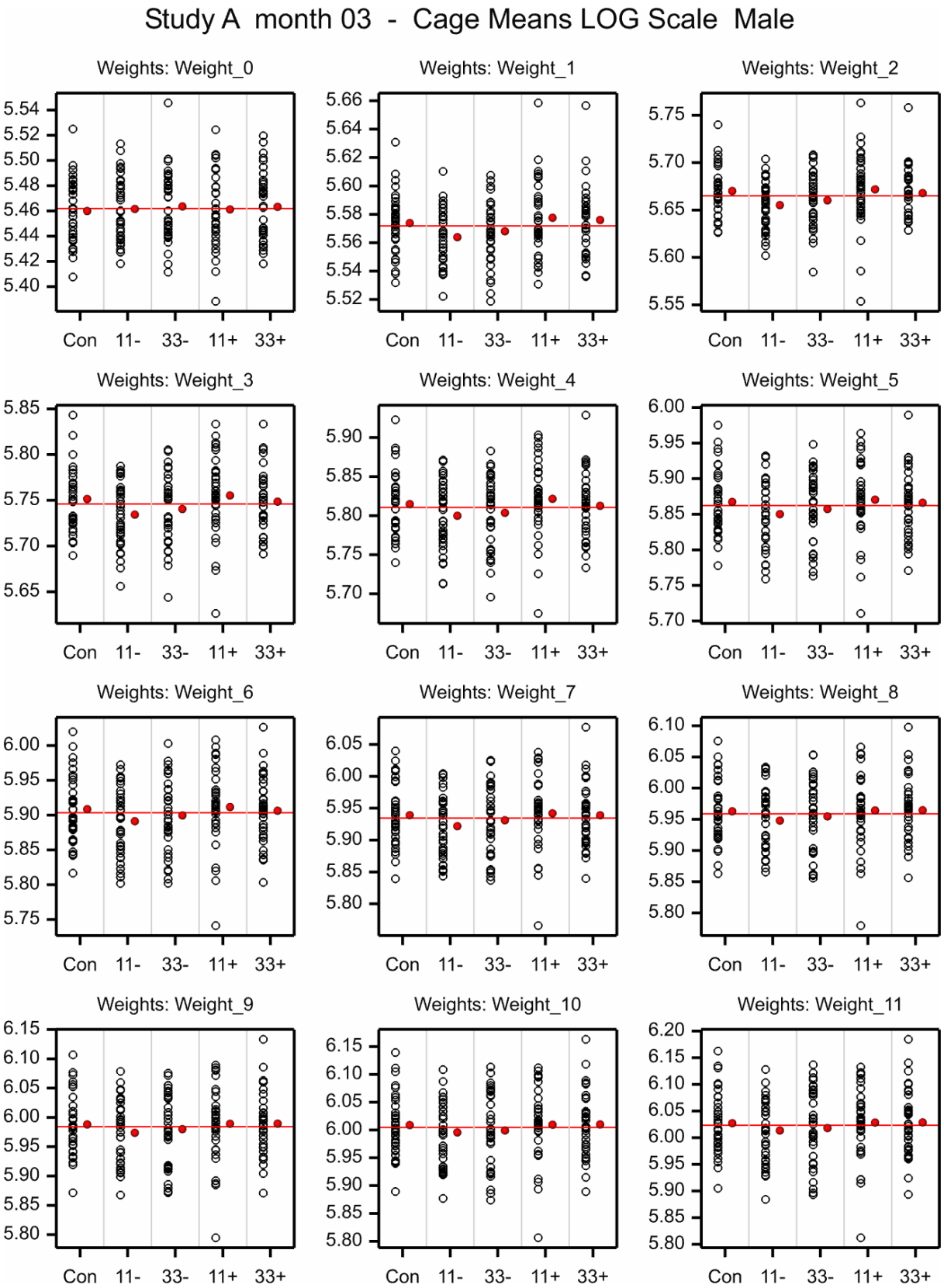
Appendix 3. Graphs of cage means on the original scale (continued)

Red symbols denote means for feeding groups while the red line denotes the overall mean.



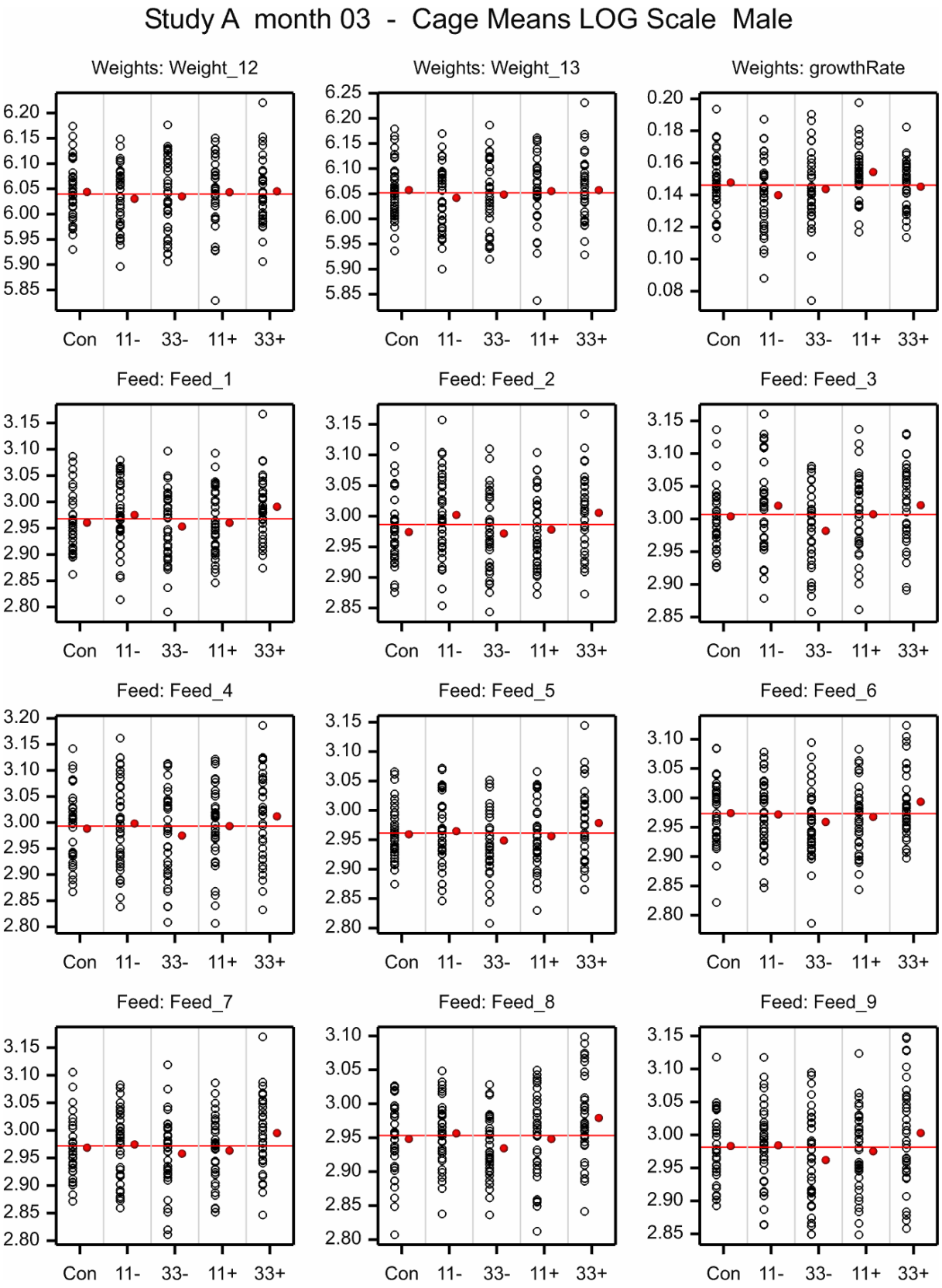
Appendix 4. Graphs of cage means on the log scale

Red symbols denote means for feeding groups while the red line denotes the overall mean.



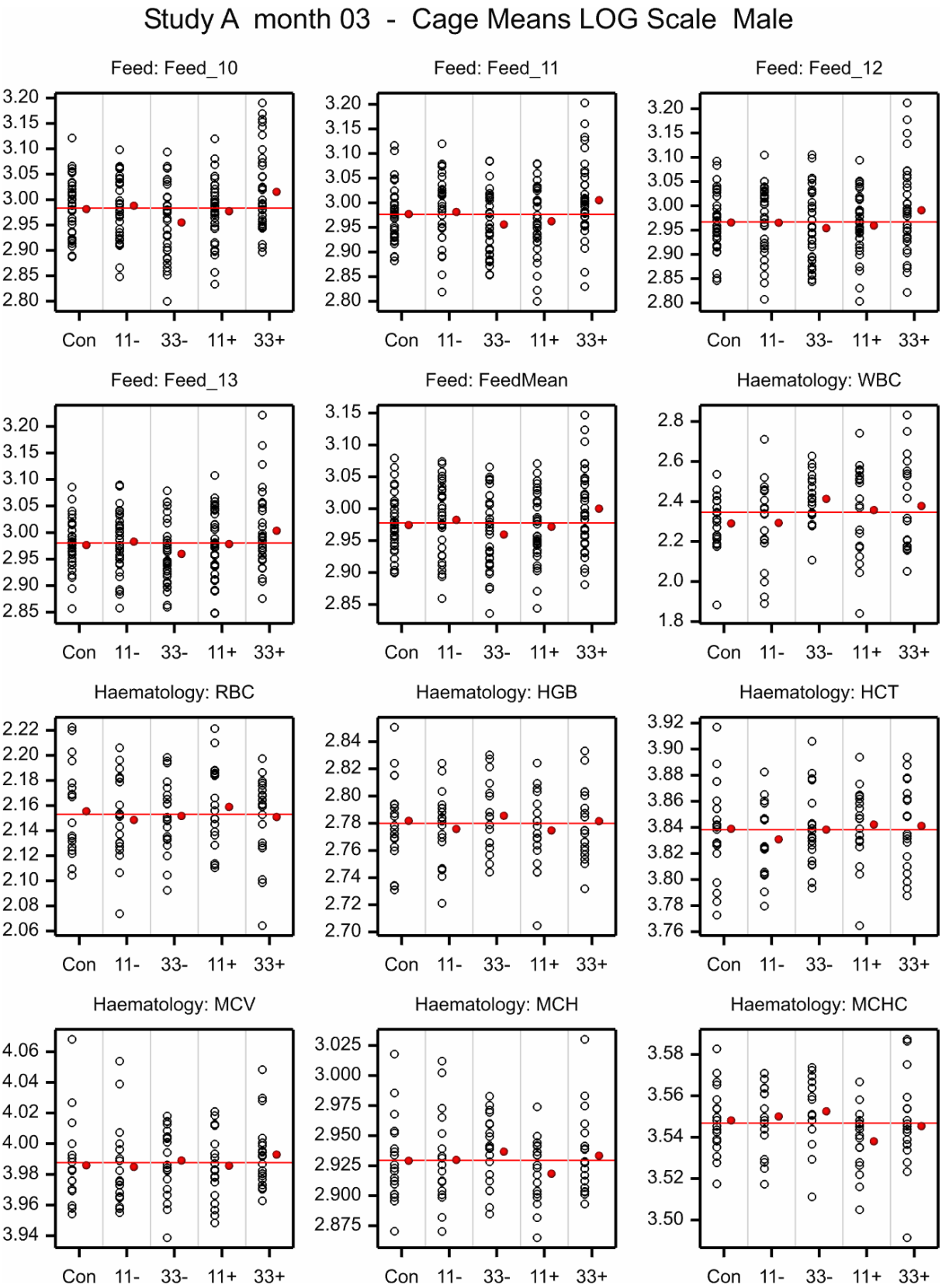
Appendix 4. Graphs of cage means on the log scale (continued)

Red symbols denote means for feeding groups while the red line denotes the overall mean.



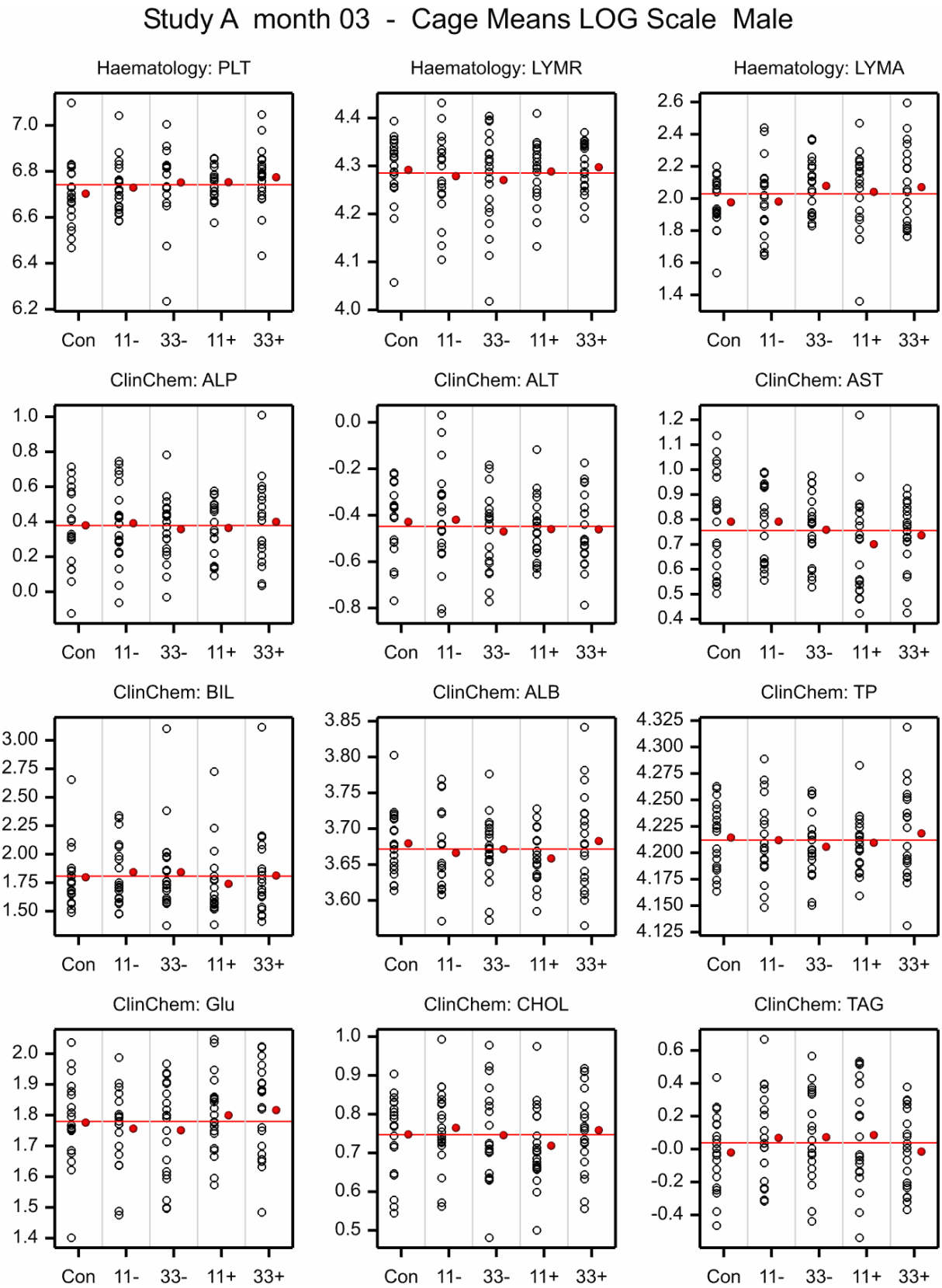
Appendix 4. Graphs of cage means on the log scale (continued)

Red symbols denote means for feeding groups while the red line denotes the overall mean.



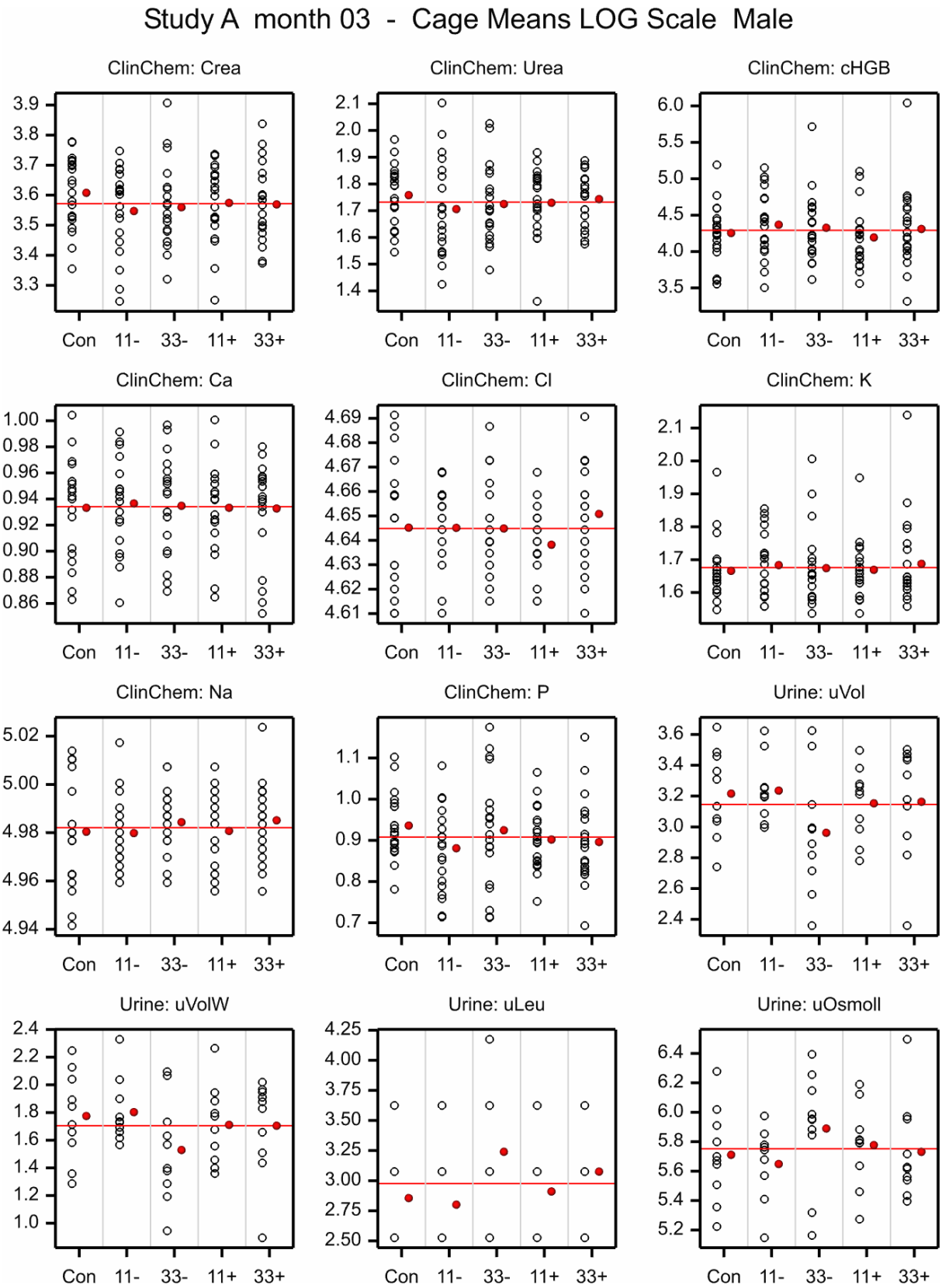
Appendix 4. Graphs of cage means on the log scale (continued)

Red symbols denote means for feeding groups while the red line denotes the overall mean.



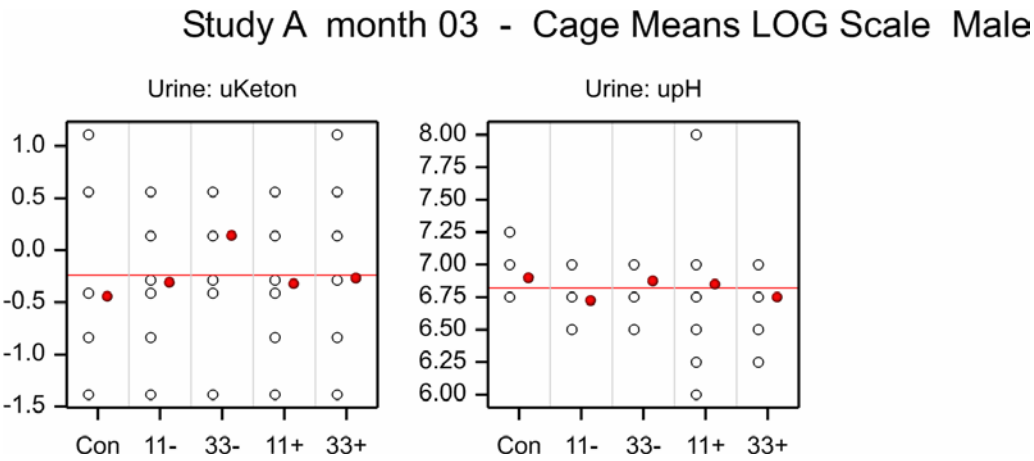
Appendix 4. Graphs of cage means on the log scale (continued)

Red symbols denote means for feeding groups while the red line denotes the overall mean.



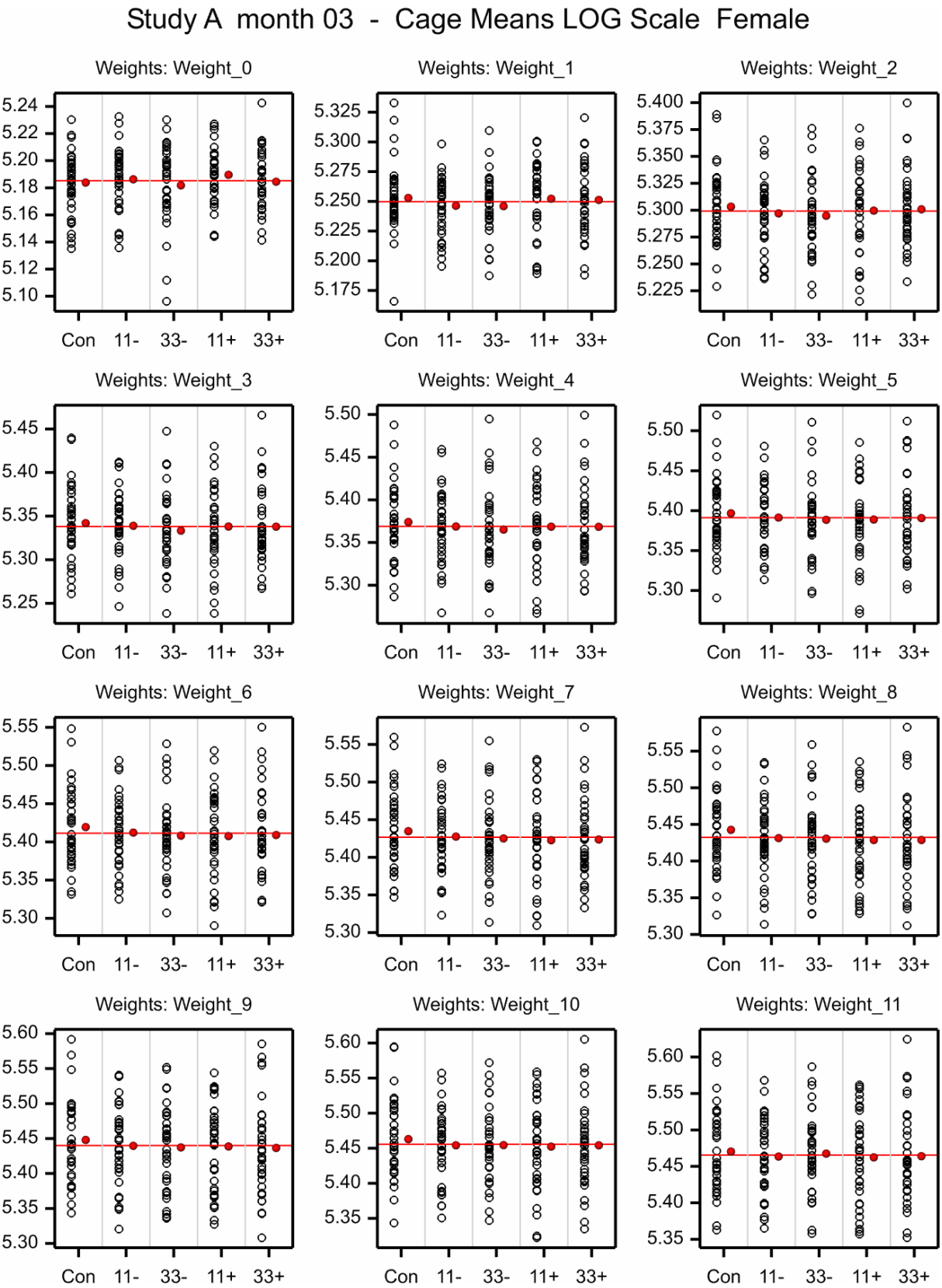
Appendix 4. Graphs of cage means on the log scale (continued)

Red symbols denote means for feeding groups while the red line denotes the overall mean.



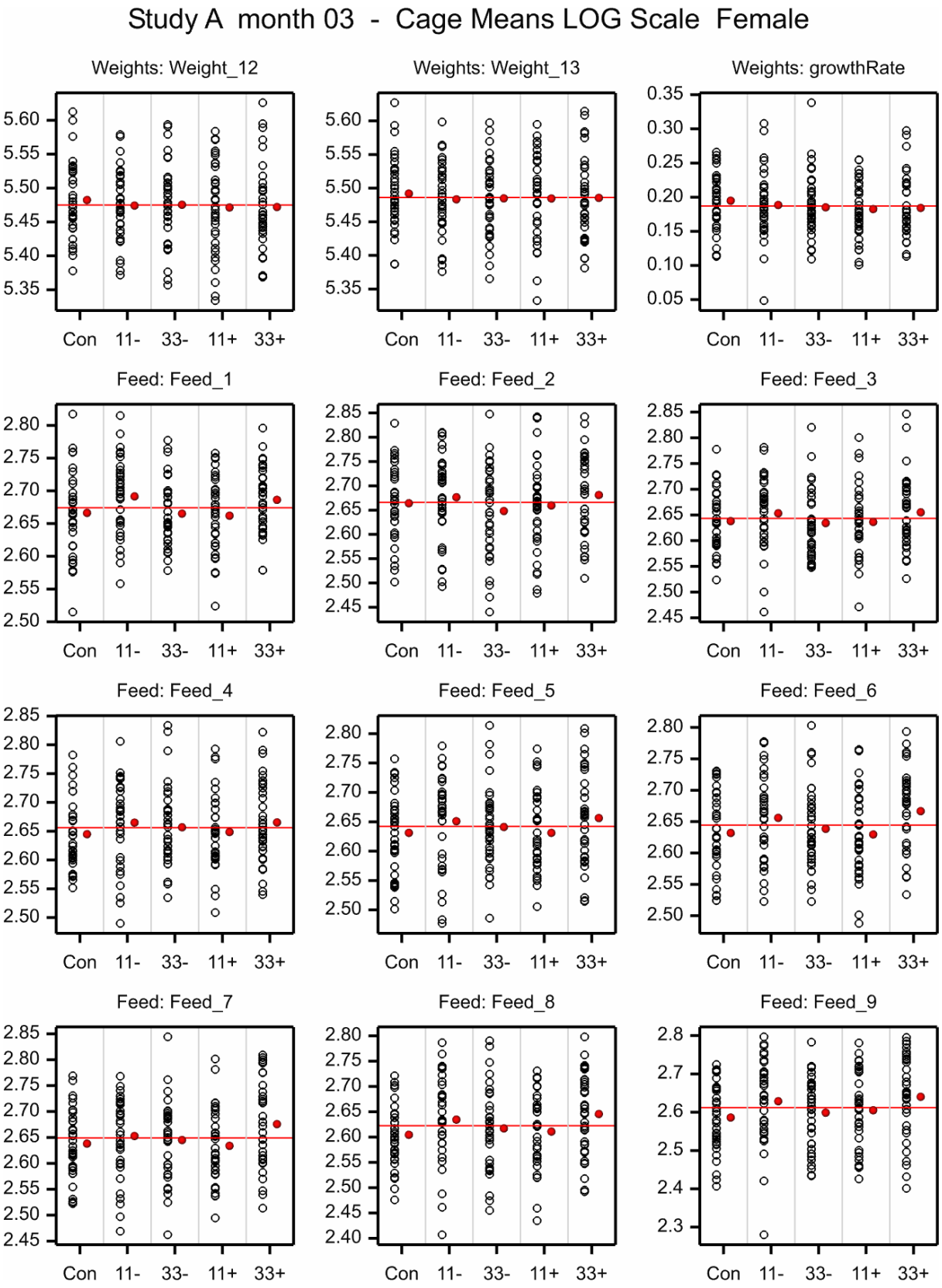
Appendix 4. Graphs of cage means on the log scale (continued)

Red symbols denote means for feeding groups while the red line denotes the overall mean.



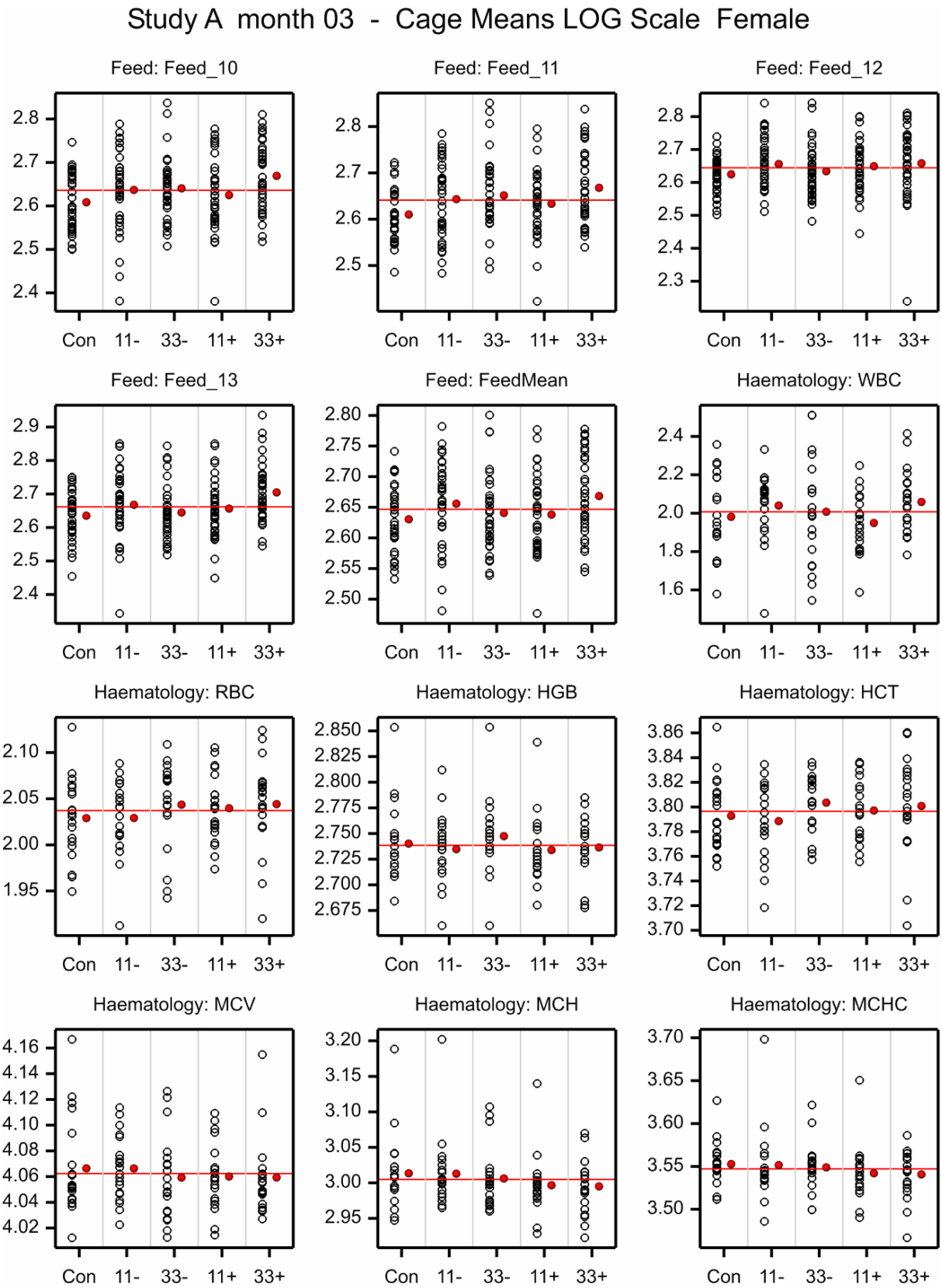
Appendix 4. Graphs of cage means on the log scale (continued)

Red symbols denote means for feeding groups while the red line denotes the overall mean.



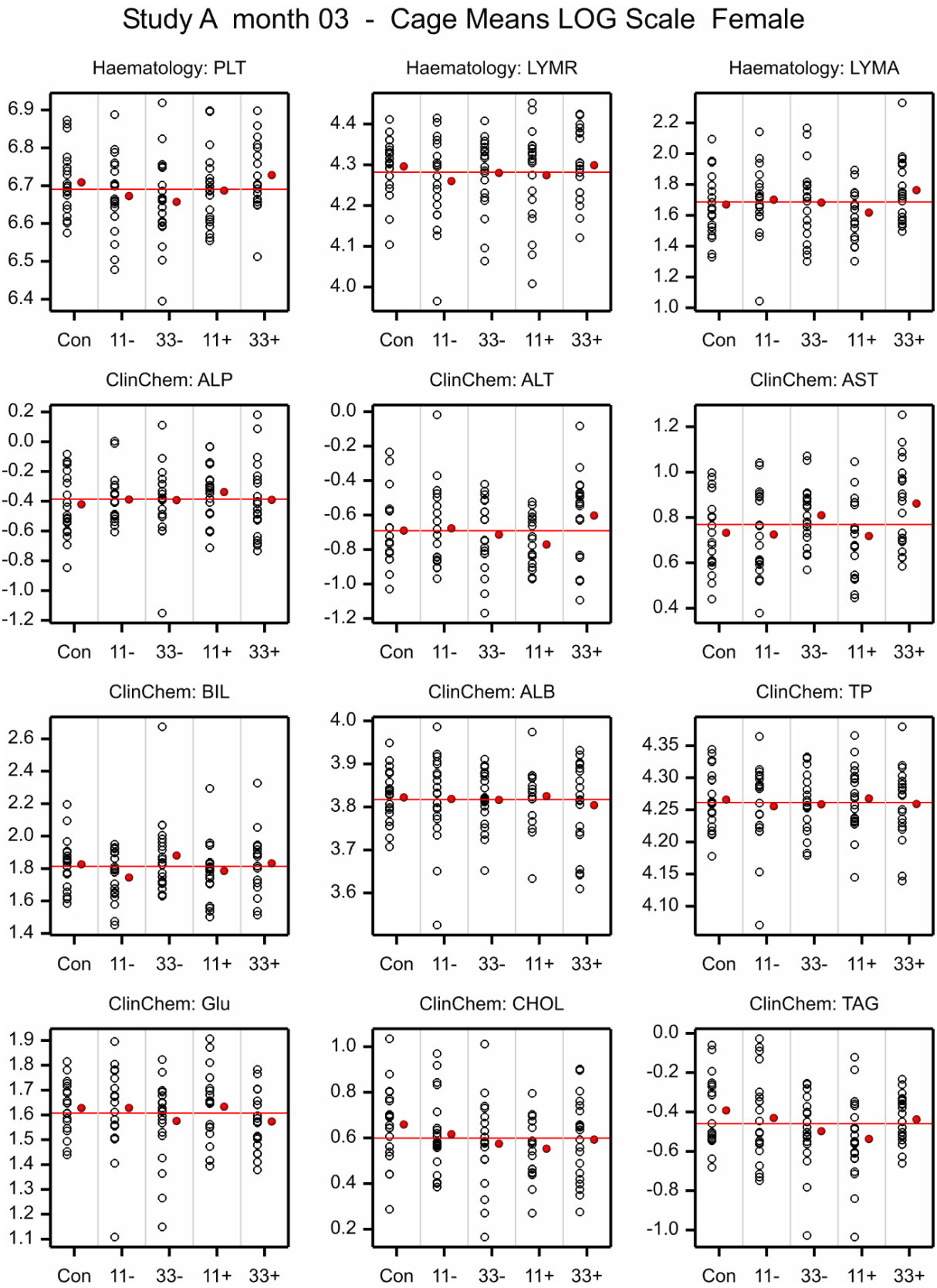
Appendix 4. Graphs of cage means on the log scale (continued)

Red symbols denote means for feeding groups while the red line denotes the overall mean.



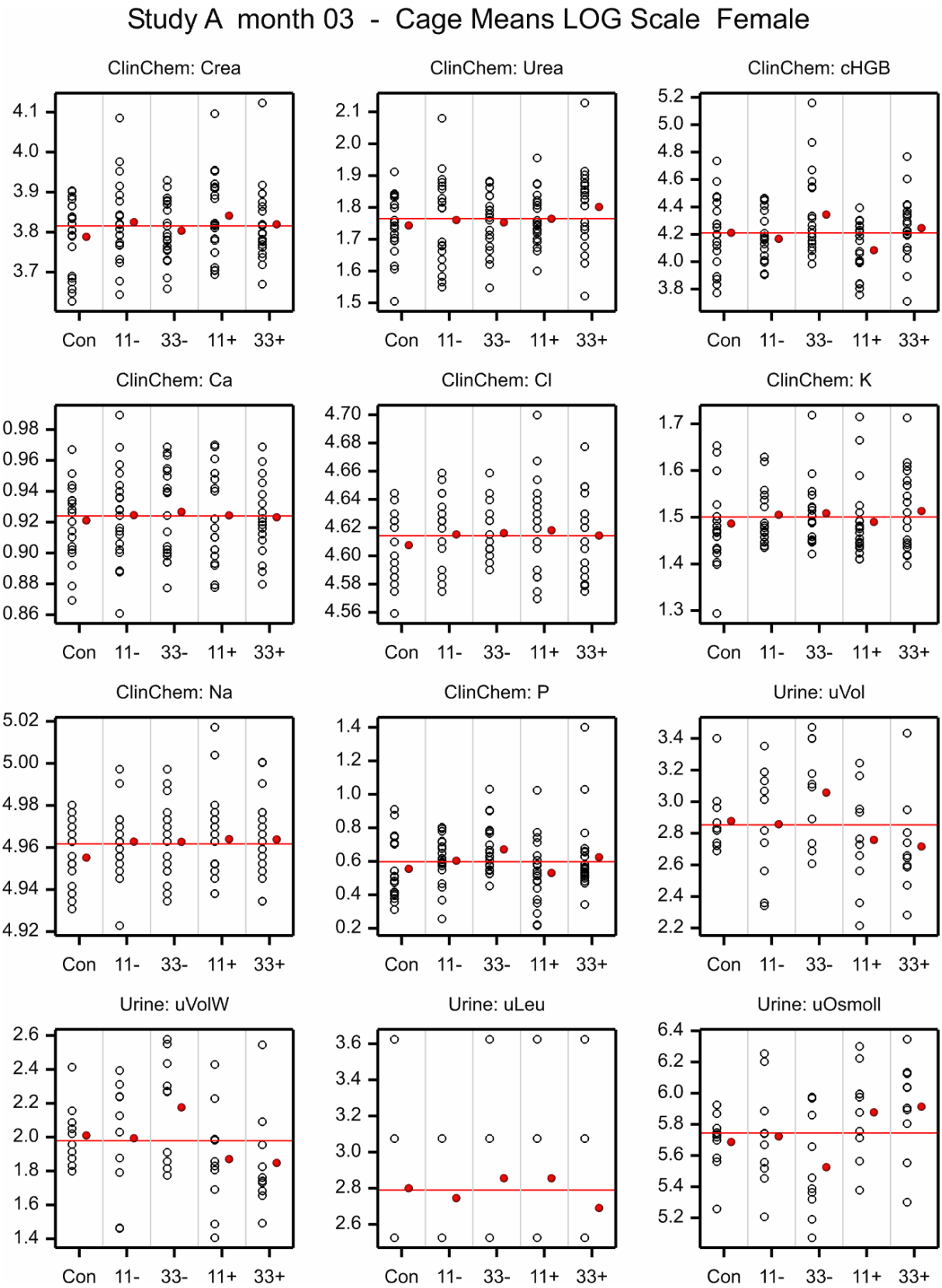
Appendix 4. Graphs of cage means on the log scale (continued)

Red symbols denote means for feeding groups while the red line denotes the overall mean.



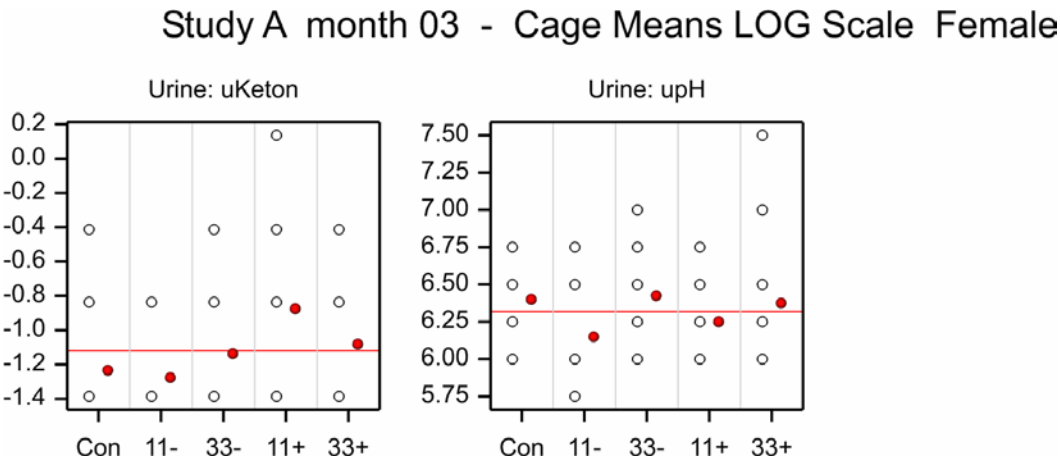
Appendix 4. Graphs of cage means on the log scale (continued)

Red symbols denote means for feeding groups while the red line denotes the overall mean.



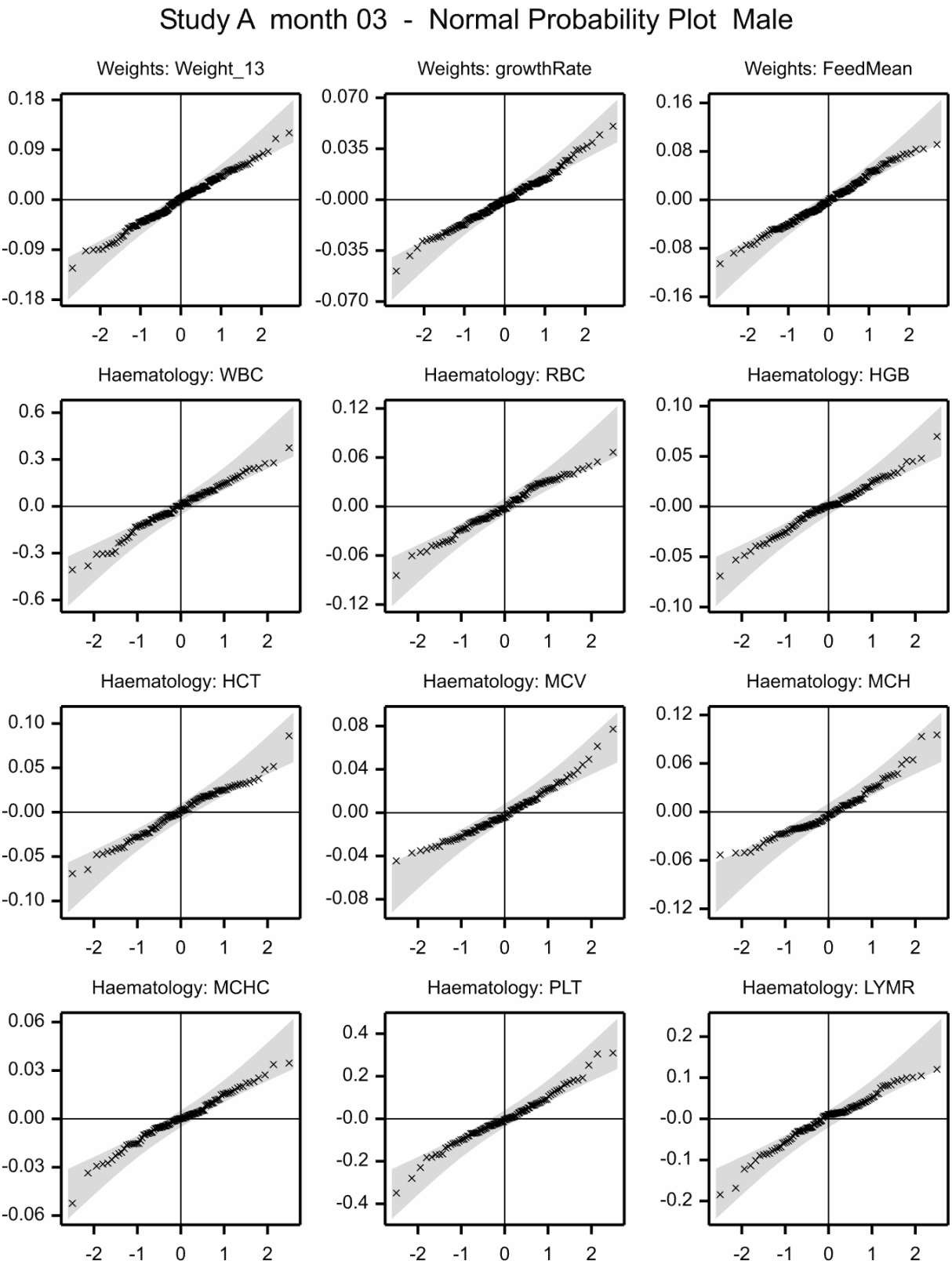
Appendix 4. Graphs of cage means on the log scale (continued)

Red symbols denote means for feeding groups while the red line denotes the overall mean.



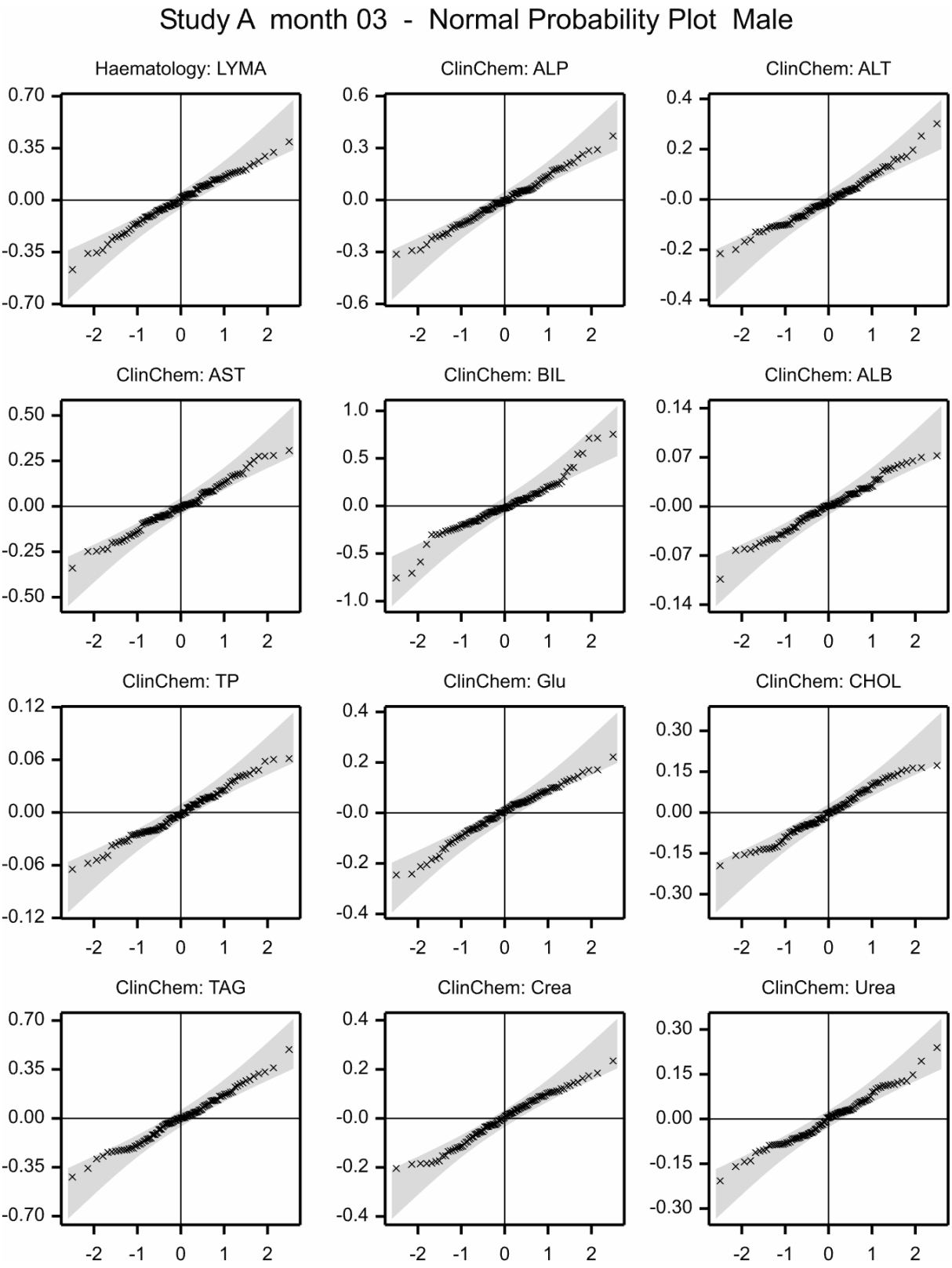
Appendix 5. Normal probability plots of residuals after ANOVA

Residuals are obtained from ANOVA of cage means (log scale). A 99% confidence envelop is added.



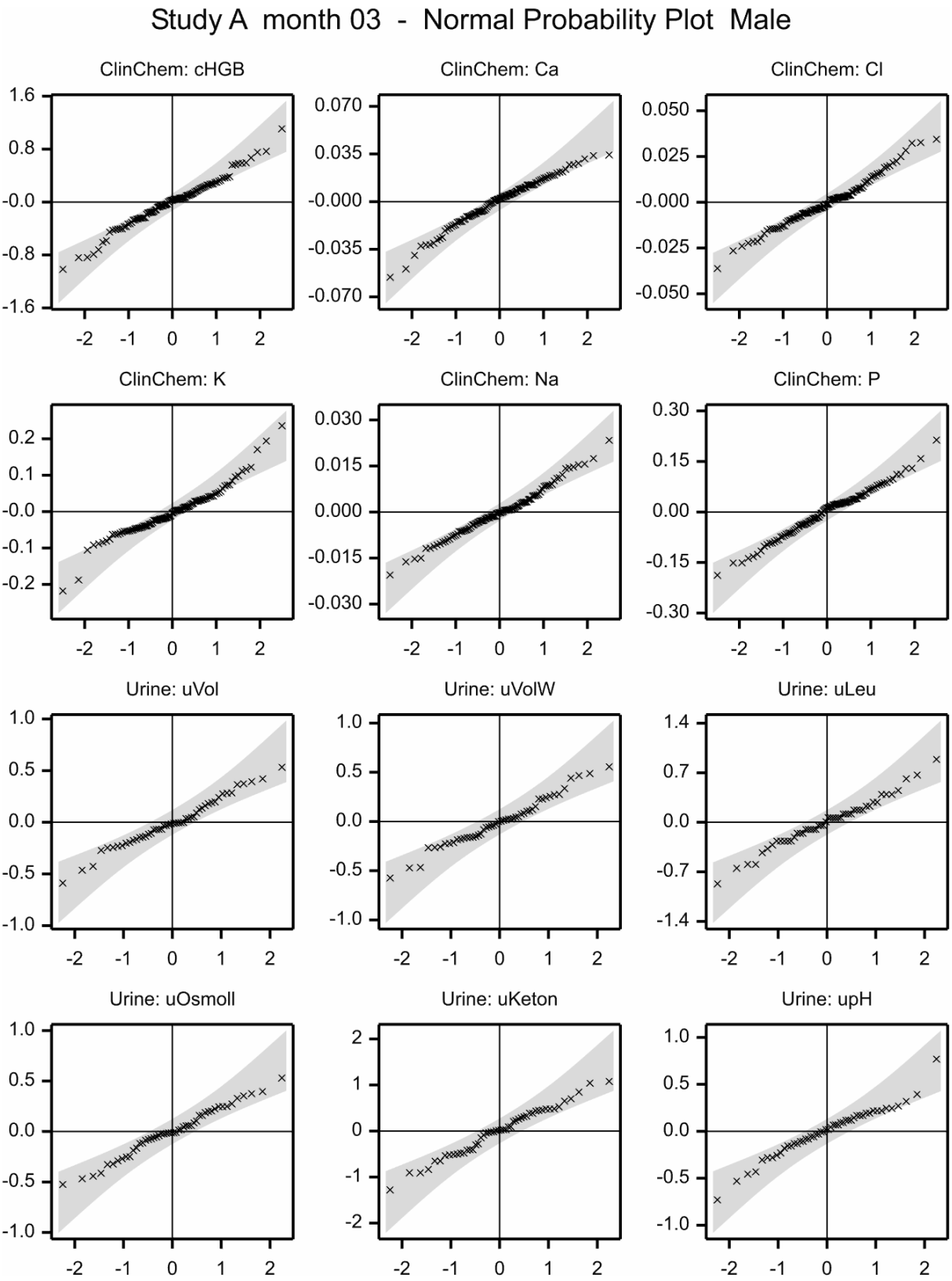
Appendix 5. Normal probability plots of residuals after ANOVA (continued)

Residuals are obtained from ANOVA of cage means (log scale). A 99% confidence envelop is added.



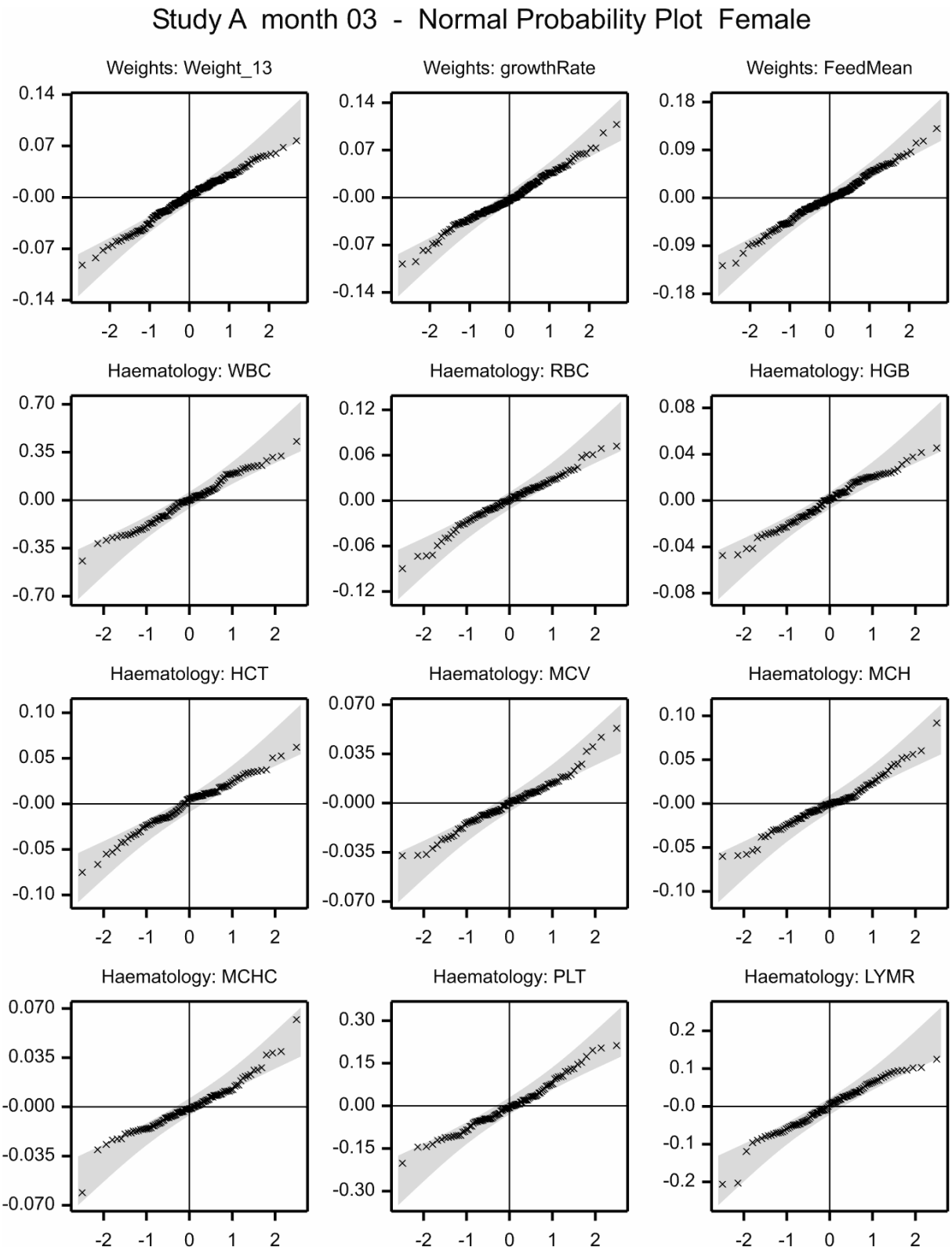
Appendix 5. Normal probability plots of residuals after ANOVA (continued)

Residuals are obtained from ANOVA of cage means (log scale). A 99% confidence envelop is added.



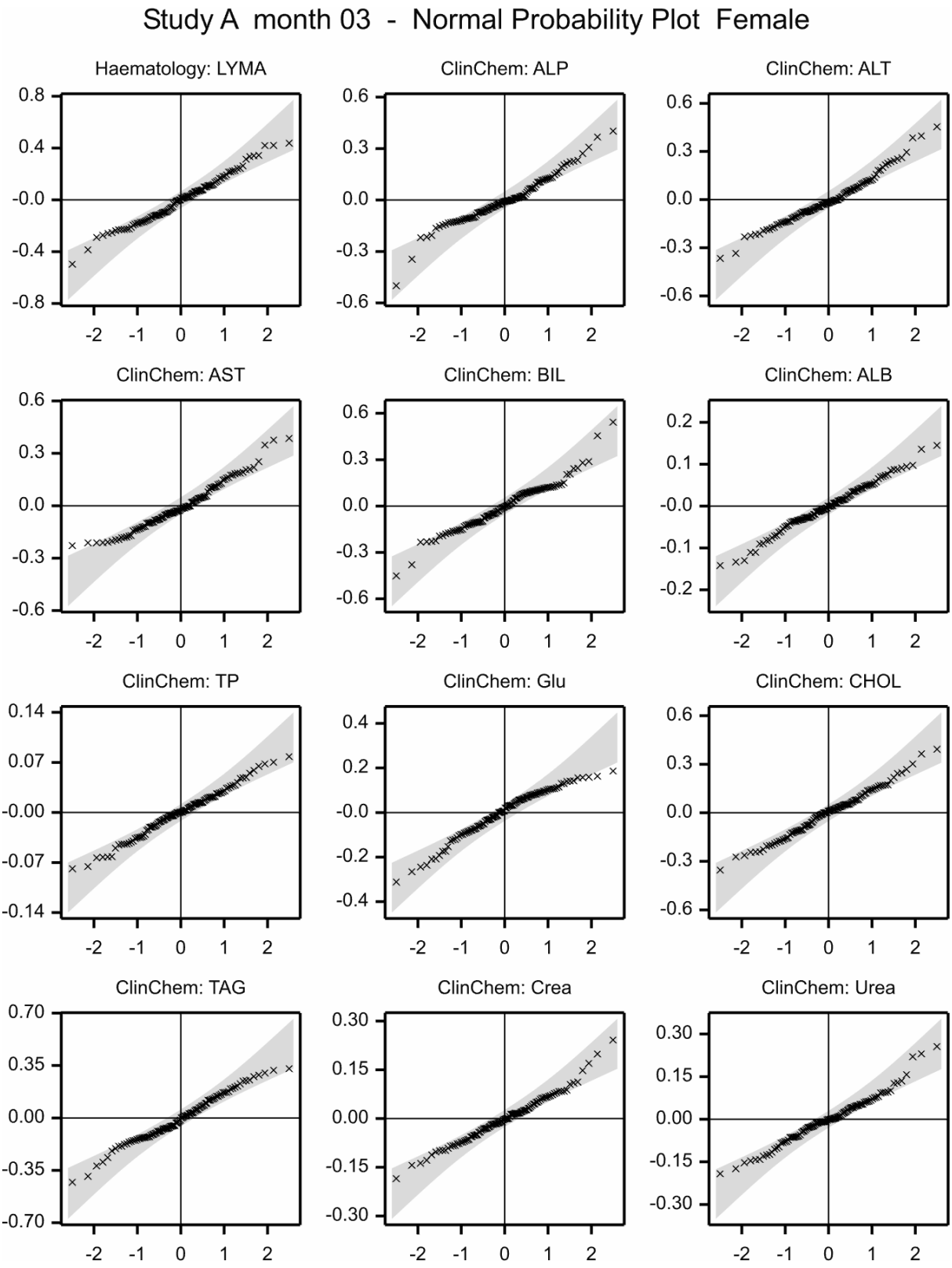
Appendix 5. Normal probability plots of residuals after ANOVA (continued)

Residuals are obtained from ANOVA of cage means (log scale). A 99% confidence envelop is added.



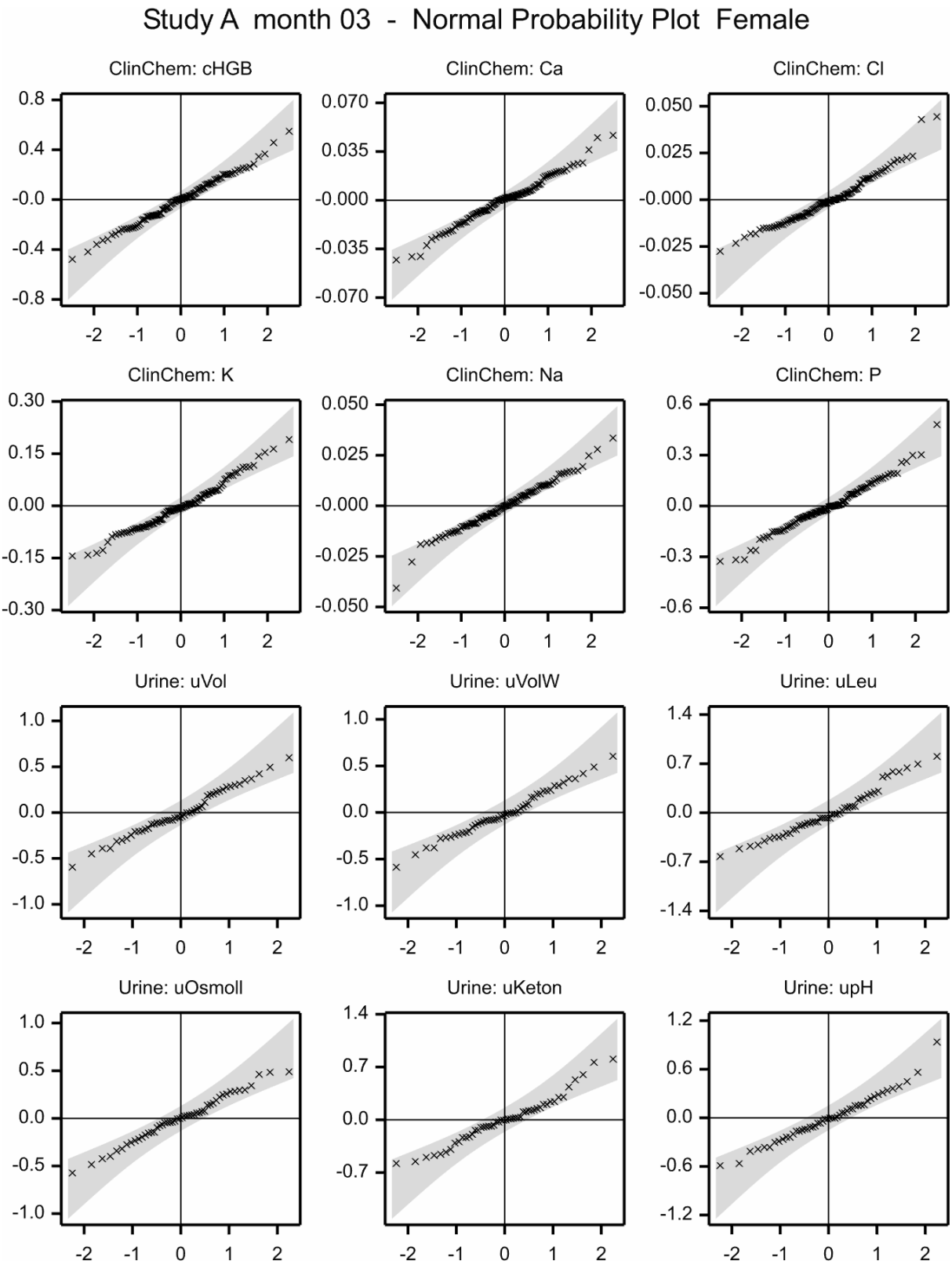
Appendix 5. Normal probability plots of residuals after ANOVA (continued)

Residuals are obtained from ANOVA of cage means (log scale). A 99% confidence envelop is added.



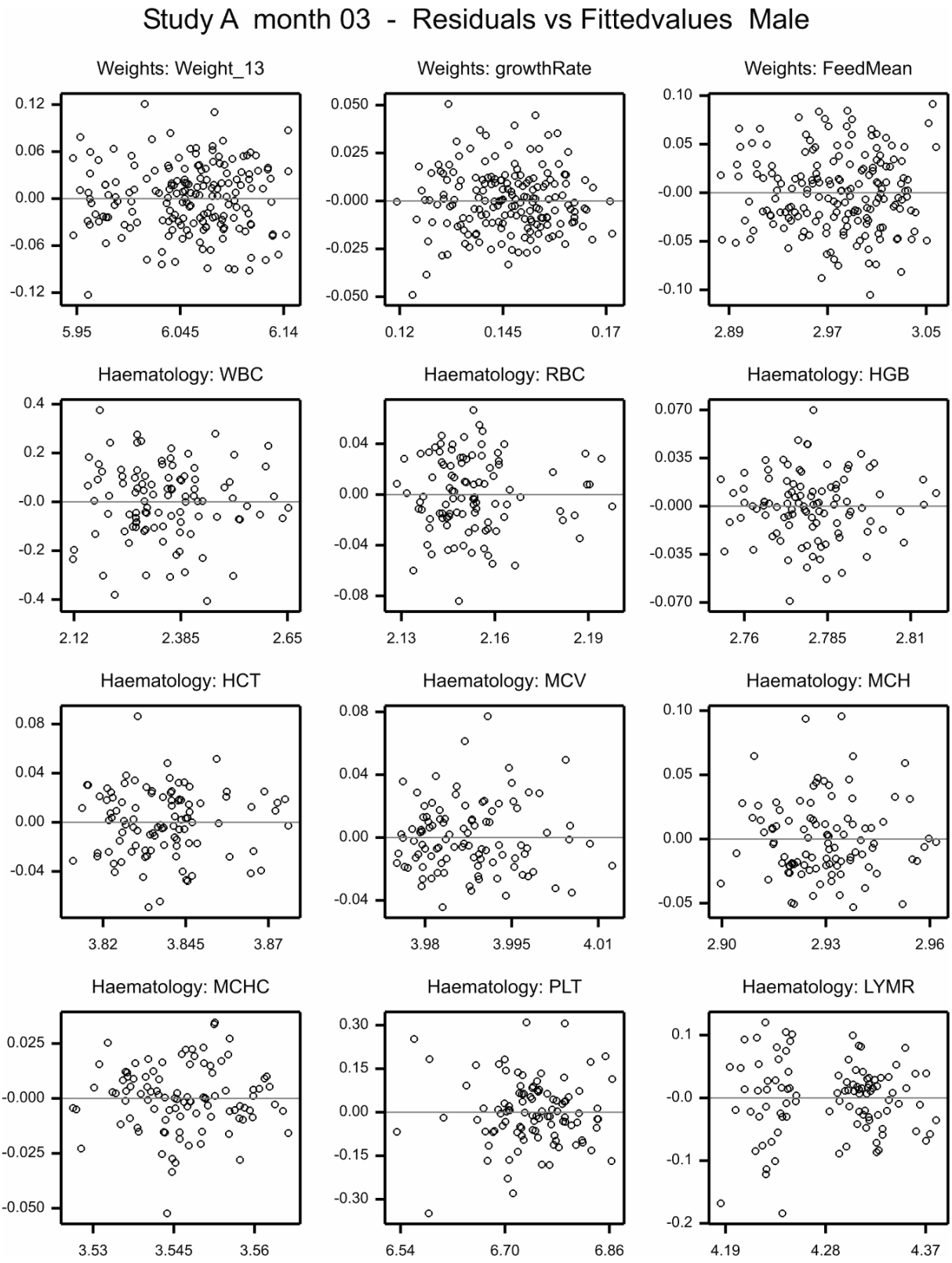
Appendix 5. Normal probability plots of residuals after ANOVA (continued)

Residuals are obtained from ANOVA of cage means (log scale). A 99% confidence envelop is added.



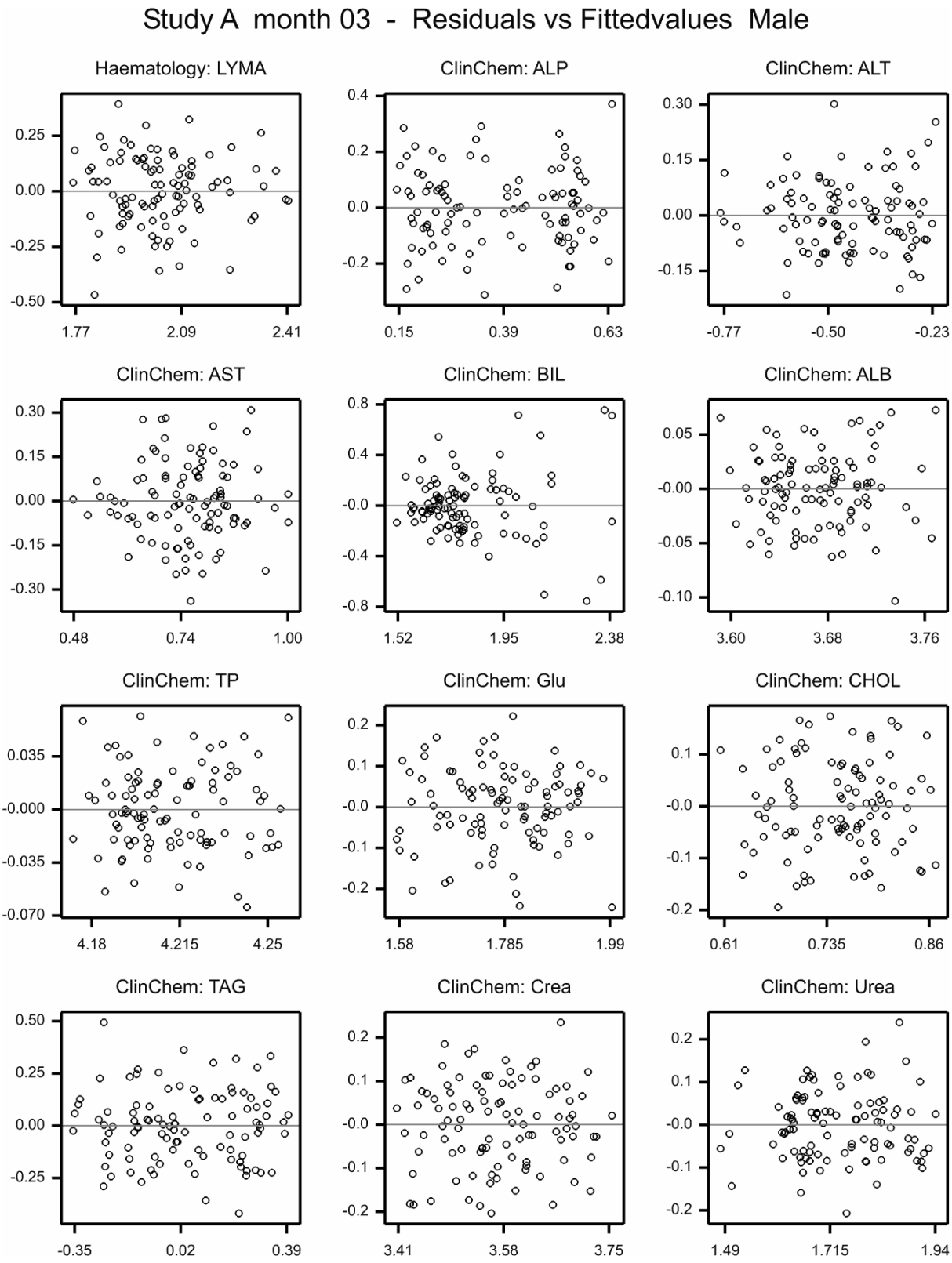
Appendix 6. Graphs of residuals versus fitted values after ANOVA

Residuals and fitted values are obtained from ANOVA of cage means (after a log transformation).



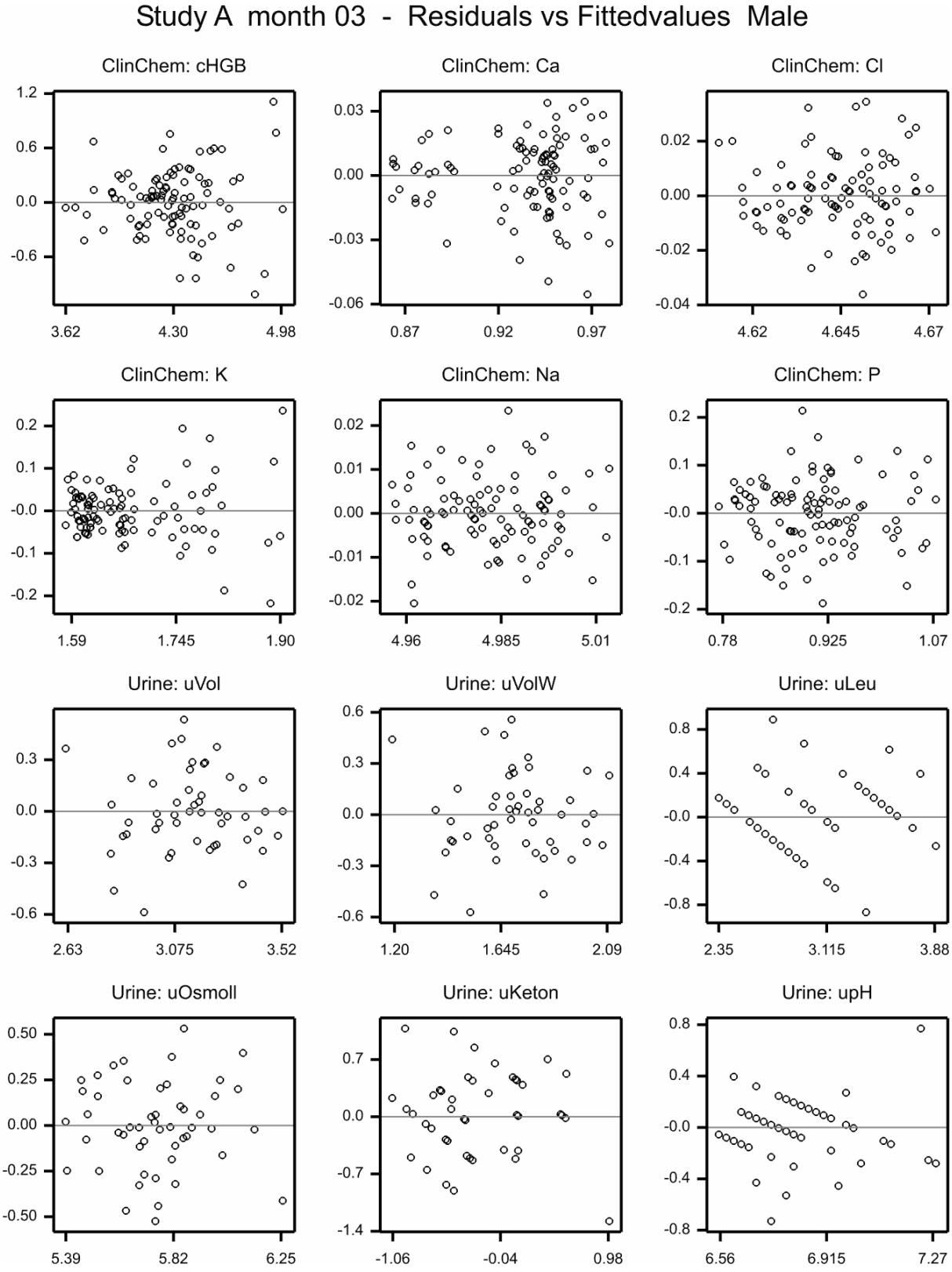
Appendix 6. Graphs of residuals versus fitted values after ANOVA (continued)

Residuals and fitted values are obtained from ANOVA of cage means (after a log transformation).



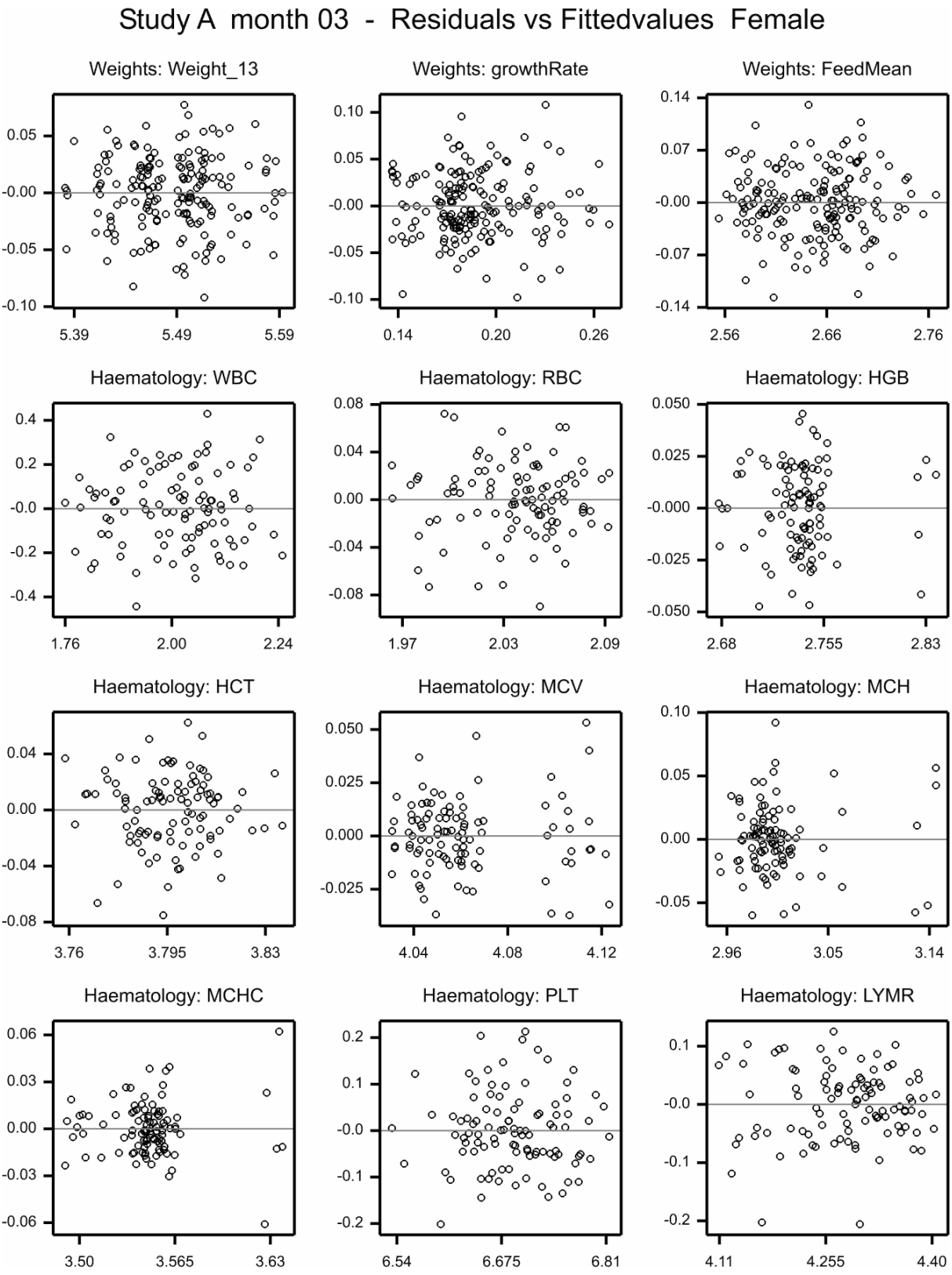
Appendix 6. Graphs of residuals versus fitted values after ANOVA (continued)

Residuals and fitted values are obtained from ANOVA of cage means (after a log transformation).



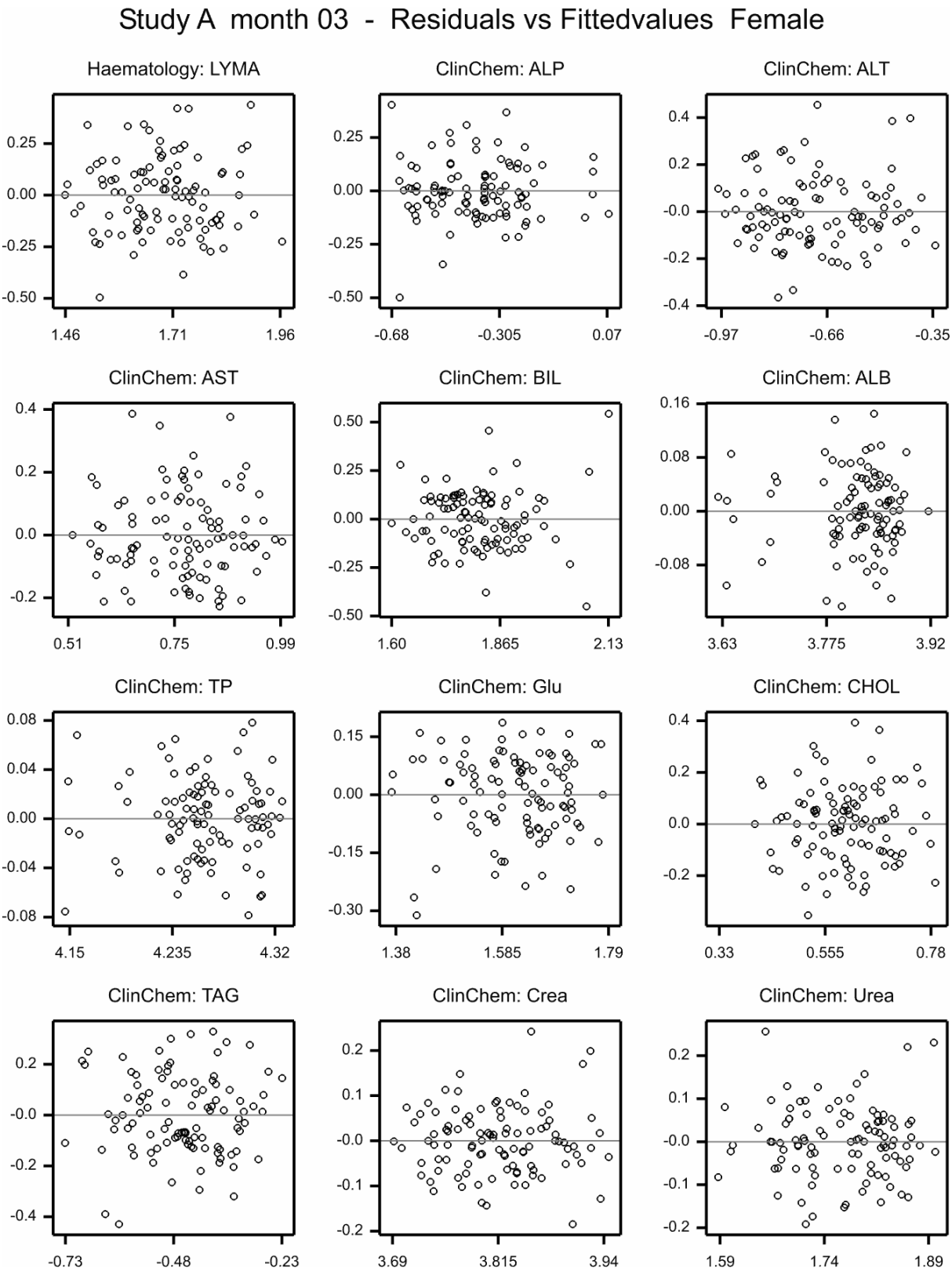
Appendix 6. Graphs of residuals versus fitted values after ANOVA (continued)

Residuals and fitted values are obtained from ANOVA of cage means (after a log transformation).



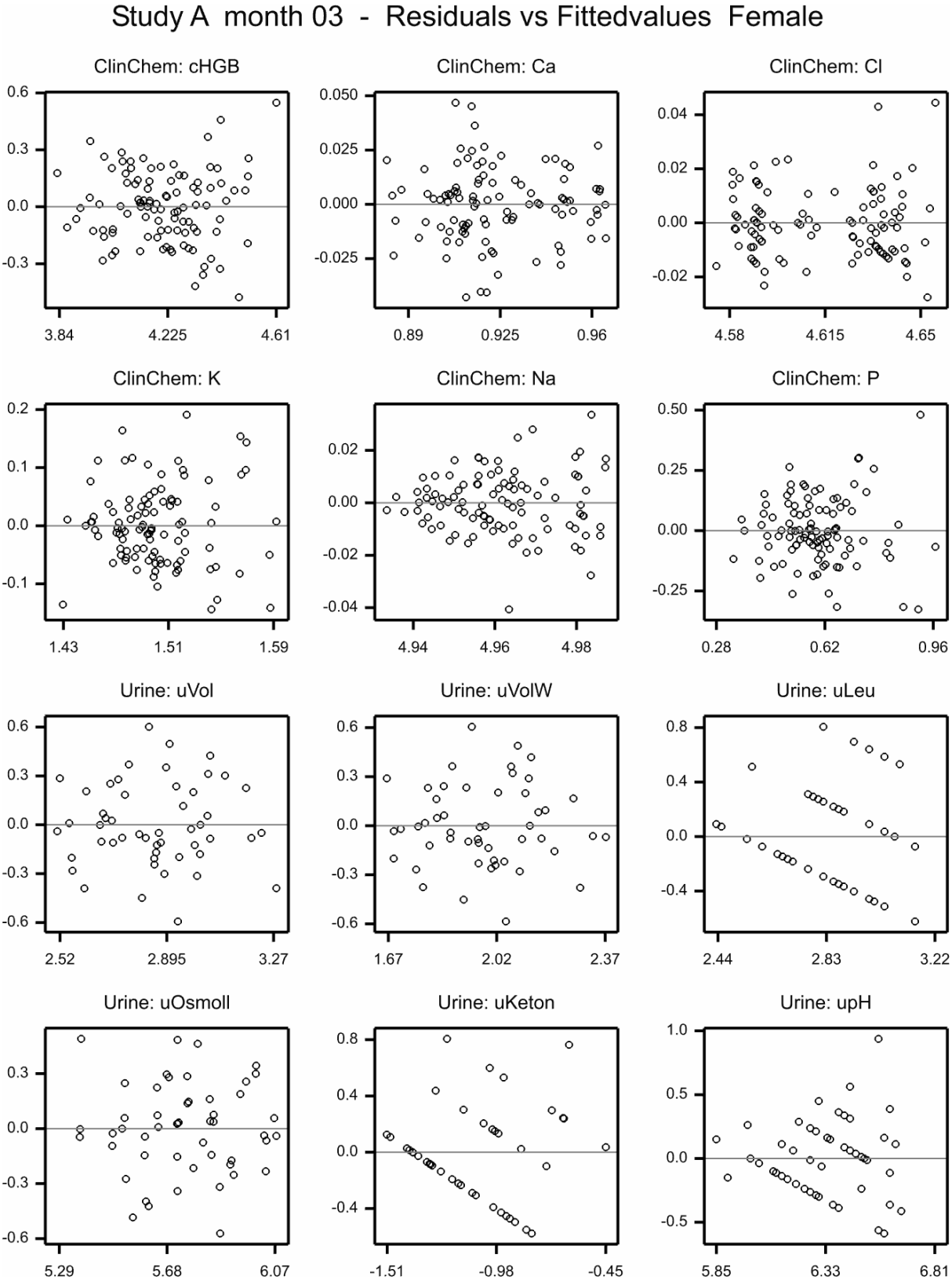
Appendix 6. Graphs of residuals versus fitted values after ANOVA (continued)

Residuals and fitted values are obtained from ANOVA of cage means (after a log transformation).



Appendix 6. Graphs of residuals versus fitted values after ANOVA (continued)

Residuals and fitted values are obtained from ANOVA of cage means (after a log transformation).



Appendix 7. Estimated differences between GMO feeds and the control feed

The differences are given along with the residual sums of squares SS_F based on ANOVA on cage means after a log-transform. The degrees of freedom for the residual sums of squares equals 136 for Weight_13, growthRate and FeedMean, 76 for the other Male variables, and 75 for the other Female variables. Degrees of freedom are sometimes one less due to an occasional missing cage mean.

Variable	Male rats					Female rats				
	NK11-	NK33-	NK11+	NK33+	SS_F	NK11-	NK33-	NK11+	NK33+	SS_F
Weight_13	-0.0155	-0.0091	-0.0020	-0.0002	0.3192	-0.0086	-0.0071	-0.0074	-0.0064	0.1771
growthRate	-0.0079	-0.0041	0.0066	-0.0026	0.0463	-0.0063	-0.0097	-0.0123	-0.0119	0.2078
FeedMean	0.0081	-0.0148	-0.0027	0.0257	0.2663	0.0254	0.0102	0.0075	0.0379	0.3366
WBC	0.0025	0.1227	0.0666	0.0872	2.2987	0.0584	0.0267	-0.0319	0.0777	2.8669
RBC	-0.0070	-0.0038	0.0034	-0.0046	0.0843	-0.0003	0.0146	0.0107	0.0152	0.0947
HGB	-0.0060	0.0037	-0.0071	-0.0002	0.0559	-0.0056	0.0072	-0.0063	-0.0038	0.0403
HCT	-0.0081	-0.0006	0.0033	0.0023	0.0708	-0.0035	0.0107	0.0043	0.0080	0.0655
MCV	-0.0011	0.0031	-0.0003	0.0070	0.0480	0.0015	-0.0071	-0.0063	-0.0071	0.0279
MCH	0.0007	0.0076	-0.0108	0.0042	0.0865	-0.0001	-0.0074	-0.0169	-0.0185	0.0704
MCHC	0.0019	0.0044	-0.0101	-0.0027	0.0215	-0.0022	-0.0038	-0.0107	-0.0120	0.0275
PLT	0.0264	0.0487	0.0499	0.0715	1.2457	-0.0358	-0.0516	-0.0217	0.0173	0.6638
LYMA	0.0049	0.1023	0.0648	0.0944	2.5624	0.0284	0.0126	-0.0523	0.0937	3.3012
ALP	0.0120	-0.0222	-0.0150	0.0198	1.8731	0.0268	0.0279	0.0825	0.0294	1.8731
ALT	0.0089	-0.0417	-0.0315	-0.0327	2.1798	0.0139	-0.0236	-0.0807	0.0872	2.1798
AST	0.0003	-0.0324	-0.0903	-0.0547	1.8135	0.0029	0.0775	-0.0142	0.1293	1.8135
BIL	0.0450	0.0448	-0.0575	0.0150	2.3118	-0.0754	0.0543	-0.0404	0.0065	2.3118
ALB	-0.0133	-0.0082	-0.0211	0.0033	0.3157	-0.0064	-0.0058	0.0030	-0.0180	0.3157
TP	-0.0025	-0.0087	-0.0049	0.0040	0.1081	-0.0099	-0.0072	0.0019	-0.0068	0.1081
Glu	-0.0197	-0.0251	0.0238	0.0407	1.1188	-0.0060	-0.0522	0.0053	-0.0544	1.1188
CHOL	0.0170	-0.0020	-0.0293	0.0109	2.0887	-0.0285	-0.0846	-0.1064	-0.0664	2.0887
TAG	0.0893	0.0933	0.1060	0.0056	2.4446	-0.0315	-0.1056	-0.1449	-0.0454	2.4446
Crea	-0.0606	-0.0481	-0.0335	-0.0386	0.5248	0.0432	0.0150	0.0528	0.0312	0.5248
Urea	-0.0523	-0.0333	-0.0285	-0.0148	0.6799	0.0180	0.0095	0.0210	0.0579	0.6799
cHGB	0.1142	0.0719	-0.0613	0.0556	3.5481	-0.0454	0.1328	-0.1274	0.0339	3.5481
Ca	0.0033	0.0015	0.0000	-0.0005	0.0285	0.0026	0.0056	0.0033	0.0021	0.0285
Cl	-0.0001	-0.0003	-0.0070	0.0056	0.0158	0.0077	0.0085	0.0105	0.0068	0.0158
K	0.0175	0.0082	0.0032	0.0214	0.4559	0.0215	0.0221	0.0034	0.0267	0.4559
Na	-0.0010	0.0035	-0.0001	0.0043	0.0136	0.0075	0.0075	0.0088	0.0087	0.0136
P	-0.0550	-0.0113	-0.0339	-0.0399	1.9047	0.0624	0.1160	-0.0257	0.0692	1.9047

Appendix 8. Intervals for equivalence tests

95% Confidence interval plus estimate for the ratio Δ of a GMO feed versus the control feed, 95% Confidence interval plus median for (upper) equivalence limits, and the confidence interval plus median for Δ on the ELSD scale. Red background colouring indicates significant differences, green background colouring indicates significant equivalences (in all remaining cases equivalence is still more likely than not).

Males NK11- versus Control									
Weights	Interval for ratio Δ			Interval for EQ limit			Interval for Δ ELSD scale		
Males NK11-	lower	esti	upper	lower	median	upper	lower	median	upper
Weight_13	0.962	0.985	1.007	1.070	1.096	1.134	-0.396	-0.166	0.080
growthRate	0.984	0.992	1.001	1.021	1.031	1.041	-0.538	-0.258	0.027
FeedMean	0.987	1.008	1.029	1.072	1.100	1.173	-0.136	0.082	0.281
Haematology	Interval for ratio Δ			Interval for EQ limit			Interval for Δ ELSD scale		
Males NK11-	lower	esti	upper	lower	median	upper	lower	median	upper
WBC	0.899	1.003	1.119	1.464	1.657	2.399	-0.218	0.005	0.224
RBC	0.972	0.993	1.014	1.091	1.114	1.148	-0.233	-0.064	0.130
HGB	0.977	0.994	1.011	1.078	1.099	1.146	-0.219	-0.062	0.117
HCT	0.973	0.992	1.011	1.090	1.112	1.148	-0.232	-0.075	0.105
MCV	0.983	0.999	1.015	1.007	1.024	1.038	-2.000	-0.050	2.000
MCH	0.980	1.001	1.022	1.018	1.042	1.065	-0.677	0.017	0.715
MCHC	0.991	1.002	1.013	1.022	1.033	1.051	-0.280	0.059	0.370
PLT	0.947	1.027	1.113	1.591	1.760	2.013	-0.096	0.046	0.170
LYMA	0.895	1.005	1.128	1.424	1.608	2.224	-0.238	0.009	0.251
ClinChem	Interval for ratio Δ			Interval for EQ limit			Interval for Δ ELSD scale		
Males NK11-	lower	esti	upper	lower	median	upper	lower	median	upper
ALP	0.917	1.012	1.117	1.300	1.419	1.590	-0.256	0.035	0.301
ALT	0.942	1.009	1.080	1.187	1.263	1.383	-0.264	0.037	0.313
AST	0.910	1.000	1.099	1.240	1.352	1.540	-0.329	0.002	0.330
ALB	0.963	0.987	1.011	1.094	1.120	1.157	-0.305	-0.116	0.099
TP	0.978	0.998	1.017	1.067	1.087	1.115	-0.245	-0.029	0.207
Glu	0.916	0.980	1.049	1.290	1.388	1.652	-0.242	-0.059	0.147
CHOL	0.955	1.017	1.083	1.217	1.307	1.631	-0.175	0.060	0.272
TAG	0.968	1.093	1.235	1.810	2.185	4.394	-0.041	0.107	0.254
Crea	0.878	0.941	1.010	1.243	1.332	1.547	-0.434	-0.205	0.033
Urea	0.896	0.949	1.005	1.196	1.280	1.610	-0.431	-0.200	0.018
Ca	0.991	1.003	1.016	1.129	1.160	1.234	-0.063	0.022	0.097
Cl	0.991	1.000	1.009	1.101	1.123	1.171	-0.083	-0.001	0.082
K	0.970	1.018	1.067	1.204	1.263	1.353	-0.130	0.074	0.252
Na	0.993	0.999	1.005	1.112	1.136	1.185	-0.048	-0.007	0.037
P	0.899	0.947	0.997	1.182	1.247	1.424	-0.466	-0.241	-0.016

Appendix 8. Intervals for equivalence tests (continued)

Males NK33- versus Control									
Weights	Interval for ratio Δ			Interval for EQ limit			Interval for Δ ELSD scale		
Males NK33-	lower	esti	upper	lower	median	upper	lower	median	upper
Weight_13	0.969	0.991	1.014	1.070	1.096	1.134	-0.320	-0.097	0.153
growthRate	0.987	0.996	1.005	1.021	1.031	1.041	-0.398	-0.134	0.157
FeedMean	0.965	0.985	1.006	1.072	1.100	1.172	-0.357	-0.150	0.064
Haematology	Interval for ratio Δ			Interval for EQ limit			Interval for Δ ELSD scale		
Males NK33-	lower	esti	upper	lower	median	upper	lower	median	upper
WBC	1.013	1.131	1.261	1.463	1.657	2.392	0.025	0.234	0.447
RBC	0.976	0.996	1.017	1.091	1.114	1.148	-0.209	-0.034	0.163
HGB	0.987	1.004	1.021	1.078	1.099	1.147	-0.143	0.038	0.198
HCT	0.980	0.999	1.019	1.090	1.112	1.148	-0.184	-0.006	0.178
MCV	0.987	1.003	1.019	1.007	1.024	1.038	-2.000	0.152	2.000
MCH	0.986	1.008	1.029	1.018	1.042	1.065	-0.413	0.186	0.864
MCHC	0.994	1.004	1.015	1.022	1.033	1.051	-0.200	0.132	0.439
PLT	0.969	1.050	1.138	1.592	1.760	2.015	-0.057	0.086	0.210
LYMA	0.987	1.108	1.243	1.425	1.609	2.232	-0.027	0.207	0.440
ClinChem	Interval for ratio Δ			Interval for EQ limit			Interval for Δ ELSD scale		
Males NK33-	lower	esti	upper	lower	median	upper	lower	median	upper
ALP	0.886	0.978	1.080	1.299	1.419	1.590	-0.319	-0.062	0.225
ALT	0.896	0.959	1.027	1.187	1.263	1.385	-0.445	-0.175	0.114
AST	0.881	0.968	1.064	1.241	1.352	1.538	-0.387	-0.105	0.212
ALB	0.968	0.992	1.016	1.094	1.120	1.156	-0.261	-0.071	0.144
TP	0.972	0.991	1.011	1.067	1.087	1.115	-0.307	-0.103	0.130
Glu	0.911	0.975	1.044	1.291	1.388	1.646	-0.255	-0.074	0.132
CHOL	0.937	0.998	1.063	1.217	1.306	1.622	-0.245	-0.007	0.235
TAG	0.972	1.098	1.240	1.810	2.184	4.348	-0.035	0.113	0.261
Crea	0.889	0.953	1.022	1.243	1.332	1.542	-0.387	-0.163	0.075
Urea	0.914	0.967	1.024	1.195	1.280	1.618	-0.343	-0.127	0.095
Ca	0.989	1.002	1.014	1.129	1.160	1.235	-0.076	0.010	0.089
Cl	0.990	1.000	1.009	1.101	1.123	1.171	-0.082	-0.003	0.080
K	0.961	1.008	1.057	1.205	1.263	1.353	-0.172	0.034	0.219
Na	0.998	1.004	1.009	1.112	1.136	1.186	-0.017	0.027	0.066
P	0.939	0.989	1.041	1.182	1.247	1.424	-0.261	-0.049	0.185

Appendix 8. Intervals for equivalence tests (continued)

Males NK11+ versus Control									
Weights	Interval for ratio Δ			Interval for EQ limit			Interval for Δ ELSD scale		
Males NK11+	lower	esti	upper	lower	median	upper	lower	median	upper
Weight_13	0.975	0.998	1.021	1.070	1.096	1.134	-0.263	-0.021	0.238
growthRate	0.998	1.007	1.015	1.021	1.031	1.041	-0.073	0.215	0.488
FeedMean	0.977	0.997	1.018	1.072	1.100	1.174	-0.234	-0.027	0.197
Haematology	Interval for ratio Δ			Interval for EQ limit			Interval for Δ ELSD scale		
Males NK11+	lower	esti	upper	lower	median	upper	lower	median	upper
WBC	0.958	1.069	1.193	1.464	1.657	2.402	-0.086	0.126	0.324
RBC	0.983	1.003	1.025	1.091	1.114	1.148	-0.163	0.032	0.209
HGB	0.976	0.993	1.010	1.078	1.099	1.146	-0.231	-0.073	0.107
HCT	0.984	1.003	1.023	1.090	1.112	1.148	-0.150	0.030	0.194
MCV	0.984	1.000	1.016	1.007	1.024	1.038	-2.000	-0.011	2.000
MCH	0.968	0.989	1.011	1.018	1.041	1.065	-0.960	-0.266	0.297
MCHC	0.980	0.990	1.001	1.022	1.033	1.052	-0.643	-0.306	0.017
PLT	0.970	1.051	1.139	1.592	1.760	2.014	-0.055	0.088	0.211
LYMA	0.950	1.067	1.198	1.424	1.609	2.237	-0.106	0.131	0.353
ClinChem	Interval for ratio Δ			Interval for EQ limit			Interval for Δ ELSD scale		
Males NK11+	lower	esti	upper	lower	median	upper	lower	median	upper
ALP	0.892	0.985	1.087	1.300	1.419	1.589	-0.304	-0.042	0.249
ALT	0.905	0.969	1.037	1.186	1.263	1.385	-0.397	-0.132	0.161
AST	0.831	0.914	1.004	1.240	1.352	1.543	-0.603	-0.294	0.014
ALB	0.955	0.979	1.003	1.094	1.120	1.156	-0.378	-0.184	0.028
TP	0.976	0.995	1.015	1.067	1.087	1.115	-0.266	-0.058	0.178
Glu	0.957	1.024	1.096	1.291	1.388	1.648	-0.134	0.070	0.253
CHOL	0.912	0.971	1.034	1.217	1.307	1.622	-0.318	-0.103	0.126
TAG	0.984	1.112	1.256	1.811	2.184	4.324	-0.020	0.129	0.279
Crea	0.902	0.967	1.037	1.244	1.332	1.541	-0.333	-0.112	0.128
Urea	0.918	0.972	1.029	1.195	1.280	1.612	-0.322	-0.108	0.115
Ca	0.987	1.000	1.013	1.129	1.160	1.235	-0.086	0.000	0.086
Cl	0.984	0.993	1.002	1.101	1.123	1.170	-0.131	-0.059	0.021
K	0.957	1.003	1.052	1.205	1.263	1.353	-0.194	0.013	0.210
Na	0.994	1.000	1.006	1.112	1.136	1.185	-0.045	-0.001	0.044
P	0.918	0.967	1.018	1.182	1.247	1.421	-0.361	-0.148	0.080

Appendix 8. Intervals for equivalence tests (continued)

Males NK33+ versus Control									
Weights	Interval for ratio Δ			Interval for EQ limit			Interval for Δ ELSD scale		
Males NK33+	lower	esti	upper	lower	median	upper	lower	median	upper
Weight_13	0.977	1.000	1.023	1.070	1.096	1.135	-0.259	-0.002	0.257
growthRate	0.989	0.997	1.006	1.021	1.031	1.041	-0.347	-0.084	0.210
FeedMean	1.005	1.026	1.048	1.072	1.100	1.173	0.047	0.262	0.486
Haematology	Interval for ratio Δ			Interval for EQ limit			Interval for Δ ELSD scale		
Males NK33+	lower	esti	upper	lower	median	upper	lower	median	upper
WBC	0.978	1.091	1.217	1.464	1.657	2.399	-0.043	0.165	0.370
RBC	0.975	0.995	1.016	1.091	1.114	1.148	-0.215	-0.043	0.153
HGB	0.983	1.000	1.017	1.078	1.099	1.145	-0.183	-0.003	0.181
HCT	0.983	1.002	1.022	1.090	1.112	1.149	-0.160	0.021	0.189
MCV	0.991	1.007	1.023	1.007	1.024	1.039	-1.013	0.335	2.000
MCH	0.983	1.004	1.026	1.018	1.042	1.065	-0.542	0.102	0.765
MCHC	0.987	0.997	1.008	1.022	1.033	1.051	-0.390	-0.082	0.254
PLT	0.991	1.074	1.164	1.592	1.759	2.014	-0.017	0.126	0.252
LYMA	0.979	1.099	1.234	1.424	1.608	2.234	-0.045	0.191	0.420
ClinChem	Interval for ratio Δ			Interval for EQ limit			Interval for Δ ELSD scale		
Males NK33+	lower	esti	upper	lower	median	upper	lower	median	upper
ALP	0.924	1.020	1.126	1.298	1.419	1.589	-0.231	0.057	0.316
ALT	0.904	0.968	1.036	1.187	1.263	1.383	-0.402	-0.137	0.156
AST	0.862	0.947	1.040	1.240	1.352	1.540	-0.466	-0.177	0.133
ALB	0.979	1.003	1.028	1.094	1.120	1.156	-0.191	0.028	0.229
TP	0.985	1.004	1.024	1.067	1.087	1.115	-0.191	0.046	0.257
Glu	0.973	1.042	1.115	1.291	1.388	1.646	-0.083	0.121	0.306
CHOL	0.949	1.011	1.076	1.217	1.307	1.625	-0.199	0.038	0.256
TAG	0.890	1.006	1.136	1.808	2.183	4.366	-0.153	0.007	0.161
Crea	0.897	0.962	1.032	1.244	1.332	1.541	-0.350	-0.130	0.111
Urea	0.931	0.985	1.043	1.195	1.280	1.610	-0.269	-0.056	0.175
Ca	0.987	0.999	1.012	1.130	1.160	1.235	-0.086	-0.003	0.082
Cl	0.996	1.006	1.015	1.101	1.123	1.171	-0.033	0.047	0.118
K	0.974	1.022	1.071	1.204	1.263	1.352	-0.112	0.090	0.268
Na	0.999	1.004	1.010	1.112	1.136	1.186	-0.011	0.033	0.073
P	0.913	0.961	1.012	1.182	1.247	1.419	-0.391	-0.175	0.052

Appendix 8. Intervals for equivalence tests (continued)

Females NK11- versus Control									
Weights	Interval for ratio Δ			Interval for EQ limit			Interval for Δ ELSD scale		
Females NK11-	lower	esti	upper	lower	median	upper	lower	median	upper
Weight_13	0.975	0.991	1.008	1.108	1.134	1.182	-0.185	-0.068	0.067
growthRate	0.975	0.994	1.012	1.009	1.031	1.053	-2.000	-0.231	2.000
FeedMean	1.002	1.026	1.050	1.093	1.126	1.214	0.015	0.208	0.401
Haematology	Interval for ratio Δ			Interval for EQ limit			Interval for Δ ELSD scale		
Females NK11-	lower	esti	upper	lower	median	upper	lower	median	upper
WBC	0.935	1.060	1.201	1.505	1.704	2.243	-0.123	0.106	0.311
RBC	0.977	1.000	1.023	1.053	1.075	1.122	-0.325	-0.004	0.321
HGB	0.980	0.994	1.009	1.053	1.069	1.095	-0.277	-0.083	0.137
HCT	0.978	0.996	1.016	1.037	1.056	1.091	-0.387	-0.063	0.293
MCV	0.989	1.001	1.014	1.027	1.038	1.053	-0.297	0.037	0.349
MCH	0.980	1.000	1.020	1.041	1.059	1.083	-0.355	-0.001	0.354
MCHC	0.986	0.998	1.010	1.013	1.026	1.038	-0.587	-0.084	0.445
PLT	0.908	0.965	1.025	1.369	1.470	1.633	-0.228	-0.092	0.061
LYMA	0.899	1.029	1.177	1.447	1.644	2.150	-0.214	0.055	0.298
ClinChem	Interval for ratio Δ			Interval for EQ limit			Interval for Δ ELSD scale		
Females NK11-	lower	esti	upper	lower	median	upper	lower	median	upper
ALP	0.928	1.027	1.137	1.224	1.340	1.495	-0.261	0.091	0.405
ALT	0.909	1.014	1.131	1.566	1.749	2.056	-0.171	0.025	0.202
AST	0.908	1.003	1.108	1.389	1.524	1.755	-0.230	0.008	0.238
ALB	0.953	0.994	1.036	1.168	1.215	1.277	-0.224	-0.033	0.180
TP	0.966	0.990	1.015	1.155	1.197	1.327	-0.170	-0.053	0.077
Glu	0.919	0.994	1.075	1.269	1.364	1.525	-0.258	-0.018	0.237
CHOL	0.873	0.972	1.082	1.080	1.212	1.395	-0.935	-0.145	0.537
TAG	0.863	0.969	1.088	1.862	2.147	2.832	-0.171	-0.041	0.106
Crea	0.990	1.044	1.102	1.263	1.351	1.675	-0.030	0.138	0.300
Urea	0.958	1.018	1.082	1.228	1.325	1.730	-0.151	0.059	0.253
Ca	0.990	1.003	1.015	1.125	1.168	1.369	-0.062	0.015	0.087
Cl	0.998	1.008	1.017	1.055	1.067	1.086	-0.023	0.117	0.241
K	0.972	1.022	1.074	1.201	1.265	1.424	-0.118	0.089	0.273
Na	0.999	1.008	1.016	1.052	1.065	1.092	-0.015	0.117	0.238
P	0.960	1.064	1.180	1.111	1.240	1.441	-0.201	0.286	0.852

Appendix 8. Intervals for equivalence tests (continued)

Females NK33- versus Control									
Weights	Interval for ratio Δ			Interval for EQ limit			Interval for Δ ELSD scale		
Females NK33-	lower	esti	upper	lower	median	upper	lower	median	upper
Weight_13	0.976	0.993	1.010	1.108	1.134	1.181	-0.173	-0.056	0.078
growthRate	0.972	0.990	1.009	1.009	1.029	1.052	-2.000	-0.359	0.955
FeedMean	0.987	1.010	1.034	1.093	1.125	1.215	-0.112	0.083	0.262
Haematology	Interval for ratio Δ			Interval for EQ limit			Interval for Δ ELSD scale		
Females NK33-	lower	esti	upper	lower	median	upper	lower	median	upper
WBC	0.908	1.027	1.162	1.505	1.704	2.256	-0.184	0.049	0.258
RBC	0.992	1.015	1.038	1.052	1.075	1.122	-0.106	0.195	0.485
HGB	0.993	1.007	1.022	1.053	1.069	1.095	-0.111	0.106	0.300
HCT	0.992	1.011	1.030	1.037	1.056	1.091	-0.150	0.192	0.517
MCV	0.981	0.993	1.005	1.027	1.038	1.053	-0.489	-0.189	0.137
MCH	0.974	0.993	1.012	1.041	1.059	1.083	-0.431	-0.125	0.215
MCHC	0.984	0.996	1.008	1.013	1.026	1.038	-0.645	-0.147	0.360
PLT	0.895	0.950	1.008	1.369	1.471	1.632	-0.270	-0.132	0.021
LYMA	0.887	1.013	1.156	1.448	1.645	2.151	-0.248	0.025	0.279
ClinChem	Interval for ratio Δ			Interval for EQ limit			Interval for Δ ELSD scale		
Females NK33-	lower	esti	upper	lower	median	upper	lower	median	upper
ALP	0.931	1.028	1.136	1.225	1.340	1.495	-0.255	0.095	0.409
ALT	0.877	0.977	1.087	1.565	1.748	2.057	-0.214	-0.041	0.152
AST	0.980	1.081	1.192	1.388	1.525	1.758	-0.050	0.181	0.392
ALB	0.954	0.994	1.036	1.168	1.215	1.277	-0.222	-0.030	0.183
TP	0.969	0.993	1.017	1.155	1.197	1.323	-0.155	-0.038	0.094
Glu	0.879	0.949	1.025	1.269	1.364	1.528	-0.389	-0.166	0.079
CHOL	0.827	0.919	1.021	1.079	1.212	1.394	-1.445	-0.438	0.123
TAG	0.803	0.900	1.008	1.862	2.148	2.828	-0.269	-0.135	0.011
Crea	0.963	1.015	1.070	1.263	1.352	1.675	-0.126	0.048	0.203
Urea	0.951	1.010	1.072	1.228	1.325	1.727	-0.184	0.031	0.230
Ca	0.993	1.006	1.018	1.124	1.169	1.372	-0.043	0.033	0.105
Cl	0.999	1.009	1.018	1.055	1.067	1.086	-0.011	0.130	0.254
K	0.973	1.022	1.074	1.201	1.265	1.420	-0.116	0.092	0.277
Na	0.999	1.008	1.016	1.052	1.065	1.091	-0.015	0.117	0.239
P	1.015	1.123	1.242	1.110	1.240	1.443	0.067	0.534	1.215

Appendix 8. Intervals for equivalence tests (continued)

Females NK11+ versus Control									
Weights	Interval for ratio Δ			Interval for EQ limit			Interval for Δ ELSD scale		
Females NK11+	lower	esti	upper	lower	median	upper	lower	median	upper
Weight_13	0.976	0.993	1.010	1.109	1.134	1.181	-0.176	-0.058	0.078
growthRate	0.970	0.988	1.006	1.009	1.029	1.053	-2.000	-0.448	0.362
FeedMean	0.984	1.008	1.032	1.093	1.125	1.216	-0.136	0.061	0.239
Haematology	Interval for ratio Δ			Interval for EQ limit			Interval for Δ ELSD scale		
Females NK11+	lower	esti	upper	lower	median	upper	lower	median	upper
WBC	0.856	0.969	1.096	1.505	1.705	2.267	-0.265	-0.059	0.174
RBC	0.988	1.011	1.034	1.053	1.075	1.123	-0.163	0.143	0.428
HGB	0.979	0.994	1.008	1.053	1.069	1.096	-0.285	-0.093	0.127
HCT	0.986	1.004	1.023	1.037	1.056	1.091	-0.273	0.076	0.401
MCV	0.982	0.994	1.006	1.027	1.038	1.053	-0.466	-0.166	0.157
MCH	0.964	0.983	1.002	1.041	1.059	1.084	-0.617	-0.289	0.043
MCHC	0.977	0.989	1.001	1.013	1.026	1.038	-0.983	-0.415	0.050
PLT	0.922	0.979	1.039	1.369	1.471	1.634	-0.190	-0.055	0.099
LYMA	0.832	0.949	1.083	1.448	1.644	2.143	-0.339	-0.102	0.163
ClinChem	Interval for ratio Δ			Interval for EQ limit			Interval for Δ ELSD scale		
Females NK11+	lower	esti	upper	lower	median	upper	lower	median	upper
ALP	0.983	1.086	1.200	1.225	1.340	1.495	-0.059	0.278	0.608
ALT	0.829	0.922	1.027	1.565	1.749	2.058	-0.314	-0.143	0.047
AST	0.894	0.986	1.087	1.388	1.525	1.757	-0.249	-0.033	0.203
ALB	0.963	1.003	1.045	1.168	1.215	1.277	-0.198	0.016	0.216
TP	0.978	1.002	1.026	1.155	1.197	1.323	-0.123	0.010	0.136
Glu	0.931	1.005	1.086	1.269	1.364	1.528	-0.236	0.017	0.257
CHOL	0.809	0.899	0.999	1.079	1.212	1.394	-1.675	-0.551	-0.004
TAG	0.772	0.865	0.969	1.862	2.149	2.834	-0.323	-0.186	-0.040
Crea	1.000	1.054	1.111	1.262	1.351	1.682	0.001	0.169	0.334
Urea	0.962	1.021	1.084	1.228	1.325	1.732	-0.140	0.070	0.264
Ca	0.991	1.003	1.016	1.124	1.168	1.368	-0.059	0.019	0.091
Cl	1.001	1.011	1.020	1.055	1.067	1.086	0.021	0.161	0.289
K	0.955	1.003	1.054	1.201	1.266	1.423	-0.196	0.014	0.215
Na	1.000	1.009	1.017	1.052	1.065	1.092	0.005	0.138	0.260
P	0.879	0.975	1.080	1.108	1.239	1.442	-0.651	-0.116	0.423

Appendix 8. Intervals for equivalence tests (continued)

Females NK33+ versus Control									
Weights	Interval for ratio Δ			Interval for EQ limit			Interval for Δ ELSD scale		
Females NK33+	lower	esti	upper	lower	median	upper	lower	median	upper
Weight_13	0.977	0.994	1.011	1.109	1.134	1.180	-0.168	-0.050	0.085
growthRate	0.970	0.988	1.007	1.009	1.029	1.053	-2.000	-0.440	0.389
FeedMean	1.014	1.039	1.063	1.093	1.125	1.215	0.107	0.313	0.521
Haematology	Interval for ratio Δ			Interval for EQ limit			Interval for Δ ELSD scale		
Females NK33+	lower	esti	upper	lower	median	upper	lower	median	upper
WBC	0.956	1.081	1.222	1.504	1.705	2.258	-0.085	0.142	0.351
RBC	0.993	1.015	1.038	1.052	1.075	1.122	-0.098	0.203	0.498
HGB	0.982	0.996	1.011	1.053	1.069	1.096	-0.251	-0.055	0.166
HCT	0.989	1.008	1.027	1.037	1.056	1.091	-0.204	0.142	0.462
MCV	0.981	0.993	1.005	1.027	1.038	1.053	-0.485	-0.184	0.140
MCH	0.963	0.982	1.001	1.041	1.059	1.083	-0.647	-0.317	0.014
MCHC	0.976	0.988	1.000	1.013	1.026	1.038	-1.055	-0.464	0.001
PLT	0.958	1.017	1.081	1.369	1.471	1.634	-0.113	0.044	0.181
LYMA	0.962	1.098	1.253	1.448	1.644	2.146	-0.076	0.183	0.430
ClinChem	Interval for ratio Δ			Interval for EQ limit			Interval for Δ ELSD scale		
Females NK33+	lower	esti	upper	lower	median	upper	lower	median	upper
ALP	0.932	1.030	1.138	1.224	1.340	1.494	-0.248	0.100	0.414
ALT	0.980	1.091	1.215	1.564	1.748	2.056	-0.035	0.155	0.327
AST	1.032	1.138	1.255	1.388	1.525	1.756	0.074	0.302	0.526
ALB	0.943	0.982	1.023	1.168	1.215	1.278	-0.275	-0.092	0.119
TP	0.970	0.993	1.017	1.155	1.197	1.324	-0.153	-0.036	0.096
Glu	0.877	0.947	1.023	1.269	1.364	1.526	-0.396	-0.172	0.074
CHOL	0.842	0.936	1.040	1.080	1.212	1.395	-1.250	-0.344	0.234
TAG	0.853	0.956	1.071	1.860	2.148	2.821	-0.186	-0.058	0.089
Crea	0.979	1.032	1.088	1.263	1.351	1.676	-0.071	0.099	0.256
Urea	0.998	1.060	1.125	1.228	1.325	1.737	-0.005	0.195	0.410
Ca	0.990	1.002	1.014	1.124	1.168	1.369	-0.066	0.012	0.085
Cl	0.998	1.007	1.016	1.055	1.067	1.086	-0.036	0.103	0.227
K	0.978	1.027	1.079	1.201	1.265	1.422	-0.096	0.110	0.295
Na	1.000	1.009	1.017	1.052	1.065	1.091	0.003	0.136	0.258
P	0.969	1.072	1.186	1.109	1.240	1.446	-0.160	0.318	0.903

Appendix 9. P-values for difference tests between GMO feeds and the control feed

Difference tests are based on log transformed cage means. P-values are given for Dunnett tests (Dunnet), for t-tests and for Wilcoxon signed rank tests (Wilcox). P-values smaller than 0.01/0.05 have a gold/yellow background.

Weights	**NK11-**			**NK33-**			**NK11+**			**NK33+**		
Males	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox
Weight_13	0.471	0.182	0.225	0.849	0.435	0.544	0.999	0.862	0.827	1.000	0.987	0.728
growthRate	0.225	0.076	0.163	0.758	0.354	0.422	0.379	0.139	0.207	0.940	0.561	0.599
FeedMean	0.858	0.444	0.565	0.432	0.163	0.093	0.997	0.800	0.942	0.055	0.016	0.020
Haematology	**NK11-**			**NK33-**			**NK11+**			**NK33+**		
Males	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox
WBC	1.000	0.963	0.956	0.093	0.029	0.004	0.563	0.230	0.330	0.327	0.117	0.133
RBC	0.909	0.510	0.648	0.989	0.720	0.956	0.992	0.744	0.729	0.977	0.661	0.898
HGB	0.891	0.485	0.522	0.979	0.669	0.368	0.823	0.410	0.784	1.000	0.979	0.701
HCT	0.820	0.407	0.409	1.000	0.949	0.812	0.991	0.735	0.475	0.998	0.813	0.596
MCV	1.000	0.894	0.812	0.985	0.694	0.330	1.000	0.971	0.701	0.791	0.381	0.202
MCH	1.000	0.947	0.985	0.888	0.481	0.430	0.705	0.316	0.409	0.985	0.696	0.622
MCHC	0.989	0.719	0.498	0.823	0.410	0.498	0.188	0.062	0.058	0.961	0.609	0.729
PLT	0.914	0.517	0.956	0.569	0.233	0.154	0.548	0.222	0.070	0.239	0.082	0.021
LYMR	0.922	0.530	0.571	0.698	0.311	0.498	0.999	0.870	0.452	0.997	0.793	0.784
LYMA	1.000	0.933	0.985	0.241	0.082	0.064	0.630	0.268	0.231	0.305	0.108	0.189
ClinChem	**NK11-**			**NK33-**			**NK11+**			**NK33+**		
Males	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox
ALP	0.998	0.809	0.729	0.976	0.656	0.475	0.994	0.763	0.869	0.984	0.691	0.898
ALT	0.997	0.796	0.898	0.559	0.227	0.090	0.766	0.361	0.261	0.743	0.343	0.277
AST	1.000	0.995	0.784	0.899	0.495	0.430	0.183	0.060	0.143	0.603	0.252	0.349
BIL	0.966	0.622	0.985	0.966	0.623	0.956	0.921	0.528	0.277	0.999	0.869	0.729
ALB	0.652	0.281	0.245	0.908	0.508	0.475	0.261	0.090	0.044	0.997	0.791	0.784
TP	0.997	0.800	0.841	0.782	0.373	0.430	0.965	0.620	0.622	0.983	0.685	0.674
Glu	0.941	0.564	0.452	0.873	0.463	0.294	0.893	0.487	0.368	0.574	0.235	0.498
CHOL	0.954	0.591	0.622	1.000	0.949	0.956	0.761	0.356	0.430	0.991	0.731	0.927

TAG	0.402	0.150	0.083	0.362	0.132	0.189	0.256	0.088	0.165	1.000	0.927	0.756
Crea	0.258	0.089	0.177	0.457	0.176	0.123	0.745	0.344	0.409	0.643	0.276	0.349
Urea	0.214	0.072	0.189	0.599	0.250	0.154	0.716	0.323	0.312	0.960	0.607	0.409
cHGB	0.796	0.386	0.701	0.951	0.584	0.927	0.972	0.641	0.330	0.980	0.672	0.927
Ca	0.958	0.601	0.648	0.998	0.812	0.622	1.000	0.998	0.927	1.000	0.933	0.985
Cl	1.000	0.991	0.869	1.000	0.947	0.888	0.392	0.145	0.173	0.579	0.239	0.368
K	0.875	0.465	0.409	0.991	0.732	0.701	1.000	0.893	0.927	0.782	0.373	0.622
Na	0.991	0.737	1.000	0.549	0.225	0.258	1.000	0.974	0.856	0.370	0.138	0.156
P	0.116	0.037	0.024	0.978	0.664	0.841	0.493	0.193	0.090	0.349	0.127	0.070
Urine	**NK11-**			**NK33-**			**NK11+**			**NK33+**		
Males	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox
uVol	0.999	0.870	1.000	0.135	0.044	0.232	0.960	0.608	0.922	0.978	0.666	1.000
uVolW	0.998	0.826	1.000	0.182	0.061	0.322	0.963	0.618	1.000	0.949	0.584	0.846
uLeu	0.994	0.757	0.854	0.112	0.036	0.206	0.994	0.757	0.850	0.542	0.220	0.387
uOsmoll	0.964	0.620	0.557	0.420	0.160	0.432	0.956	0.601	0.922	1.000	0.873	0.922
uKeton	0.965	0.622	0.726	0.120	0.038	0.148	0.975	0.655	0.726	0.912	0.518	0.483
upH	0.496	0.196	0.086	0.999	0.852	1.000	0.987	0.709	0.730	0.625	0.267	0.188

Weights	**NK11-**			**NK33-**			**NK11+**			**NK33+**		
Females	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox
Weight_13	0.710	0.318	0.385	0.824	0.409	0.461	0.807	0.394	0.728	0.869	0.456	0.368
growthRate	0.908	0.506	0.385	0.690	0.304	0.201	0.496	0.194	0.168	0.526	0.209	0.256
FeedMean	0.110	0.034	0.024	0.806	0.393	0.692	0.921	0.527	0.668	0.007	0.002	0.003
Haematology	**NK11-**			**NK33-**			**NK11+**			**NK33+**		
Females	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox
WBC	0.761	0.356	0.258	0.979	0.667	0.927	0.961	0.607	0.674	0.533	0.213	0.368
RBC	1.000	0.979	0.798	0.506	0.199	0.189	0.743	0.342	0.097	0.470	0.181	0.261
HGB	0.866	0.453	0.623	0.724	0.328	0.097	0.806	0.393	0.165	0.962	0.610	0.596
HCT	0.988	0.712	0.651	0.610	0.255	0.064	0.973	0.644	0.368	0.806	0.394	0.701
MCV	0.998	0.815	0.798	0.592	0.245	0.294	0.688	0.303	0.430	0.603	0.251	0.430

MCH	1.000	0.992	0.860	0.863	0.449	0.245	0.249	0.085	0.030	0.184	0.060	0.312
MCHC	0.990	0.724	0.258	0.921	0.528	0.261	0.236	0.080	0.048	0.157	0.051	0.083
PLT	0.590	0.243	0.123	0.260	0.089	0.114	0.881	0.470	0.388	0.945	0.571	0.709
LYMR	0.256	0.088	0.104	0.887	0.478	0.784	0.735	0.336	0.388	1.000	0.897	0.841
LYMA	0.981	0.675	0.374	0.999	0.850	0.898	0.847	0.433	0.409	0.429	0.162	0.312
ClinChem	**NK11-**			**NK33-**			**NK11+**			**NK33+**		
Females	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox
ALP	0.957	0.599	0.798	0.948	0.578	0.409	0.294	0.103	0.080	0.938	0.558	0.841
ALT	0.997	0.800	0.595	0.978	0.662	0.927	0.377	0.138	0.076	0.310	0.110	0.123
AST	1.000	0.954	0.984	0.333	0.119	0.133	0.995	0.774	0.674	0.036	0.010	0.027
BIL	0.478	0.185	0.490	0.728	0.331	0.622	0.879	0.469	0.498	1.000	0.907	0.841
ALB	0.994	0.759	0.829	0.996	0.780	0.522	1.000	0.884	0.927	0.793	0.382	0.546
TP	0.835	0.420	0.709	0.933	0.548	0.330	1.000	0.874	0.784	0.947	0.575	0.622
Glu	1.000	0.879	0.891	0.469	0.181	0.261	1.000	0.891	0.869	0.432	0.163	0.133
CHOL	0.957	0.597	0.465	0.318	0.113	0.123	0.147	0.047	0.058	0.532	0.212	0.277
TAG	0.953	0.588	0.798	0.205	0.068	0.030	0.045	0.013	0.064	0.844	0.429	0.498
Crea	0.315	0.112	0.145	0.945	0.571	0.368	0.153	0.049	0.040	0.586	0.242	0.349
Urea	0.938	0.557	0.515	0.993	0.753	0.812	0.893	0.487	0.231	0.177	0.058	0.048
cHGB	0.915	0.518	0.709	0.175	0.057	0.177	0.204	0.068	0.036	0.966	0.623	0.927
Ca	0.982	0.681	0.760	0.779	0.370	0.330	0.955	0.593	0.812	0.992	0.737	0.927
Cl	0.299	0.105	0.156	0.202	0.067	0.030	0.081	0.025	0.103	0.390	0.144	0.154
K	0.806	0.393	0.374	0.781	0.372	0.261	1.000	0.890	0.869	0.655	0.282	0.452
Na	0.258	0.089	0.055	0.240	0.082	0.015	0.131	0.041	0.016	0.141	0.045	0.024
P	0.566	0.230	0.210	0.082	0.025	0.008	0.965	0.620	0.418	0.462	0.177	0.202
Urine	**NK11-**			**NK33-**			**NK11+**			**NK33+**		
Females	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox
uVol	0.980	0.673	0.820	0.485	0.190	0.160	0.791	0.383	0.375	0.582	0.241	0.232
uVolW	0.987	0.706	0.910	0.539	0.217	0.232	0.675	0.297	0.275	0.559	0.228	0.275
uLeu	0.964	0.620	0.824	0.994	0.758	0.713	0.994	0.758	0.830	0.927	0.539	0.346
uOsmoll	0.954	0.593	0.820	0.547	0.222	0.232	0.406	0.152	0.084	0.260	0.090	0.084
uKeton	1.000	0.920	1.000	0.936	0.556	0.679	0.110	0.035	0.054	0.761	0.358	0.341
upH	0.227	0.077	0.054	0.999	0.871	0.931	0.728	0.333	0.254	0.999	0.871	0.672

Appendix 10. Tests for normality and homogeneity of variance

P-values for the Shapiro-Wilks (SW) normality test are given separately for each feeding group, and also for the ANOVA residuals. In addition P-values for Bartlett and Levene test for homogeneity of variance are given. P-values smaller than 0.01/0.05 have a gold/yellow background.

Male Weights	SW Control	SW NK11-	SW NK33-	SW NK11+	SW NK33+	SW residual	Bartlett	Levene
Weight_13	0.806	0.770	0.290	0.043	0.739	0.894	0.800	0.602
growthRate	0.719	0.998	0.233	0.662	0.614	0.440	0.054	0.251
FeedMean	0.419	0.467	0.584	0.806	0.944	0.529	0.492	0.377
Male Haematology	**SW Control**	**SW NK11-**	**SW NK33-**	**SW NK11+**	**SW NK33+**	**SW residual**	**Bartlett**	**Levene**
WBC	0.121	0.526	0.872	0.334	0.156	0.464	0.028	0.004
RBC	0.225	0.721	0.879	0.535	0.059	0.533	0.910	0.742
HGB	0.650	0.808	0.730	0.707	0.405	0.847	0.916	0.932
HCT	0.887	0.645	0.285	0.330	0.565	0.315	0.720	0.734
MCV	0.003	0.015	0.252	0.442	0.051	0.029	0.832	0.898
MCH	0.283	0.243	0.714	0.944	0.044	0.002	0.646	0.944
MCHC	0.987	0.194	0.090	0.836	0.341	0.255	0.331	0.652
PLT	0.253	0.141	0.002	0.293	0.456	0.364	0.039	0.523
LYMR	0.012	0.874	0.287	0.395	0.245	0.070	0.046	0.100
LYMA	0.088	0.374	0.431	0.195	0.137	0.780	0.115	0.105
Male ClinChem	**SW Control**	**SW NK11-**	**SW NK33-**	**SW NK11+**	**SW NK33+**	**SW residual**	**Bartlett**	**Levene**
ALP	0.504	0.641	0.836	0.081	0.468	0.960	0.408	0.466
ALT	0.297	0.850	0.638	0.482	0.781	0.329	0.251	0.367
AST	0.209	0.016	0.392	0.149	0.135	0.649	0.221	0.059
BIL	0.002	0.122	0.000	0.001	0.001	0.001	0.337	0.739
ALB	0.225	0.274	0.557	0.982	0.949	0.536	0.080	0.063
TP	0.398	0.719	0.413	0.468	0.848	0.538	0.205	0.085
Glu	0.580	0.220	0.148	0.855	0.405	0.328	0.894	0.548
CHOL	0.078	0.671	0.629	0.560	0.514	0.206	0.953	0.906
TAG	0.998	0.553	0.823	0.303	0.245	0.843	0.609	0.330
Crea	0.458	0.228	0.482	0.143	0.670	0.336	0.954	0.990

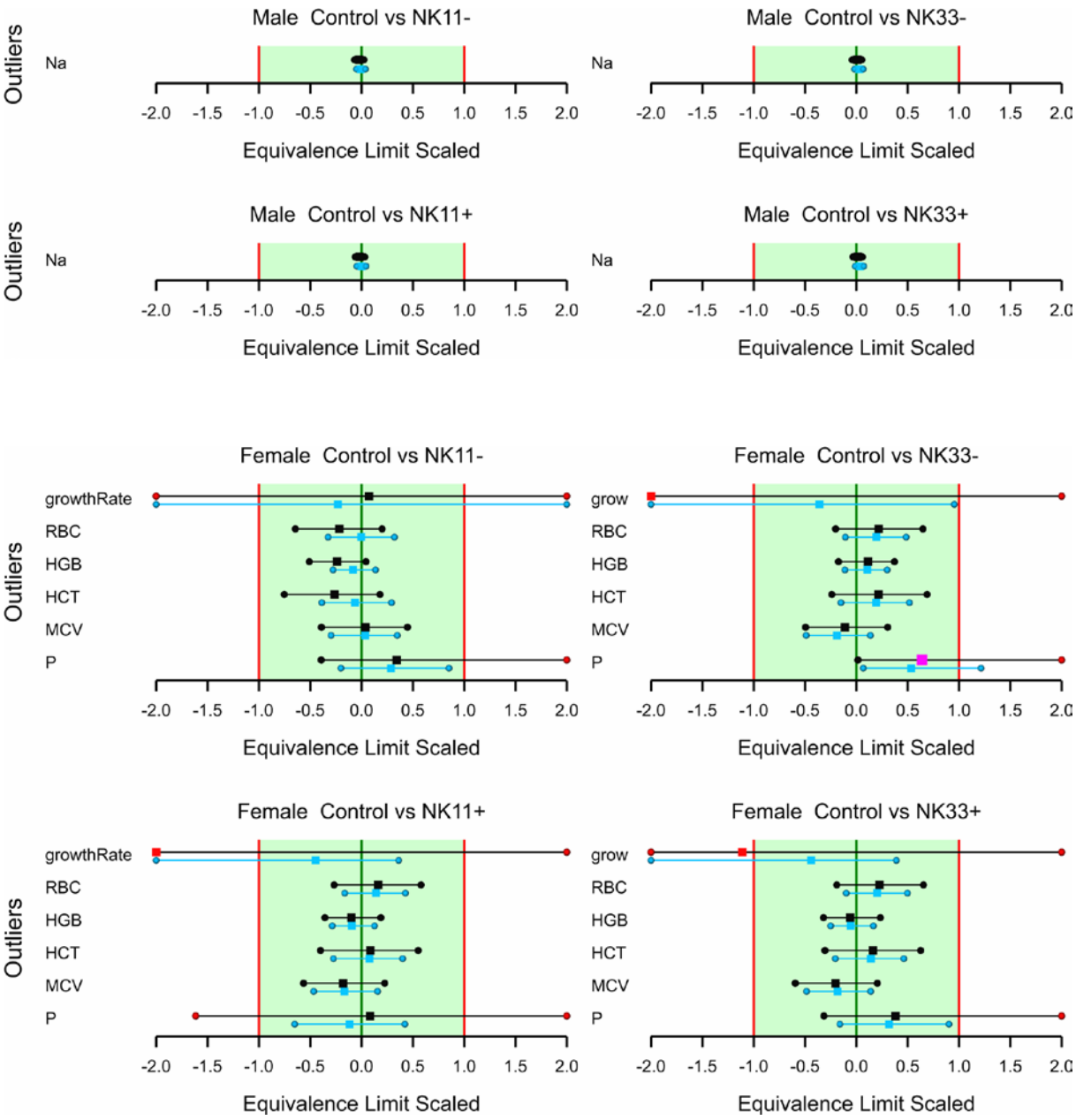
Urea	0.935	0.599	0.547	0.112	0.326	0.455	0.095	0.124
cHGB	0.412	0.850	0.059	0.096	0.036	0.306	0.591	0.767
Ca	0.496	0.665	0.738	0.775	0.004	0.079	0.968	0.933
Cl	0.190	0.273	0.452	0.664	0.850	0.308	0.071	0.016
K	0.002	0.112	0.003	0.012	0.000	0.001	0.267	0.449
Na	0.218	0.302	0.718	0.738	0.810	0.611	0.148	0.190
P	0.747	0.804	0.498	0.911	0.475	0.827	0.068	0.093
Male Urine	**SW Control**	**SW NK11-**	**SW NK33-**	**SW NK11+**	**SW NK33+**	**SW residual**	**Bartlett**	**Levene**
uVol	0.937	0.179	0.799	0.749	0.086	0.806	0.235	0.302
uVolW	0.899	0.062	0.795	0.694	0.032	0.572	0.694	0.621
uLeu	0.001	0.000	0.124	0.001	0.006	0.787	0.877	0.674
uOsmoll	0.993	0.559	0.208	0.605	0.067	0.786	0.689	0.842
uKeton	0.172	0.700	0.002	0.463	0.281	0.735	0.863	0.753
upH	0.008	0.017	0.000	0.152	0.074	0.178	0.003	0.074

Female Weights	**SW Control**	**SW NK11-**	**SW NK33-**	**SW NK11+**	**SW NK33+**	**SW residual**	**Bartlett**	**Levene**
Weight_13	0.852	0.884	0.992	0.679	0.392	0.326	0.823	0.784
growthRate	0.659	0.140	0.073	0.401	0.023	0.381	0.814	0.984
FeedMean	0.670	0.572	0.142	0.327	0.324	0.725	0.644	0.704
Female Haematology	**SW Control**	**SW NK11-**	**SW NK33-**	**SW NK11+**	**SW NK33+**	**SW residual**	**Bartlett**	**Levene**
WBC	0.551	0.013	0.739	0.975	0.687	0.635	0.064	0.049
RBC	0.940	0.145	0.017	0.807	0.119	0.343	0.780	0.972
HGB	0.012	0.978	0.013	0.011	0.102	0.349	0.984	0.968
HCT	0.349	0.593	0.136	0.629	0.236	0.319	0.139	0.317
MCV	0.006	0.840	0.190	0.513	0.000	0.109	0.407	0.438
MCH	0.001	0.000	0.001	0.000	0.935	0.078	0.614	0.914
MCHC	0.124	0.000	0.027	0.001	0.252	0.003	0.254	0.875
PLT	0.369	0.984	0.843	0.146	0.577	0.279	0.797	0.968
LYMR	0.187	0.285	0.059	0.178	0.512	0.022	0.265	0.230

LYMA	0.770	0.099	0.429	0.780	0.082	0.521	0.665	0.843
Female ClinChem	SW Control	SW NK11-	SW NK33-	SW NK11+	SW NK33+	SW residual	Bartlett	Levene
ALP	0.450	0.018	0.075	0.819	0.275	0.009	0.249	0.403
ALT	0.284	0.044	0.420	0.161	0.208	0.069	0.243	0.422
AST	0.447	0.379	0.735	0.763	0.410	0.013	0.547	0.253
BIL	0.293	0.305	0.001	0.061	0.171	0.016	0.291	0.810
ALB	0.998	0.130	0.385	0.049	0.048	0.812	0.058	0.075
TP	0.676	0.048	0.561	0.938	0.608	0.811	0.487	0.650
Glu	0.957	0.055	0.058	0.701	0.857	0.007	0.125	0.441
CHOL	0.975	0.106	0.545	0.923	0.798	0.856	0.528	0.720
TAG	0.249	0.253	0.056	0.863	0.600	0.416	0.130	0.210
Crea	0.043	0.763	0.832	0.279	0.020	0.342	0.628	0.695
Urea	0.620	0.377	0.596	0.984	0.429	0.137	0.100	0.055
cHGB	0.919	0.128	0.019	0.382	0.820	0.971	0.170	0.368
Ca	0.904	1.000	0.076	0.162	0.744	0.452	0.826	0.399
Cl	0.190	0.256	0.162	0.341	0.264	0.004	0.201	0.164
K	0.390	0.060	0.007	0.001	0.223	0.161	0.423	0.432
Na	0.386	0.665	0.822	0.036	0.371	0.488	0.737	0.817
P	0.070	0.272	0.131	0.722	0.000	0.232	0.185	0.600
Female Urine	**SW Control**	**SW NK11-**	**SW NK33-**	**SW NK11+**	**SW NK33+**	**SW residual**	**Bartlett**	**Levene**
uVol	0.014	0.534	0.374	0.937	0.224	0.854	0.669	0.404
uVolW	0.357	0.226	0.145	0.891	0.072	0.928	0.495	0.317
uLeu	0.002	0.000	0.001	0.001	0.000	0.114	0.632	0.307
uOsmoll	0.204	0.701	0.359	0.917	0.550	0.856	0.556	0.437
uKeton	0.000	0.000	0.000	0.086	0.002	0.180	0.214	0.101
upH	0.042	0.012	0.328	0.074	0.008	0.481	0.240	0.189

Appendix 11. Statistical analysis of data including outliers

For male animals there are outlying values for Na (2×), while for females there are outlying values for growthRate (3×), RBC (1×), HGB (1×), HCT (1×), MCV (1×), BIL (2×), cHGB (2×) and P (1×); see Table 6 for a list of outliers. The results of the equivalence tests, using the historical GRACE data, are given below; the black lines are for the analysis including outliers while the blue lines are for the analysis without outliers as in Figure 5 - Figure 8.



Results of the classical analysis without and with outliers are given in the tables below. Note that the top tables are identical to the values in Table 12 and Table 13.

Without Outliers	Control		NK11-			NK33-			NK11+			NK33+		
Males	Mean	CV	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig
Na	145.6	2.3	145.5	1.5		146.1	1.3		145.6	1.5		146.2	1.6	
With Outliers	**Control**		**NK11-**			**NK33-**			**NK11+**			**NK33+**		
Males	Mean	CV	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig
Na	146.0	2.5	145.5	1.5		146.1	1.3		145.6	1.5		146.2	1.6	

Without Outliers	Control		NK11-			NK33-			NK11+			NK33+		
Females	Mean	CV	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig
growthRate	0.195	20.8	0.189	25.9		0.185	25.4		0.183	23.2		0.184	25.1	
RBC	7.618	4.3	7.618	4.0		7.731	4.6		7.697	3.7		7.734	4.8	
HGB	15.51	3.8	15.42	3.4		15.61	3.7		15.41	3.4		15.44	3.3	
HCT	44.41	2.9	44.23	3.1		44.89	2.3		44.60	2.5		44.78	3.9	
MCV	58.41	3.9	58.38	2.6		57.97	3.3		58.01	2.6		57.97	3.0	
BIL	6.360	16.2	5.888	15.0		6.875	29.5		6.145	22.1		6.387	19.9	
cHGB	72.05	26.2	68.40	19.9		85.25	39.1		61.89	19.2	w	72.43	25.0	
P	1.780	18.8	1.865	13.7		2.002	16.2	tW	1.765	24.5		1.957	32.9	
With Outliers	**Control**		**NK11-**			**NK33-**			**NK11+**			**NK33+**		
Females	Mean	CV	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig
growthRate	0.195	20.8	0.195	35.0		0.185	25.4		0.183	23.2		0.189	28.5	
RBC	7.618	4.3	7.534	5.4		7.731	4.6		7.697	3.7		7.734	4.8	
HGB	15.51	3.8	15.30	4.7		15.61	3.7		15.41	3.4		15.44	3.3	
HCT	44.41	2.9	43.89	4.4		44.89	2.3		44.60	2.5		44.78	3.9	
MCV	58.41	3.9	58.38	2.6		58.17	3.8		58.01	2.6		57.97	3.0	
BIL	7.033	43.7	5.888	15.0		7.072	40.2		6.145	22.1		6.387	19.9	
cHGB	83.36	64.2	68.40	19.9		92.32	63.4		61.89	19.2	tw	72.43	25.0	
P	1.780	18.8	1.865	13.7		2.002	16.2	tW	1.865	32.9		1.957	32.9	

Conclusion: for males there are no difference between the analysis with and without outliers. For females there are hardly any differences; only for P equivalence cannot be established for any of the GM feeding groups.