

G-TwYST Study A

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

Statistical report, 24 months data

Paul W. Goedhart & Hilko van der Voet



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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 24 months.

Hazard and mortality after 24 months were considered as the primary variables of interest. For the hazard ratio no significant differences were found between the five feeding groups for both males and females. The estimated hazards of the 8 GM groups were in only in a minority of cases higher than the hazard of the Control group. However, in a factorial analysis on cages with male rats the hazard ratio for the two RoundUp groups was on average higher by a factor 1.73 than for the two GM groups without Roundup ($P=0.04$). With respect to mortality, a significant difference ($P=0.03$) was found in males between the Control group (36% mortality) and the GM group with 33% GM inclusion rate and RoundUp (54% mortality). This also showed up as a significantly higher average mortality in the two RoundUp groups compared to the two GM feeding groups without RoundUp (45% vs. 31%, $P=0.03$). For females, no significant differences were found, although in fact the GM feeding groups had estimated hazards and mortalities that were equal or better than for the non-GM feeding group. It can be noted that the test results have not been corrected for multiplicity: overall, among 32 tests for hazard ratios and 16 tests for mortality (male or female, feeding groups or factorial structure, animal or cage level), three tests (6%) resulted in a P-value (just) below 0.05, which is close to the theoretically expected rate of false positives (5%).

In addition to this primary analysis, data for animals still alive at 24 month were analysed. It was found that equivalence testing, in which differences in the current 24 months data were compared to historical 3 months data, was of little use due to the large variability in the current study as compared to the variability in the historical studies. 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 data obtained after 24 months. For all rats the time of death has been observed. Furthermore the following data have been obtained:

- Body weights and feed intake;
- Haematology, for those rats that survived for 24 months, and for a subset of rats that did not survive;
- Clinical biochemistry in blood, for rats that survived and for a subset of rats that did not survive;
- Clinical biochemistry in urine, only for part of the rats that survived for 24 months;
- Urine volume and colour, only for part of the rats that survived for 24 months;
- Organ weights as percentage of body weights, only for those rats that did not survive.

Note that data for the non-surviving rats can be used for inspection of potential reasons for not surviving until 24 month. However, data for the non-surviving rats cannot be combined with data for the surviving rats in a meaningful way. Therefore, in addition to the statistical analysis of survival and mortality for all rats, only data for animals that survived the experiment were statistically analysed.

This report is organised as follows. Section 2 describes the data obtained after 24 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 24 months in G-TwYST study A

The available files for the data obtained after 24 months in G-TwYST study A are given in Table 2. There are two “*Tab_7a*” and “*Tab_8a*” files, one file with Clinical Chemistry in Blood data for animals that survived for 24 months, and another file for animals that died prematurely. The latter file also

lists the time of premature death. Table 1 lists the number of animals in each feeding group which survived for 24 months. Most of the statistical analyses, tables and figures are based on these rats.

Table 1 Number of rats (#Rats) that survived for 24 months for each feeding group, and the number of cages with 0 rats that survived (#Cage0), with 1 rat that survived (#Cage1) and with two rats that survived (#Cage2). There were initially 50 rats in each group.

Group	Males				Females			
	#Rats	#Cage0	#Cage1	#Cage2	#Rats	#Cage0	#Cage1	#Cage2
Control	32	4	10	11	26	7	10	8
NK11-	36	2	10	13	24	8	10	7
NK33-	33	3	11	11	30	5	10	10
NK11+	32	2	14	9	31	3	13	9
NK33+	23	6	15	4	33	3	11	11

GenStat programs “24-Males.gen” and “24-Females.gen” were used to combine all the data into single Excel files, separately for males and females. Some endpoints were given as bounds; the endpoint, bound and number of such bounds 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, uGlu and uUrobilin is not very useful. Therefore, only the Urine variables uVol, uVolW, uLeu, uOsmoll, uProtein, uHemoglu, Keton and upH were statistically analysed.

Table 2 Data files for G-TwYST study A after 15/18/21/24 months.

Data files after 15 months (weights/feed intake)	Date	Time	Size (b)
Tab_1_G_TwYST_2yr st_A_15_mon_Body weight_Mal.xlsx	18-12-2017	13:58	109,999
Tab_2_G_TwYST_2yr st_A_15_mon_Body weight_Fem.xlsx	19-12-2017	10:25	118,318
Tab_3_G_TwYST_2yr st_A_15_mon_Feed cons_Mal.xlsx	19-12-2017	09:21	94,153
Tab_4_G_TwYST_2yr st_A_15_mon_Feed cons_Fem.xlsx	19-12-2017	10:50	103,538
Data files after 18 months (weights/feed intake)	Date	Time	Size (b)
Tab_1_G_TwYST_2yr st_A_18_mon_Body weight_Mal.xlsx	18-12-2017	14:00	100,875
Tab_2_G_TwYST_2yr st_A_18_mon_Body weight_Fem.xlsx	18-12-2017	14:40	107,086
Tab_3_G_TwYST_2yr st_A_18_mon_Feed cons_Mal.xlsx	19-12-2017	09:36	86,959
Tab_4_G_TwYST_2yr st_A_18_mon_Feed cons_Fem.xlsx	19-12-2017	11:18	97,443
Data files after 21 months (weights/feed intake)	Date	Time	Size (b)
Tab_1_G_TwYST_2yr st_A_21_mon_Body weight_Mal.xlsx	18-12-2017	14:03	111,196
Tab_2_G_TwYST_2yr st_A_21_mon_Body weight_Fem.xlsx	15-12-2017	12:14	118,349
Tab_3_G_TwYST_2yr st_A_21_mon_Feed cons_Mal.xlsx	19-12-2017	09:54	100,857
Tab_4_G_TwYST_2yr st_A_21_mon_Feed cons_Fem.xlsx	19-12-2017	11:40	108,226
Data files after 24 months	Date	Time	Size (b)
Tab_1_G_TwYST_2yr st_A_24_mon_Body weight_Mal.xlsx	18-12-2017	14:06	111,429
Tab_2_G_TwYST_2yr st_A_24_mon_Body weight_Fem.xlsx	18-12-2017	14:43	115,940
Tab_3_G_TwYST_2yr st_A_24_mon_Feed cons_Mal.xlsx	19-12-2017	10:10	104,550
Tab_4_G_TwYST_2yr st_A_24_mon_Feed cons_Fem.xlsx	19-12-2017	11:57	113,115
Tab_5_G_TwYST_2yr st_A_24_mon_Haematology_Mal.xlsx	23-10-2017	11:33	108,236
Tab_6_G_TwYST_2yr st_A_24_mon_Haematology_Femal.xlsx	23-10-2017	13:35	108,678

Tab_7a_G_TwYST_2yr st_A_24 mon_Clin_Chem_bl_Mal.xlsx	19-10-2017	13:12	118,558
Tab_7a_G_TwYST_2yr st_A_24 mon_Clin_Chem_bl_Mal_exit..xlsx	19-10-2017	13:49	115,411
Tab_7b_G_TwYST_2yr st_A_24 mon_Clin_Chem_ur_Mal.xlsx	23-10-2017	08:46	105,766
Tab_8a_G_TwYST_2yr st_A_24 mon_Clin_Chem_bl_Femal.xlsx	23-10-2017	09:05	116,559
Tab_8a_G_TwYST_2yr st_A_24 mon_Clin_Chem_bl_Fem_exit..xlsx	23-10-2017	09:05	114,517
Tab_8b_G_TwYST_2yr st_A_24 mon_Clin_Chem_ur_Femal.xlsx	23-10-2017	09:04	107,075
Tab_9_G_TwYST_2yr st_A_24 mon_Abs.org.w_exit_Mal.xlsx	05-12-2017	07:36	74,865
Tab_11_G_TwYST_2yr st_A_24 mon_Abs.org.w_exit_Fem.xlsx	05-12-2017	14:17	74,420
JT final Database - study A - hematology - euthanasia 6.2.18.xlsx	06-02-2017	14:56	53,917
Bl_ur_24 mon_G_TwYST_2yr st_A_Fem_tim.cour_NECR.xlsx	16-01-2018	12:21	148,392
Bl_ur_24 mon_G_TwYST_2yr st_A_Mal_tim.cour_NECR.xlsx	19-12-2017	13:54	150,638

Table 3 Number of animals which survived for 24 months 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	-	-	-	-	-	1	-	-
cHGB < 27.5	1	-	-	-	-	2	5	2	4	2
cHGB > 522.5	1	1	-	-	-	1	-	-	-	-
ALP < 0.17	-	1	1	-	-	1	-	1	1	-
Glu < 0.56	1	1	-	-	-	-	1	-	-	-

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

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, for animals that survived for 24 months, with only a limited set of observed values which are given in the heading of each sub-tables The table entries give the number of times each value occurs for male and female rats. Only uLeu, uProtein, uHemogl and uKeton were statistically analysed.

uColour	Missing	1	2	3		
Male	27	2	122	5		
Female	29	-	114	1		
uBil	Missing	0				
Male	27	129				
Female	29	115				
uLeu	Missing	0	25	100	500	
Male	27	-	3	7	119	
Female	29	12	14	32	57	
uNit	Missing	0				
Male	32	124				
Female	34	110				
uProtein	Missing	0.00	0.25	0.75	1.50	5.0
Male	27	6	6	3	27	87
Female	29	30	21	18	26	20
uGlu	Missing	1				
Male	27	129				
Female	29	115				
uHemogl	Missing	0	10	25	50	250
Male	27	90	11	5	6	17
Female	29	98	2	2	2	11
uKeton	Missing	0.0	0.5	1.5	5.0	
Male	27	63	32	34	-	
Female	29	36	39	38	2	
uUrobili	Missing	1				
Male	27	129				
Female	30	114				

2.2 Growth curves and feed intake

Appendix 1 displays the observed weights; larger symbols are used for those rats that survived for 24 months. It is evident that many rats are facing problems at the end of the experiment, or in the weeks before premature death. No general growth curves could be fitted, and therefore only the final weight for those animals that survived for 24 months were statistically analysed. The mean weight for each feeding group, only using animals that survived for 24 month, 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 depicted in Appendix 2. The mean feed consumption for each feeding group, again for those animals that survived for 24 months, is given in Figure 3.

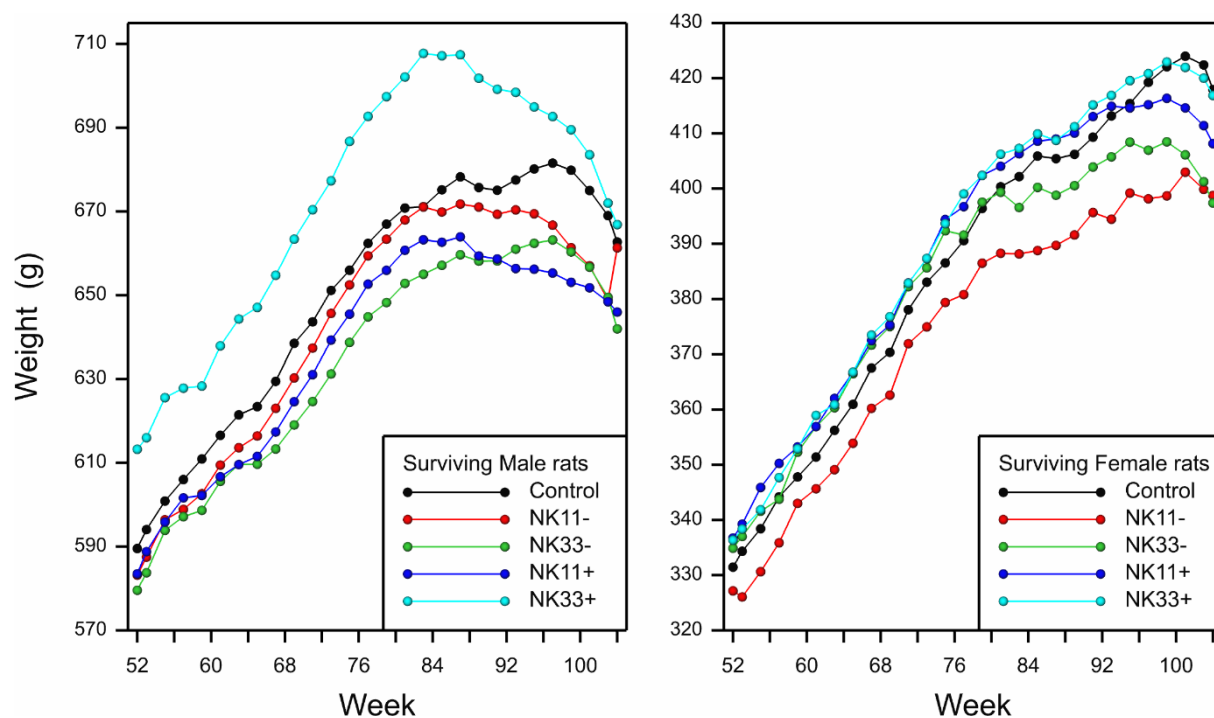


Figure 1 Mean body weights, based on those rats that survived for 24 months, versus week for each feeding group for male rats (left) and for female rats (right).

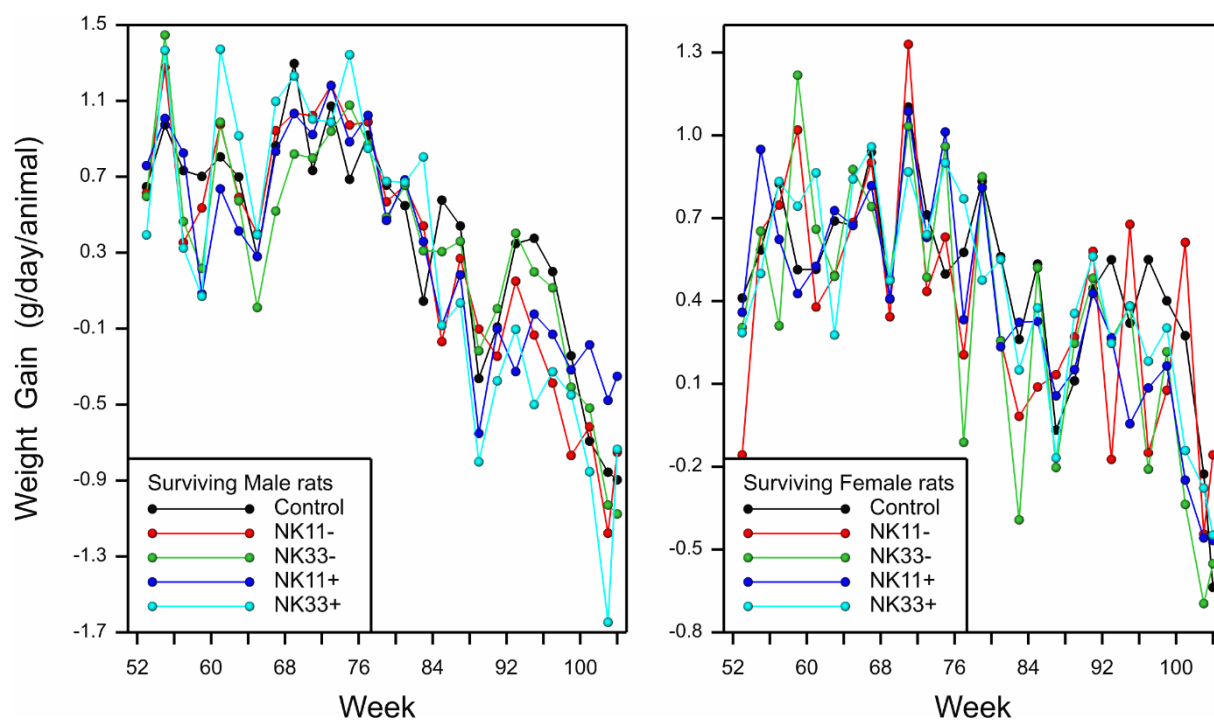


Figure 2 Mean body weights gain (g/day/animal) , based on rats that survived for 24 months, versus week for each feeding group for male rats (left) and for female rats (right).

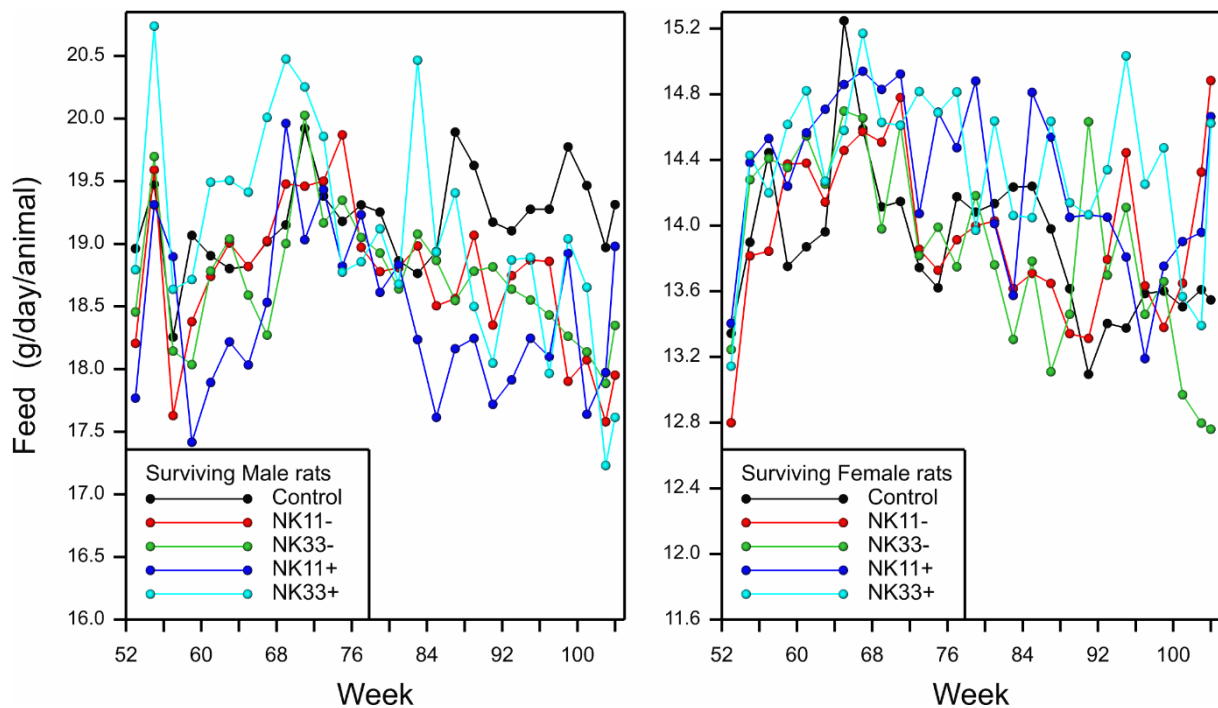


Figure 3 Mean feed consumption (g/day/animal) , based on rats that survived for 24 months, versus week for each feeding group for male rats (left) and for female rats (right).

2.3 Outliers and checking of ANOVA assumptions

These analyses and changes to the data were made before the feeding group codes were unblinded. Only data for animals that survived for 24 months were statistically analysed. Due to the resulting unequal number of animals and cages with 1 or 2 remaining animals per feeding group (Table 1), the individual data per rat, after a log-transformation, were statistically analysed to identify outliers. These analyses were performed by means of REML in GenStat (VSN International, 2015) employing random block and random cage effects within blocks. Note that for the 3, 6 and 12 months data, cage means rather than individual data were statistically analysed. 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 and Figure 5. 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
Males	Weight_52	32	16	635.62	635.12	Weight at start of this period must equal last weight in previous period
Males	Weight_52	102	51	568.12	568.62	Weight at start of this period must equal last weight in previous period
Males	Weight_69	139	70	599.19	559.19	Typo
Males	Weight_77	171	86	659	600.59	Weight at start of this period must equal last weight in previous period
Males	Weight_77	193	97	608.076	608.76	Weight at start of this period must equal last weight in previous period
Males	Weight_77	249	125	654.45	650.45	Weight at start of this period must equal last weight in previous period
Males	Weight_81	200	100	543.18	593.18	Typo
Males	Weight_97	115	58	369.04	639.04	Typo
Males	Weight_99	95	48	675.8	625.8	Typo
Males	Weight_104	130	65	308.24	outlier	Do not delete
Males	Weight_104	139	70	328.59	outlier	Do not delete
Males	RBC	315	158	4.79	outlier	Do not delete
Males	RBC	92	46	4.97	outlier	Do not delete
Males	RBC	162	81	5.23	outlier	Do not delete
Males	HGB	315	158	6.4	delete	Smaller than for 03/06/12 data
Males	HCT	315	158	23.5	delete	Smaller than for 03/06/12 data
Males	HCT	92	46	28.9	outlier	Do not delete
Males	HCT	162	81	29.7	outlier	Do not delete
Males	HCT	99	50	30.9	outlier	Do not delete
Males	HCT	242	121	67.1	delete	Extremely large
Males	MCV	110	55	48.3	outlier	Do not delete
Males	MCH	315	158	13.4	delete	Close to value for 03/06/12 data
Males	MCH	174	87	32.5	delete	Extremely large
Males	MCHC	315	158	27.2	delete	Delete
Males	MCHC	327	164	31	outlier	Do not delete
Males	MCHC	174	87	56.5	delete	Extremely large
Males	PLT	130	65	343	delete	Delete
Males	PLT	50	25	1950	delete	Delete
Males	LYMR	162	81	13.6	delete	Delete
Males	ALP	107	54	0.17	outlier	Do not delete
Males	ALT	107	54	0.08	delete	Extremely small
Males	ALT	130	65	5.92	outlier	Extremely large: Liver damage?
Males	ALT	242	121	6.18	outlier	Extremely large: Liver damage?

Males	AST	130	65	19.05	delete	Extremely large
Males	BIL	36	18	27.6	outlier	Do not delete
Males	BIL	91	46	39.3	outlier	Do not delete
Males	BIL	174	87	76	delete	Extremely large
Males	BIL	107	54	85.9	delete	Extremely large
Males	TP	130	65	49.8	outlier	Do not delete
Males	TP	139	70	50.5	outlier	Do not delete
Males	TP	92	46	55	outlier	Do not delete
Males	TP	174	87	96.1	delete	Delete
Males	TP	107	54	100.3	delete	Delete
Males	Glu	165	83	0.53	outlier	Do not delete
Males	Glu	130	65	0.56	outlier	Do not delete
Males	Glu	325	163	0.56	outlier	Do not delete
Males	Glu	36	18	0.7	outlier	Do not delete
Males	Glu	339	170	0.72	outlier	Do not delete
Males	TAG	334	167	48.02	delete	Extremely large
Males	Crea	92	46	167.4	outlier	Do not delete
Males	Crea	266	133	194	outlier	Do not delete
Males	Crea	182	91	339.5	outlier	Do not delete
Males	Crea	339	170	345.9	outlier	Do not delete
Males	Crea	345	173	418.3	outlier	Do not delete
Males	Crea	162	81	603.4	outlier	Do not delete
Males	Urea	59	30	15	outlier	Do not delete
Males	Urea	345	173	18.1	outlier	Do not delete
Males	Urea	92	46	20.19	outlier	Do not delete
Males	Urea	182	91	24.74	outlier	Do not delete
Males	Urea	339	170	30.18	outlier	Do not delete
Males	Urea	162	81	57.11	delete	Extremely large
Males	Ca	139	70	2.01	outlier	Do not delete
Males	Ca	345	173	3	outlier	Do not delete
Males	Ca	182	91	3.23	outlier	Do not delete
Males	Ca	162	81	3.69	outlier	Do not delete
Males	K	91	46	8.2	delete	Close to value for 03/06/12 data
Males	K	107	54	10	delete	Larger than for 03/06/12 data
Males	K	174	87	11.2	delete	Larger than for 03/06/12 data
Males	Na	130	65	154	outlier	Do not delete
Males	P	182	91	4.26	outlier	Do not delete
Males	P	339	170	5.04	outlier	Do not delete
Males	P	162	81	5.22	outlier	Do not delete
Males	upH	123	62	9	delete	Extremely large
Sex	Variable	Animal	Cage	oldValue	newValue	Comment
Females	Weight_61	547	524	427.63	407.63	Typo
Females	Weight_65	755	628	470.72	470.77	Weight at start of this period must equal last weight in previous period
Females	Weight_67	623	562	298.73	328.73	Typo
Females	Weight_67	676	588	342.07	432.07	Typo
Females	Weight_77	802	651	558.43	558.42	Weight at start of this period must equal last weight in previous period
Females	Weight_79	838	669	374.92	394.92	Typo

Females	Weight_83	595	548	434.68	454.68	Typo
Females	Weight_83	637	569	364.53	346.53	Typo
Females	Weight_83	638	569	317.42	327.42	Typo
Females	Weight_85	532	516	344.77	394.77	Typo
Females	Weight_87	544	522	372.23	332.23	Typo
Females	Weight_87	602	551	447.95	477.95	Typo
Females	Weights_95	661	581	407.05	437.05	Typo
Females	WBC	540	520	69.2	outlier	Do not delete
Females	WBC	737	619	92.2	delete	Delete
Females	WBC	548	524	96.9	delete	Delete
Females	RBC	548	524	2.71	delete	Smaller than for 03/06/12 data
Females	RBC	678	589	3.28	delete	Smaller than for 03/06/12 data
Females	RBC	737	619	4.37	delete	Smaller than for 03/06/12 data
Females	RBC	709	605	4.44	delete	Smaller than for 03/06/12 data
Females	HGB	678	589	6.5	delete	Smaller than for 03/06/12 data
Females	HGB	548	524	6.7	delete	Smaller than for 03/06/12 data
Females	HGB	540	520	7.7	delete	Smaller than for 03/06/12 data
Females	HGB	709	605	7.7	delete	Smaller than for 03/06/12 data
Females	HGB	664	582	9.2	outlier	Do not delete
Females	HGB	737	619	9.3	outlier	Do not delete
Females	HGB	690	595	10.4	outlier	Do not delete
Females	HGB	831	666	10.6	outlier	Do not delete
Females	HGB	845	673	20.3	outlier	Do not delete
Females	HCT	678	589	23.1	delete	Smaller than for 03/06/12 data
Females	HCT	548	524	24.8	delete	Smaller than for 03/06/12 data
Females	HCT	709	605	26	delete	Smaller than for 03/06/12 data
Females	HCT	664	582	27.7	outlier	Do not delete
Females	HCT	540	520	29.4	outlier	Do not delete
Females	HCT	831	666	30.3	outlier	Do not delete
Females	HCT	690	595	30.7	outlier	Do not delete
Females	MCV	678	589	70.4	outlier	Do not delete
Females	MCV	675	588	71.2	outlier	Do not delete
Females	MCV	763	632	74	outlier	Do not delete
Females	MCV	737	619	74.6	outlier	Do not delete
Females	MCV	548	524	91.5	delete	Extremely large
Females	MCH	540	520	14.8	outlier	Do not delete
Females	MCHC	540	520	26.2	outlier	Do not delete
Females	MCHC	548	524	27	outlier	Do not delete
Females	MCHC	678	589	28.1	outlier	Do not delete
Females	MCHC	737	619	28.5	outlier	Do not delete
Females	MCHC	709	605	29.6	outlier	Do not delete
Females	PLT	663	582	55	delete	Extremely small
Females	PLT	746	623	156	outlier	Do not delete
Females	PLT	846	673	164	outlier	Do not delete
Females	PLT	539	520	315	outlier	Do not delete
Females	LYMR	521	511	15.3	delete	Extremely small
Females	LYMA	699	600	20.8	delete	Extremely large
Females	ALP	831	666	4.13	delete	Extremely large
Females	ALT	663	582	0.24	outlier	Do not delete

Females	ALT	845	673	5.22	outlier	Extremely large: Liver damage?
Females	BIL	746	623	15.7	outlier	Do not delete
Females	BIL	846	673	42.8	outlier	Do not delete
Females	BIL	663	582	63.1	delete	Extremely large
Females	BIL	747	624	80.9	delete	Extremely large
Females	ALB	831	666	25.5	outlier	Do not delete
Females	ALB	540	520	25.8	outlier	Do not delete
Females	ALB	747	624	59.1	delete	Extremely large
Females	TP	771	636	53.9	outlier	Do not delete
Females	TP	747	624	102.6	outlier	Do not delete
Females	Glu	592	546	0.56	outlier	Do not delete
Females	Glu	699	600	0.71	outlier	Do not delete
Females	Glu	567	534	0.91	outlier	Do not delete
Females	Glu	737	619	1.27	outlier	Do not delete
Females	Ca	664	582	2.86	outlier	Do not delete
Females	K	663	582	7.9	delete	Close to value for 03/06/12 data
Females	K	747	624	9.9	delete	Larger than for 03/06/12 data
Females	uVol	754	627	2	outlier	Do not delete

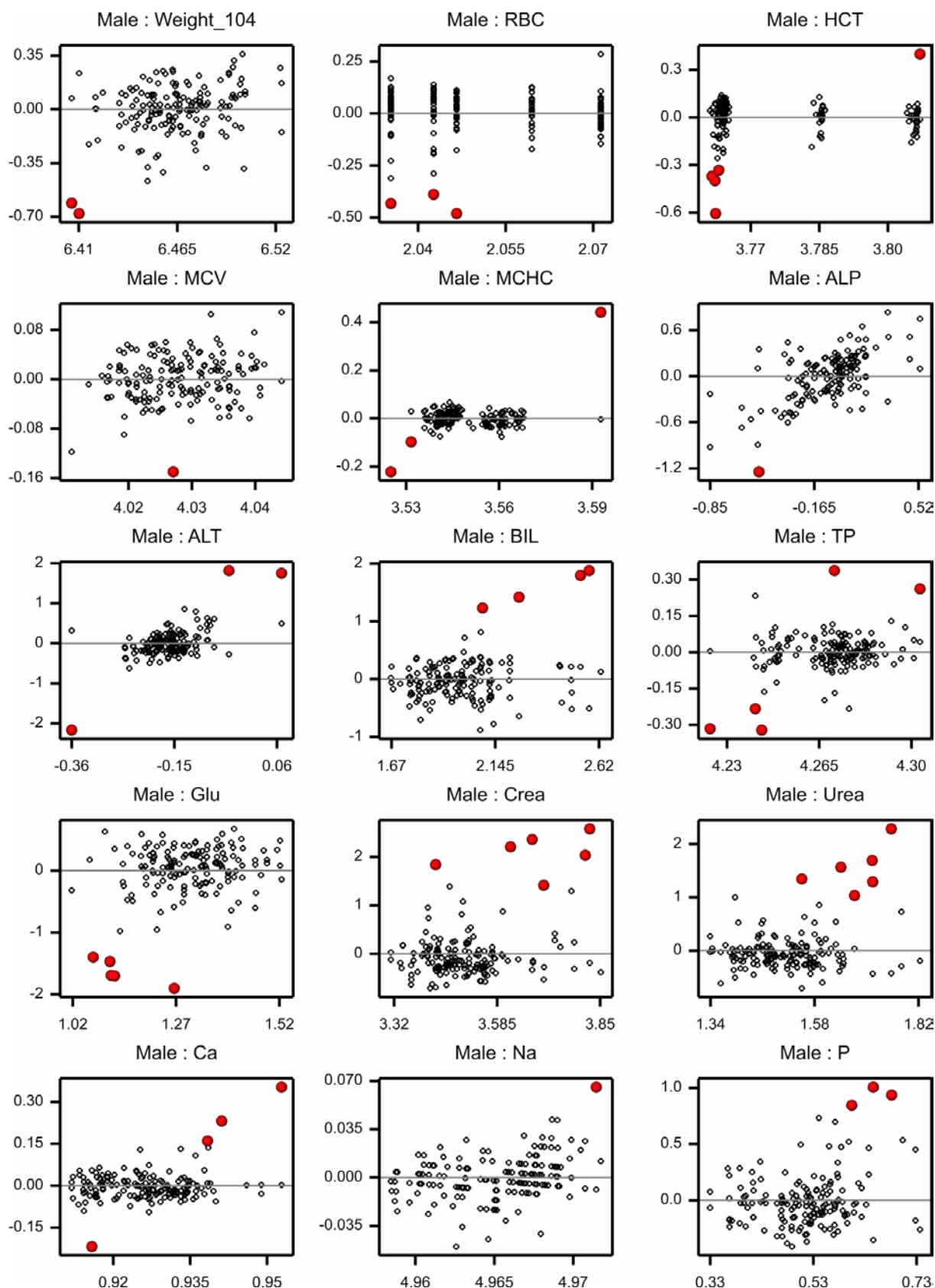


Figure 4 Residuals along the y-axis versus fitted values along the x-axis resulting from a REML analysis for Males on log-transformed individual data. Red symbols denote outliers found by sequentially applying Grubbs' outlier test at the 1% level to the residuals.

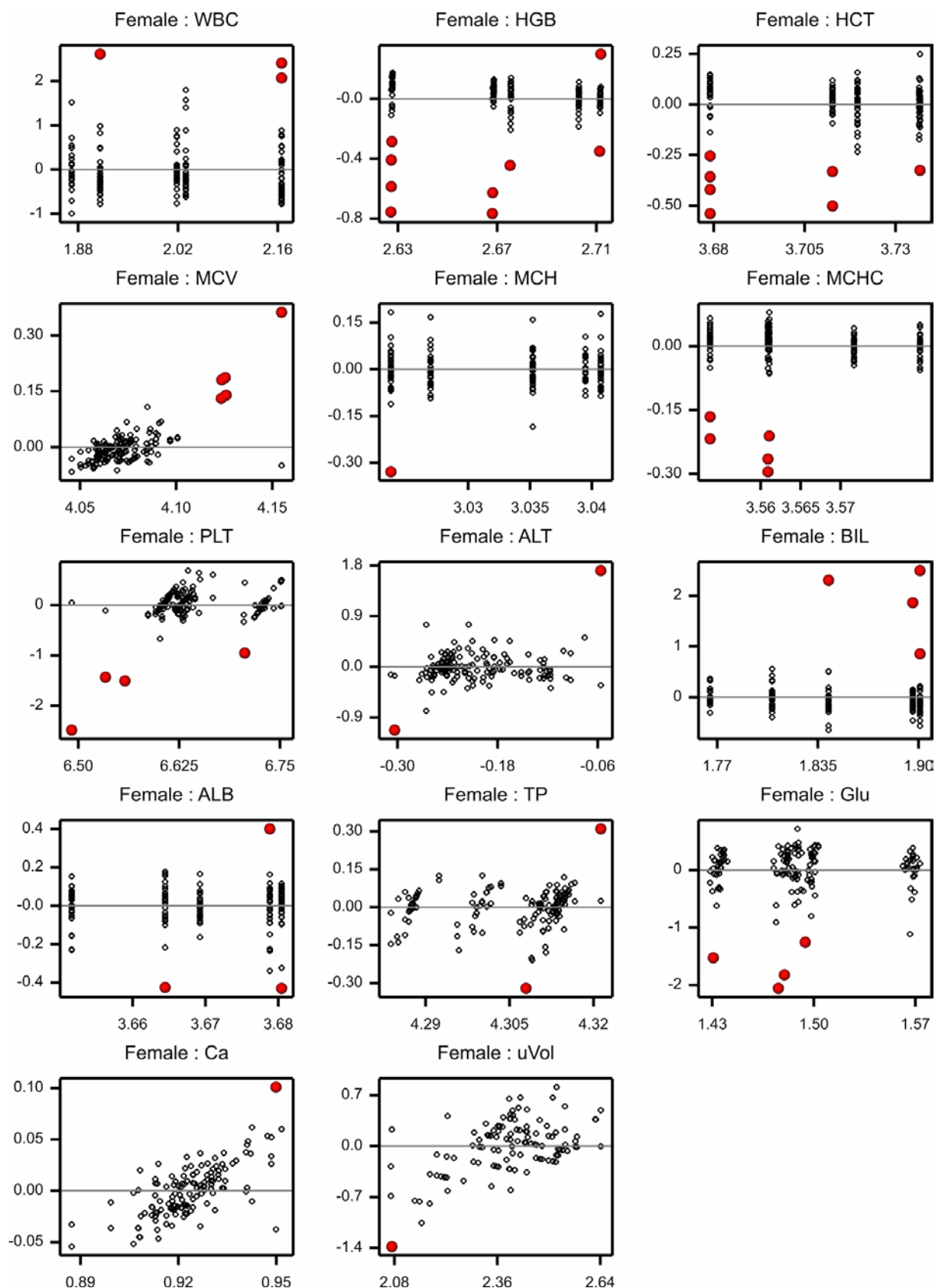


Figure 5 Residuals along the y-axis versus fitted values along the x-axis resulting from a REML analysis for Females on log-transformed individual data. Red symbols denote outliers found by sequentially applying Grubbs' outlier test at the 1% level to the residuals.

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 for weights, 20 for haematology, differential WBC and clinical biochemistry, and 10 for Urine data.

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 only employing rats that survived for 24 months.

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_104	21	656	104	15.9	23	659	76	11.5	22	644	59	9.2	23	634	85	13.4	19	654	126	19.3
FeedMean	21	19.1	1.16	6.1	23	18.8	1.57	8.3	22	18.9	1.60	8.5	23	18.2	1.48	8.1	19	19.7	2.11	10.7
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	21	9.4	3.57	37.8	23	9.9	4.82	48.7	21	8.6	2.97	34.5	23	9.8	3.39	34.6	19	11.2	5.70	51.0
RBC	20	7.89	0.42	5.3	23	7.76	0.63	8.1	21	7.96	0.50	6.2	23	7.86	0.69	8.7	19	7.88	0.61	7.8
HGB	20	15.4	0.90	5.8	23	15.0	1.33	8.9	21	15.6	0.90	5.8	23	15.3	1.27	8.3	19	15.5	1.16	7.5
HCT	20	44.1	2.50	5.7	22	44.2	2.70	6.1	21	44.5	1.95	4.4	23	43.9	3.27	7.4	19	44.2	3.32	7.5
MCV	21	55.6	2.10	3.8	23	56.5	1.57	2.8	21	56.6	2.09	3.7	23	56.0	1.59	2.8	19	56.2	1.86	3.3
MCH	20	19.5	0.76	3.9	23	19.5	0.71	3.7	21	19.6	0.90	4.6	23	19.5	0.86	4.4	19	19.7	0.96	4.9
MCHC	20	34.9	0.77	2.2	23	34.6	0.67	1.9	21	34.7	0.86	2.5	23	34.8	0.76	2.2	19	35.1	0.86	2.4
PLT	21	827	118	14.3	23	850	87	10.2	21	881	187	21.3	23	867	193	22.2	17	859	146	17.0
LYMR	19	58.4	13.5	23.2	22	61.5	14.1	22.9	21	61.0	12.1	19.7	22	61.1	11.8	19.3	15	56.9	13.9	24.5
LYMA	19	4.68	1.84	39.3	22	5.14	1.59	30.9	21	5.04	2.03	40.3	22	5.31	1.50	28.3	15	4.75	1.54	32.4
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	21	1.09	0.44	40.6	23	1.18	0.56	47.3	21	0.95	0.35	37.1	23	1.00	0.32	31.5	19	0.84	0.23	27.0
ALT	21	0.83	0.17	20.3	23	0.90	0.30	33.6	21	0.88	0.26	29.2	23	0.88	0.24	26.8	19	0.90	0.27	30.3
AST	21	2.60	0.66	25.4	23	3.05	0.94	31.0	21	2.73	0.66	24.3	23	2.85	0.95	33.3	19	2.80	0.82	29.5
BIL	21	7.42	2.75	37.0	23	7.71	2.82	36.5	21	7.70	2.57	33.4	23	7.23	2.28	31.5	18	6.78	1.94	28.6
ALB	21	35.8	3.43	9.6	23	36.1	4.04	11.2	21	37.7	2.15	5.7	23	37.2	4.13	11.1	19	36.0	3.11	8.6
TP	21	71.3	3.71	5.2	23	71.8	4.79	6.7	21	72.4	3.11	4.3	23	71.7	4.61	6.4	19	71.7	3.74	5.2
Glu	19	4.18	1.10	26.2	23	4.26	1.08	25.4	21	4.36	1.15	26.4	23	4.08	1.12	27.6	18	3.94	1.26	32.0
CHOL	21	4.59	1.60	34.8	23	4.31	2.01	46.6	21	4.03	1.14	28.3	23	4.31	1.98	45.9	19	4.72	1.87	39.7
TAG	21	2.08	0.95	45.8	23	2.62	1.26	48.2	21	2.25	0.88	39.2	23	2.40	1.52	63.4	19	2.52	1.47	58.5
Crea	20	30.4	6.9	22.6	23	35.2	22.6	64.1	21	31.0	12.9	41.5	22	30.7	9.2	30.1	19	41.9	33.4	79.8
Urea	20	4.03	0.72	17.8	23	5.00	1.92	38.4	21	4.32	1.12	25.9	22	4.42	0.91	20.5	18	4.35	1.18	27.0
cHGB	21	107	81	75.9	23	143	76	53.4	21	111	47	42.1	23	115	67	57.9	19	135	112	83.1

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Ca	21	2.53	0.09	3.4	23	2.54	0.12	4.9	21	2.51	0.08	3.2	22	2.49	0.06	2.2	19	2.54	0.11	4.3
Cl	21	102	1.83	1.8	23	102	1.64	1.6	21	102	1.58	1.5	23	103	2.13	2.1	19	102	2.48	2.4
K	21	4.61	0.40	8.7	23	4.72	0.49	10.3	21	4.60	0.27	6.0	23	4.85	0.43	8.8	19	4.69	0.41	8.7
Na	21	143	1.48	1.0	23	143	2.24	1.6	21	144	1.49	1.0	23	144	2.19	1.5	19	143	2.27	1.6
P	20	1.67	0.36	21.5	23	1.81	0.41	22.7	21	1.52	0.26	16.9	22	1.64	0.30	18.5	19	1.83	0.62	33.8
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	16	12.0	4.45	37.0	18	12.6	4.36	34.6	19	9.4	2.50	26.7	20	12.4	5.22	42.0	19	12.5	4.32	34.5
uVolW	16	1.80	0.64	35.4	18	2.06	0.86	41.7	19	1.46	0.41	28.3	20	1.95	0.80	40.8	19	1.94	0.77	39.5
uLeu	16	488	50	10.3	18	476	71	14.9	19	489	46	9.4	20	412	168	40.8	19	489	46	9.4
uOsmoll	16	739	154	20.8	18	713	172	24.2	19	798	116	14.6	20	711	237	33.3	19	755	239	31.6
uProtein	16	3.76	1.41	37.6	18	3.75	1.57	41.8	19	3.68	1.73	47.0	20	3.60	2.06	57.2	19	4.05	1.50	37.0
uHemogl	16	39.4	75.1	190.7	18	37.5	66.2	176.7	19	30.7	65.7	214.3	20	33.4	79.1	236.9	19	44.7	82.7	184.9
uKeton	16	0.38	0.50	133.3	18	0.50	0.55	109.8	19	0.64	0.54	83.1	20	0.47	0.63	132.2	19	0.83	0.68	82.3
upH	16	6.16	0.42	6.8	18	6.28	0.55	8.7	19	6.21	0.44	7.0	20	6.22	0.40	6.4	19	6.33	0.29	4.6

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 only employing rats that survived for 24 months.

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_104	18	418	62.7	15.0	17	398	61.1	15.4	20	398	59.5	15.0	22	405	54.9	13.6	22	418	71.2	17.0
FeedMean	18	14.1	0.91	6.5	17	14.1	1.02	7.2	20	14.0	0.81	5.8	22	14.0	0.96	6.8	22	14.5	1.05	7.2
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	17	7.8	5.9	75.0	17	7.8	2.6	33.7	19	6.9	3.4	50.1	22	10.4	10.2	97.8	22	8.1	3.6	44.0
RBC	17	7.19	0.57	8.0	17	7.15	0.45	6.3	19	7.19	0.68	9.4	21	7.08	0.77	10.9	22	7.26	0.50	6.9
HGB	16	15.2	0.56	3.7	17	14.9	0.84	5.6	19	14.8	0.87	5.9	21	15.0	1.09	7.3	22	15.1	0.67	4.4
HCT	16	42.6	2.62	6.1	17	42.0	2.82	6.7	20	41.3	2.84	6.9	21	42.2	2.81	6.7	22	42.1	1.75	4.2
MCV	17	58.2	1.91	3.3	17	58.8	2.09	3.6	18	57.6	2.30	4.0	20	58.5	1.77	3.0	22	57.7	1.66	2.9
MCH	17	20.9	0.81	3.9	17	20.9	0.87	4.2	20	20.8	1.24	6.0	22	20.8	1.19	5.7	22	20.8	0.99	4.8
MCHC	17	35.8	0.59	1.6	17	35.6	0.90	2.5	19	35.5	1.02	2.9	21	35.5	0.93	2.6	22	35.8	0.72	2.0
PLT	17	784	102	13.0	17	763	165	21.7	19	837	168	20.0	22	842	199	23.6	22	889	190	21.3
LYMR	16	56.8	9.1	16.0	16	55.2	10.3	18.8	18	56.5	9.4	16.6	19	57.5	10.6	18.4	21	56.8	9.8	17.3
LYMA	16	3.47	1.29	37.1	16	4.11	1.58	38.5	18	3.23	0.89	27.4	19	3.44	0.86	25.1	22	3.72	1.36	36.4
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	16	0.58	0.18	31.2	17	0.56	0.17	30.6	20	0.60	0.18	29.6	22	0.59	0.12	21.0	22	0.55	0.12	21.2
ALT	17	0.85	0.23	26.5	17	0.80	0.17	20.6	20	0.81	0.15	18.2	22	0.83	0.15	18.2	22	0.83	0.16	19.6
AST	17	3.15	0.98	31.2	17	2.92	0.76	26.1	20	3.27	0.68	20.7	22	3.21	0.86	26.8	22	3.10	0.68	22.1
BIL	17	6.20	0.90	14.5	17	5.90	0.96	16.2	19	6.01	0.88	14.7	22	5.90	1.47	25.0	22	6.15	1.05	17.1
ALB	16	40.0	2.84	7.1	17	39.5	2.26	5.7	20	39.6	2.49	6.3	22	38.8	2.44	6.3	22	40.1	2.42	6.0
TP	17	73.8	4.58	6.2	17	74.8	3.98	5.3	20	75.6	3.53	4.7	22	73.0	3.76	5.1	22	74.9	3.46	4.6
Glu	17	4.96	0.86	17.4	17	5.19	1.20	23.1	19	4.75	1.01	21.3	22	4.81	1.16	24.1	22	4.58	0.87	19.0
CHOL	17	3.19	0.76	23.8	17	3.29	1.74	52.7	20	2.97	0.87	29.2	22	2.76	0.80	29.1	22	3.31	1.14	34.3
TAG	17	1.32	0.47	35.3	17	1.48	0.65	43.8	20	1.18	0.47	39.9	22	1.39	0.69	49.9	22	1.60	1.58	98.8
Crea	17	32.4	4.13	12.8	17	35.2	3.65	10.4	20	37.5	6.27	16.7	22	35.7	5.26	14.7	22	36.6	5.37	14.7
Urea	17	4.67	0.61	13.0	17	4.82	0.83	17.3	20	4.98	0.67	13.5	22	4.93	0.78	15.9	22	4.67	0.75	16.0
cHGB	17	87.5	76.5	87.5	17	74.8	27.5	36.7	20	79.2	43.4	54.8	22	78.9	42.3	53.6	22	93.0	74.9	80.6
Ca	17	2.51	0.064	2.6	17	2.54	0.093	3.7	20	2.53	0.079	3.1	22	2.51	0.055	2.2	22	2.51	0.085	3.4

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Cl	17	97.3	2.31	2.4	17	96.2	2.51	2.6	20	97.1	2.94	3.0	22	97.1	2.64	2.7	22	96.6	2.52	2.6
K	17	4.34	0.34	7.9	17	3.99	0.39	9.9	20	4.31	0.49	11.4	22	4.43	0.50	11.4	22	4.32	0.45	10.3
Na	17	142	2.03	1.4	17	142	2.73	1.9	20	143	2.05	1.4	22	142	2.16	1.5	22	141	1.85	1.3
P	17	1.53	0.22	14.4	17	1.50	0.29	19.2	20	1.71	0.41	24.3	22	1.62	0.22	13.4	22	1.48	0.25	16.9
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	17	11.7	3.09	26.4	15	12.3	6.41	52.2	18	12.0	3.88	32.4	18	10.7	4.51	42.3	17	13.2	3.22	24.4
uVolW	17	2.79	0.62	22.3	15	3.12	1.48	47.4	18	2.93	0.94	32.1	18	2.68	1.20	44.7	17	3.28	1.12	34.2
uLeu	17	242	208	85.8	15	275	203	73.9	18	268	194	72.5	18	303	214	70.6	17	283	225	79.6
uOsmoll	17	671	175	26.1	15	641	300	46.8	18	647	162	25.0	18	694	173	24.9	17	595	113	19.1
uProtein	17	0.64	0.67	105.4	15	1.61	1.65	102.6	18	1.63	1.83	112.4	18	1.58	2.00	126.1	17	1.36	1.70	124.9
uHemogl	17	36.8	85.7	233.2	15	8.3	32.3	387.3	18	23.9	66.6	278.7	18	37.8	83.1	220.0	17	15.4	41.3	267.8
uKeton	17	0.97	1.17	120.1	15	0.58	0.63	108.3	18	0.86	0.87	100.7	18	0.92	0.56	60.6	17	0.62	0.55	89.5
upH	17	5.82	0.50	8.6	15	6.17	0.59	9.5	18	6.25	0.39	6.3	18	5.94	0.66	11.0	17	6.00	0.48	8.1

3 Statistical analysis

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

3.1 Survival at 24 months

Kaplan-Meier estimates of the survival curves per sex and per feeding group based on individual rats, and based on cages, are given in Figure 6. The event for a cage was defined as the day at which the first animal died. This latter event respects the fact that cage is the experimental unit.

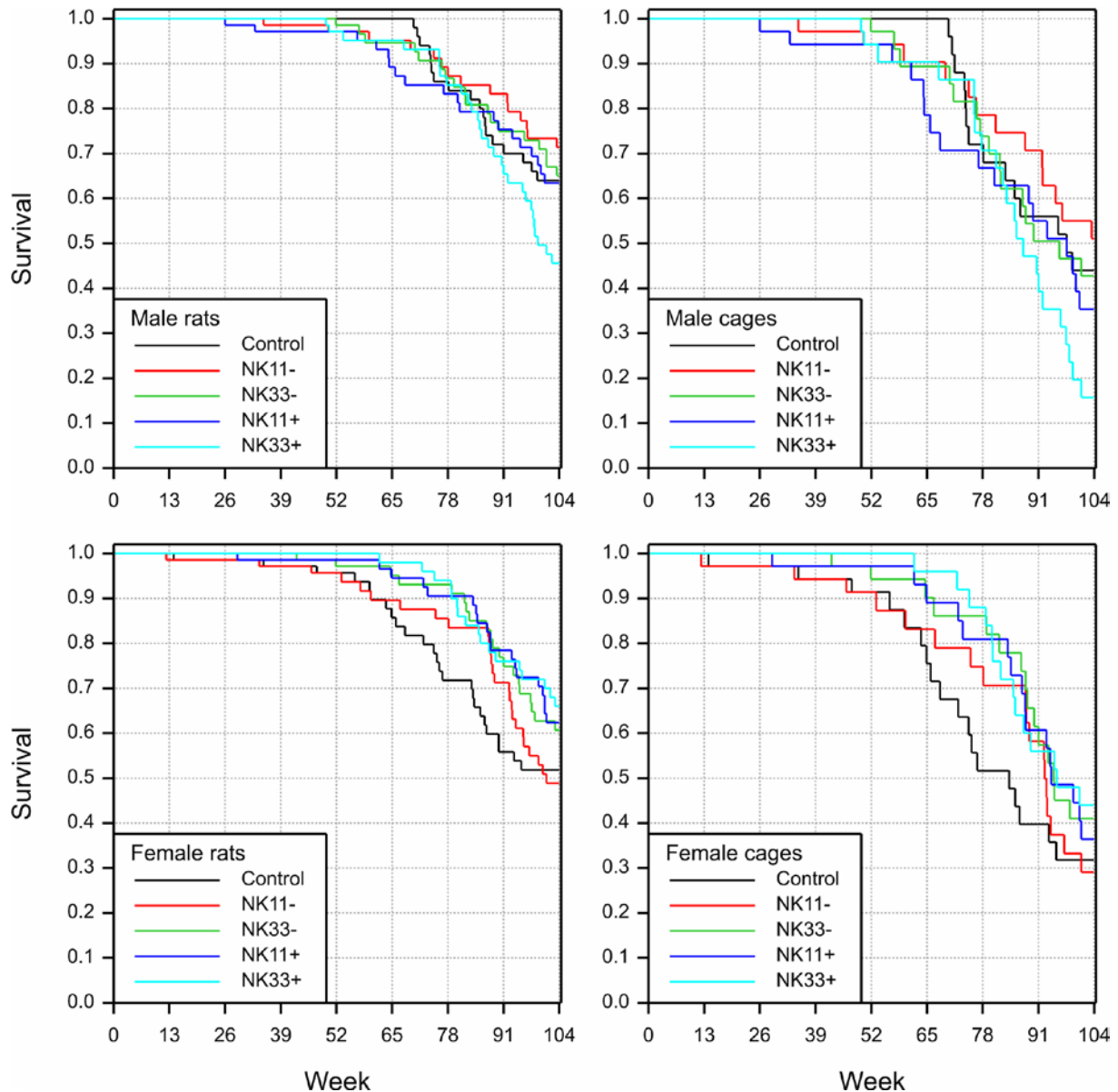


Figure 6 Kaplan-Meier estimates of the survival curves for all 350 rats per sex (left figures), and for cages (right figures) where the event per cage is the day of death of the first animal.

P-values of four overall tests, testing the null hypothesis that the survival curves are identical, are given in Table 9. According to these tests, which do not account for differences between blocks, there were no significant differences between the survival curves at the 5% level. On a more detailed

level, employing the proportional hazards model, the null hypothesis was tested whether the hazard ratio of each of the four GM feeding groups relative to the control non-GM group was equal to or smaller than one. The hazard ratios, one-sided lower confidence limits and P-values are given in Table 10, and the hazard ratios relative to the control non-GM group are graphically depicted in Figure 7. The null hypothesis is never rejected although the estimated hazard ratio for NK33+ in males (animals and cages) is somewhat large. Note that for 12 of the 16 tests performed, including all tests in females, the hazard ratio is smaller than one suggesting that the GM feeding groups would more likely have a better than worse survival rate.

Table 9 P-values for significance tests of equality of survival curves.

Overall significance test	Males		Females	
	Animal	Cage	Animal	Cage
Log-rank	0.132	0.165	0.179	0.451
Wilcoxon (Breslow)	0.244	0.398	0.079	0.181
Tarone-Ware	0.179	0.270	0.118	0.279
Wilcoxon (Peto-Prentice)	0.223	0.382	0.095	0.199

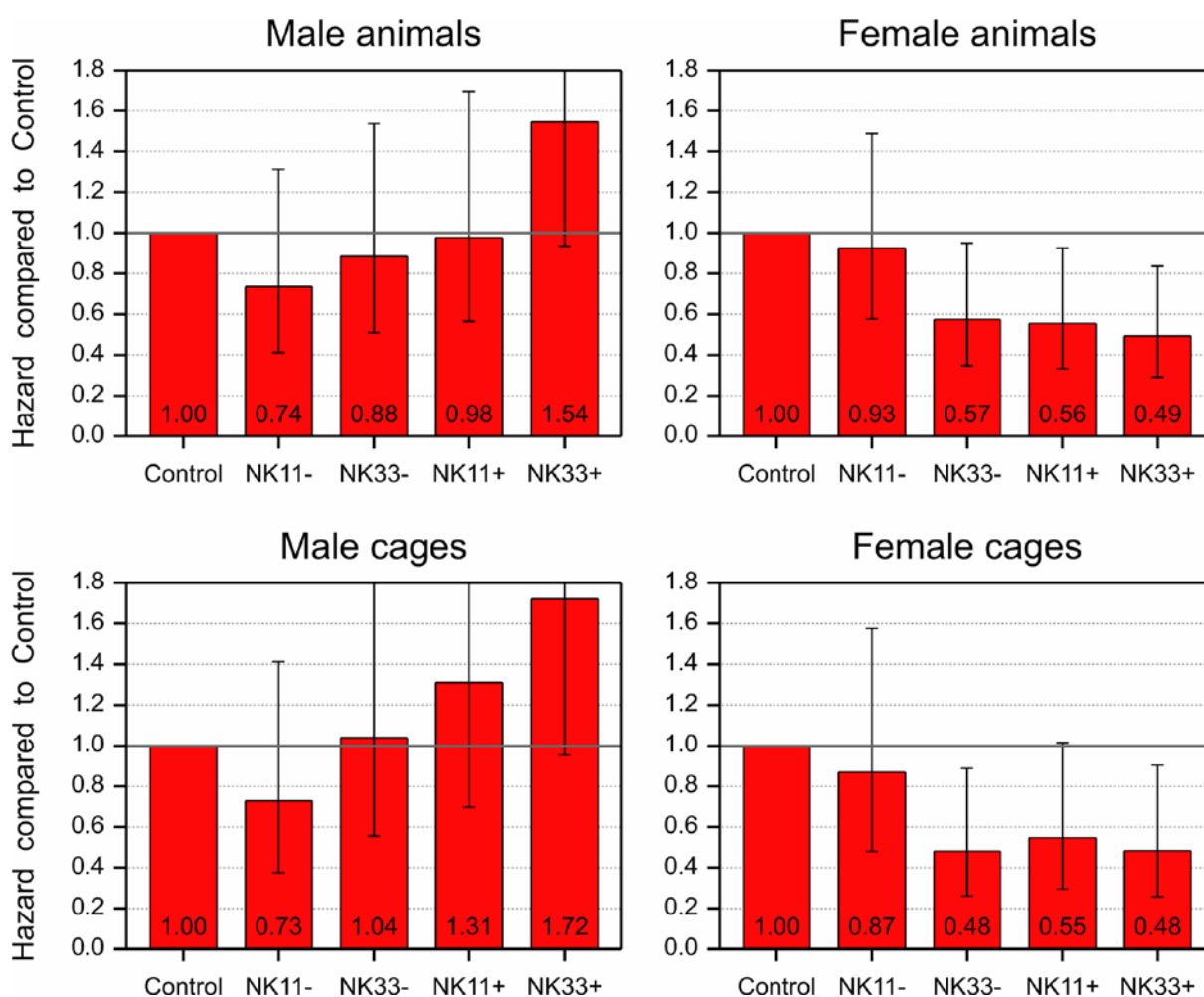


Figure 7 Hazard ratios according to the proportional hazards model relative to the hazard of the control non-GM feeding group. 90% confidence intervals for hazard ratios are indicated by error bars. The hazard ratio is also given at the bottom of each bar.

Table 10 Hazard ratios for GM feeding groups versus the control non-GM group, lower one-sided confidence limits for the hazard ratio and P-values for the one-sided null hypothesis that the hazard ratio is equal to or smaller than one.

Feed	Male animals			Female animals		
	Hazard ratio	Lower 95% CI limit	P-value	Hazard ratio	Lower 95% CI limit	P-value
NK11-	0.735	0.412	0.809	0.926	0.576	0.605
NK33-	0.884	0.509	0.643	0.574	0.347	0.965
NK11+	0.977	0.564	0.528	0.555	0.332	0.971
NK33+	1.545	0.935	0.077	0.493	0.291	0.986
Feed	Male cages			Female cages		
	Hazard ratio	Lower 95% CI limit	P-value	Hazard ratio	Lower 95% CI limit	P-value
NK11-	0.728	0.376	0.784	0.870	0.480	0.650
NK33-	1.039	0.555	0.460	0.482	0.261	0.975
NK11+	1.311	0.697	0.241	0.548	0.296	0.946
NK33+	1.720	0.953	0.065	0.483	0.258	0.972

In addition a factorial analysis has been performed employing chi-squared likelihood ratio testing in the proportional hazards model. P-values of these two-sided tests are given in Table 11, and factorial effects are graphically depicted in Figure 8. There are indications that there is an effect of Roundup in males (P-values equal to 0.053 and 0.037). The ratio of the hazard for Roundup GM feeds versus non-Roundup GM feeds is estimated by 1.52 for male animals and 1.73 for male cages. This indicates that the non-Roundup GM feeds have a better survival rate. There is also an indication that in females the GM feeds could have a better survival rate than the non-GM control feed (P-values equal to 0.053 and 0.065). The estimated hazard ratio for the GM feeds versus the control feed equals 0.62 for female animals and 0.58 for female cages.

Table 11 P-values for factorial tests of equality of hazard ratios.

Overall significance test	Males		Females	
	Animal	Cage	Animal	Cage
GM versus non-GM control	0.933	0.622	0.053	0.065
GM inclusion rate	0.130	0.235	0.157	0.162
Roundup	0.053	0.037	0.117	0.342
Interaction Inclusion.Roundup	0.556	0.874	0.427	0.397

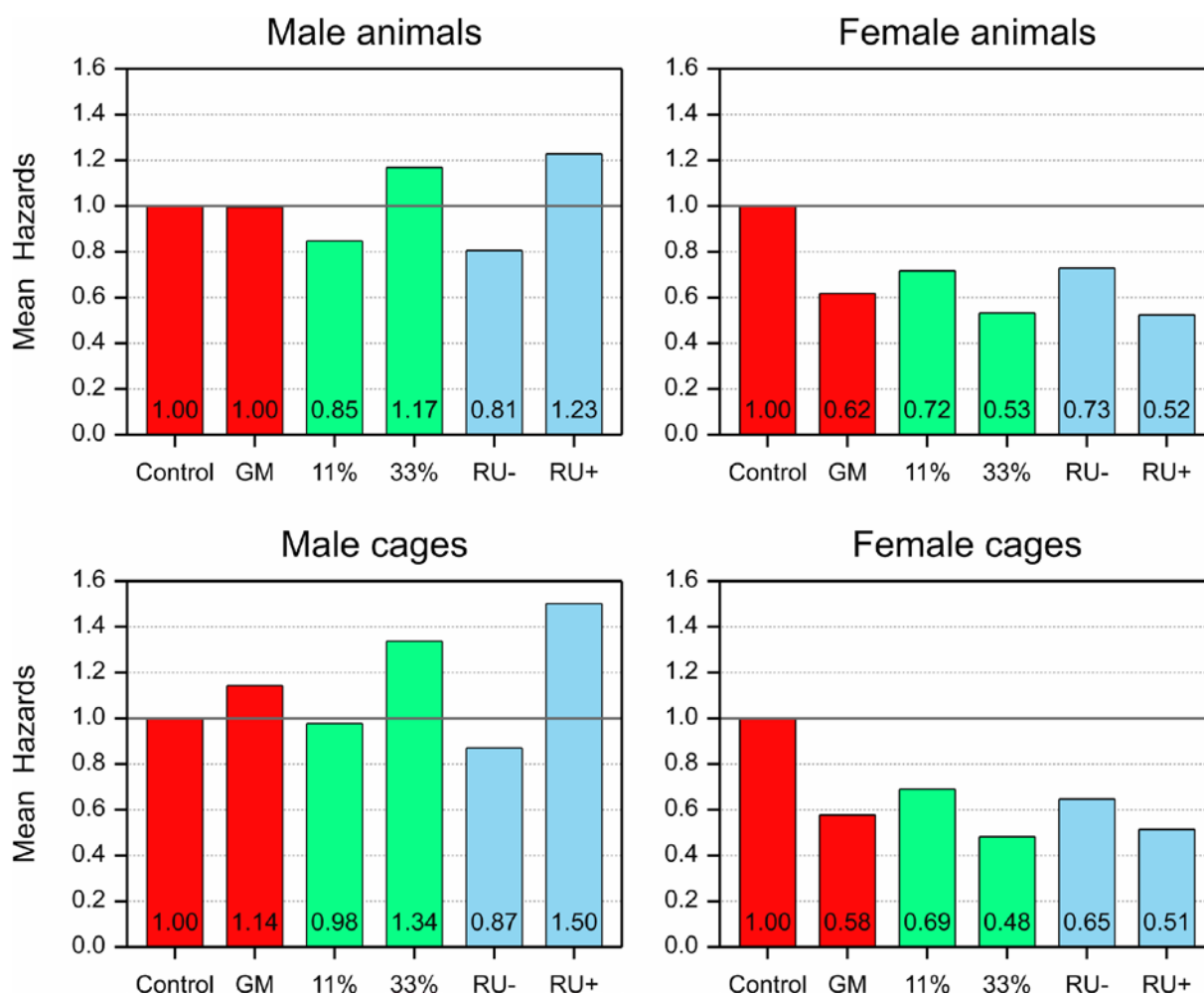


Figure 8 Mean hazard ratios for the overall GM versus non-GM control (red bars), for the 11% and 33% GM inclusion rates (green bars), and for the GM feeds without Roundup (RU-) and with Roundup (RU+, blue bars).

3.2 Mortality at 24 months

In this analysis only the 50 animals per sex and feeding group that were part of the 2-year cohort were statistically analysed. The percentages of dead animals at 24 months in each group are given in Figure 9. Male animals in feeding group NK33+ seem to have a somewhat higher mortality as compared to the other feeding groups in males.

Fitting the beta-binomial regression model to the number of dead animals in each cage as response variable revealed that the estimate of the over-dispersion parameter ϕ equals its bounded value of 0.0001 (males and females). This indicates that there was no over-dispersion and therefore the ordinary logistic model was used to analyse the number of dead animals per cage. After allowing for differences between blocks one-sided pairwise Wald tests were performed with null hypothesis that the mortality probability of a GM feed is smaller than the mortality probability of the non-GM control feed. The P-values of these one-sided tests are given in Table 12. There is an indication ($P=0.029$) that the mortality rate for NK33+ in males is larger than for the control non-GM feed.

P-values for the factorial analysis, employing chi-squared likelihood ratio testing in the logistic regression model, are given in Table 13. This reveals that there is an indication for a GM inclusion

rate effect ($P=0.062$) and for a Roundup effect ($P=0.030$) in males. The mean percentages dead for GM inclusion rates 11% and 33% were 32% and 44% respectively, while for without Roundup and with Roundup the mean percentages are 31% and 45%.

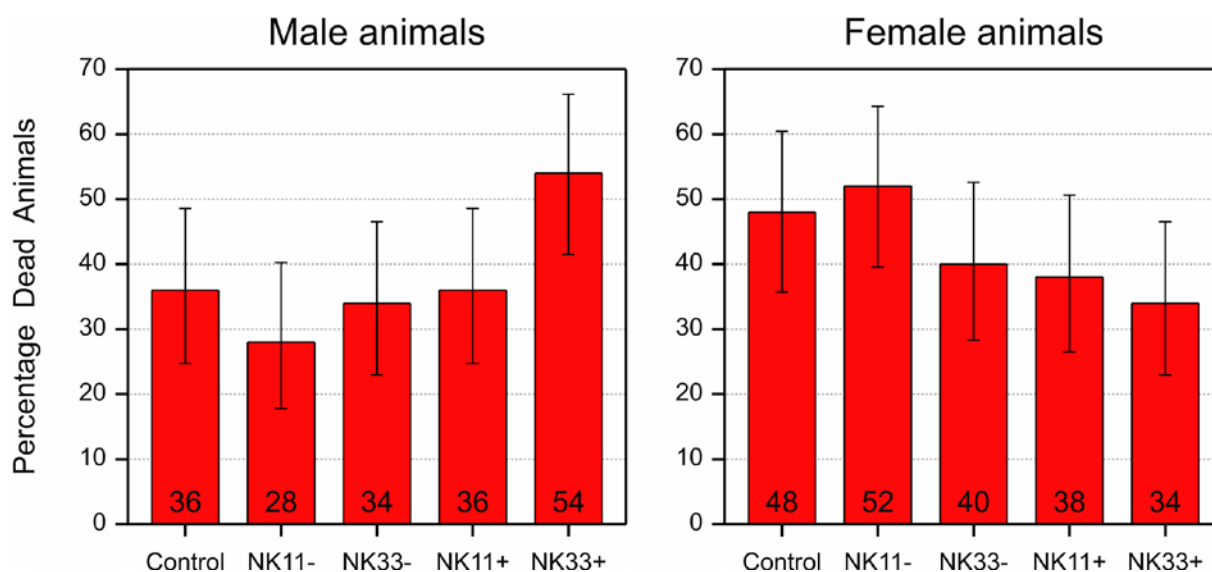


Figure 9 Percentage dead animals after 24 month in the 2-year cohort. 90% confidence intervals for the percentage are indicated by error bars. The percentage is also given at bottom of each bar.

Table 12 P-values for the one-sided test of the null hypothesis that the mortality probability of a GM feed is smaller than the mortality probability of the non-GM control feed.

Test	Males	Females
NK11- vs Control	0.816	0.339
NK33- vs Control	0.587	0.798
NK11+ vs Control	0.500	0.852
NK33+ vs Control	0.029	0.929

Table 13 P-values for factorial tests of equality of mortality probabilities.

Test	Males	Females
GM versus non-GM control	0.783	0.354
Inclusion Rate	0.062	0.230
Roundup	0.030	0.134
Interaction Inclusion.Roundup	0.413	0.574

3.3 Equivalence testing using historical data

Equivalence testing was only performed for those variables that were also observed in the GRACE study. Note that this is a comparison between data obtained after 24 months for the current study, and data obtained after 3 months for the historical GRACE study. It should be noted that the residual variances between cages are much larger after 24 months than after 3 months (Figure 10). This is indicated by a yellow background colour of the endpoint labels in Figure 11 to Figure 14, and it shows

that the model for equivalence testing which compares the current 24 months data to reference data obtained after 3 months data is not useful. The results reported in this section are only meant to illustrate this fact and are given for completeness only. In the main report an alternative model is suggested.

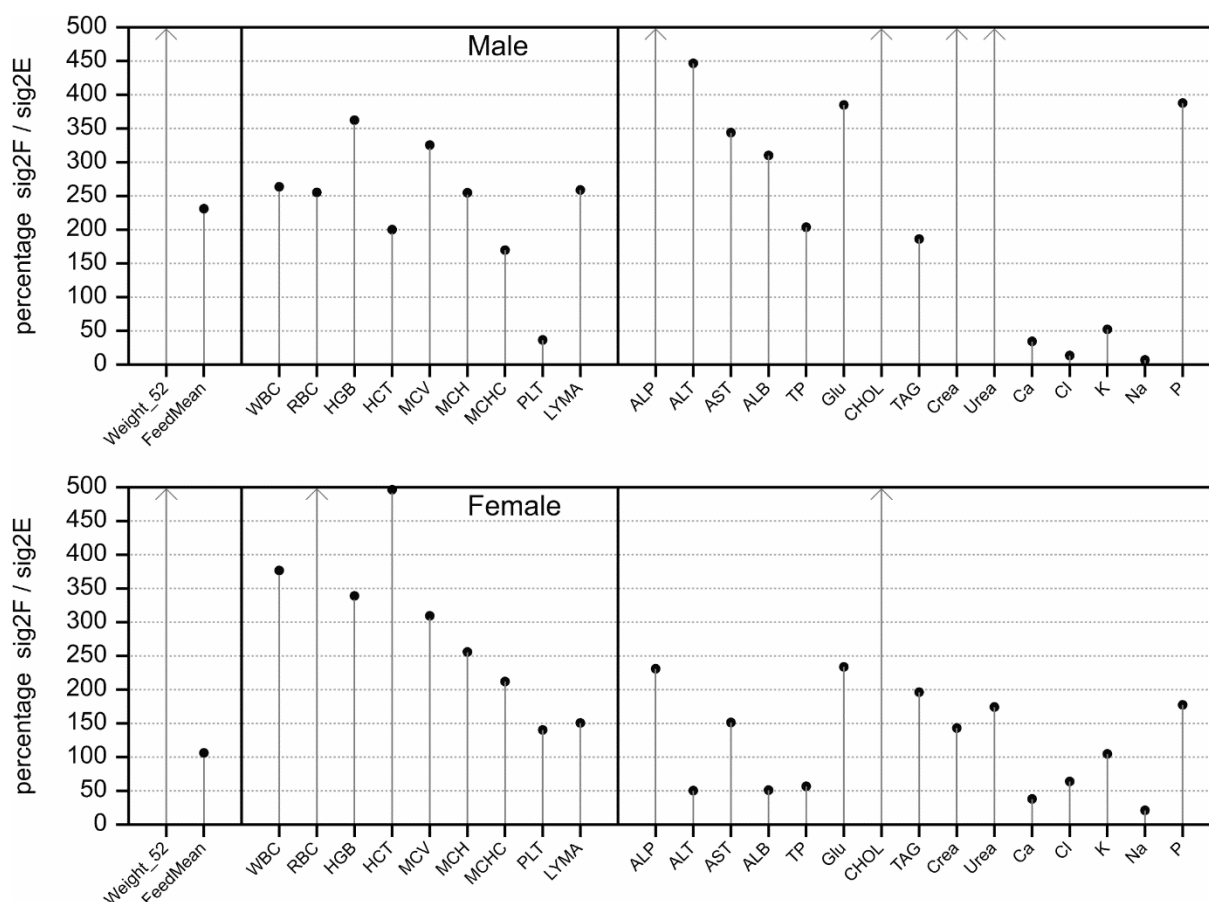


Figure 10 Residual variance (sig2F or σ_F^2) in the current G-TwYST A study as a percentage of the residual variance (sig2E or σ_E^2) in the historical GRACE studies for males (top panel) and females (bottom panel) that survived for 24 months.

Preliminary regulatory values $\alpha = 0.05$, $\beta = 0.05$ and $n_0 = 20$ were employed, where n_0 was set to a value similar to the number of cages left at the end of the trial (Table 7 and Table 8). 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 30 variables are given in Figure 11 to Figure 14. 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 14 and Table 15. For the majority of cases there was a failure to prove equivalence.

Although not the primary result of the equivalence analysis, it can also be observed from the fuchsia symbols in Figure 11 to Figure 14 and from Table 14 and Table 15 that very few difference tests are significant at the 5% level. For all difference tests, i.e. including those for which the equivalence test was not performed, 11 out of 296 t-tests were significant which is 3.7% of the tests.

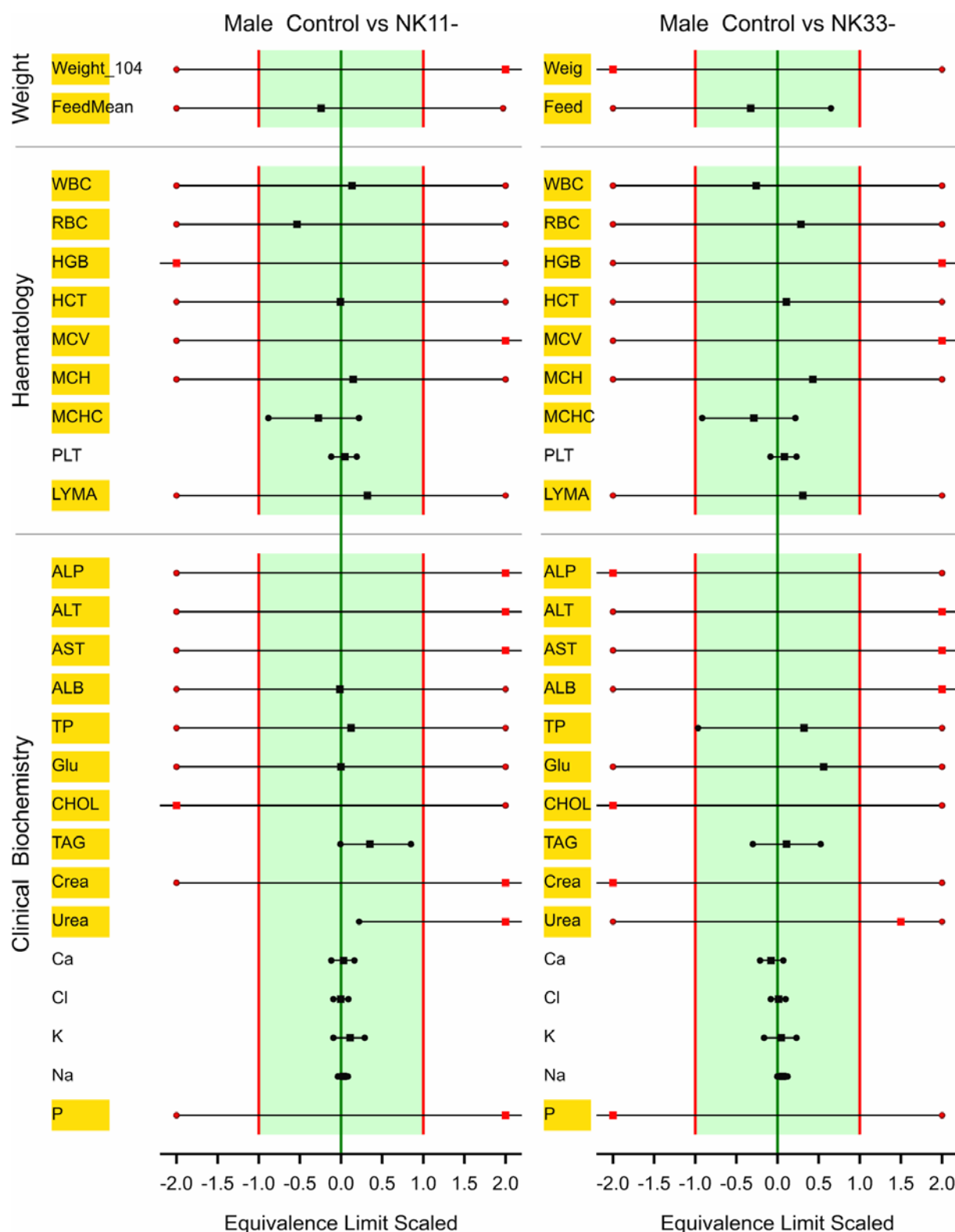


Figure 11 Equivalence testing of NK11- and NK33- versus the control feed for males that survived for 24 months. For estimates (square symbols) on the left of zero the GM feed has a smaller mean than the control feed (see also Table 14). Endpoints labelled with a golden background have a large residual variance compared to the historical studies (VR>150%). Fuchsia coloured symbols denote a significant difference.

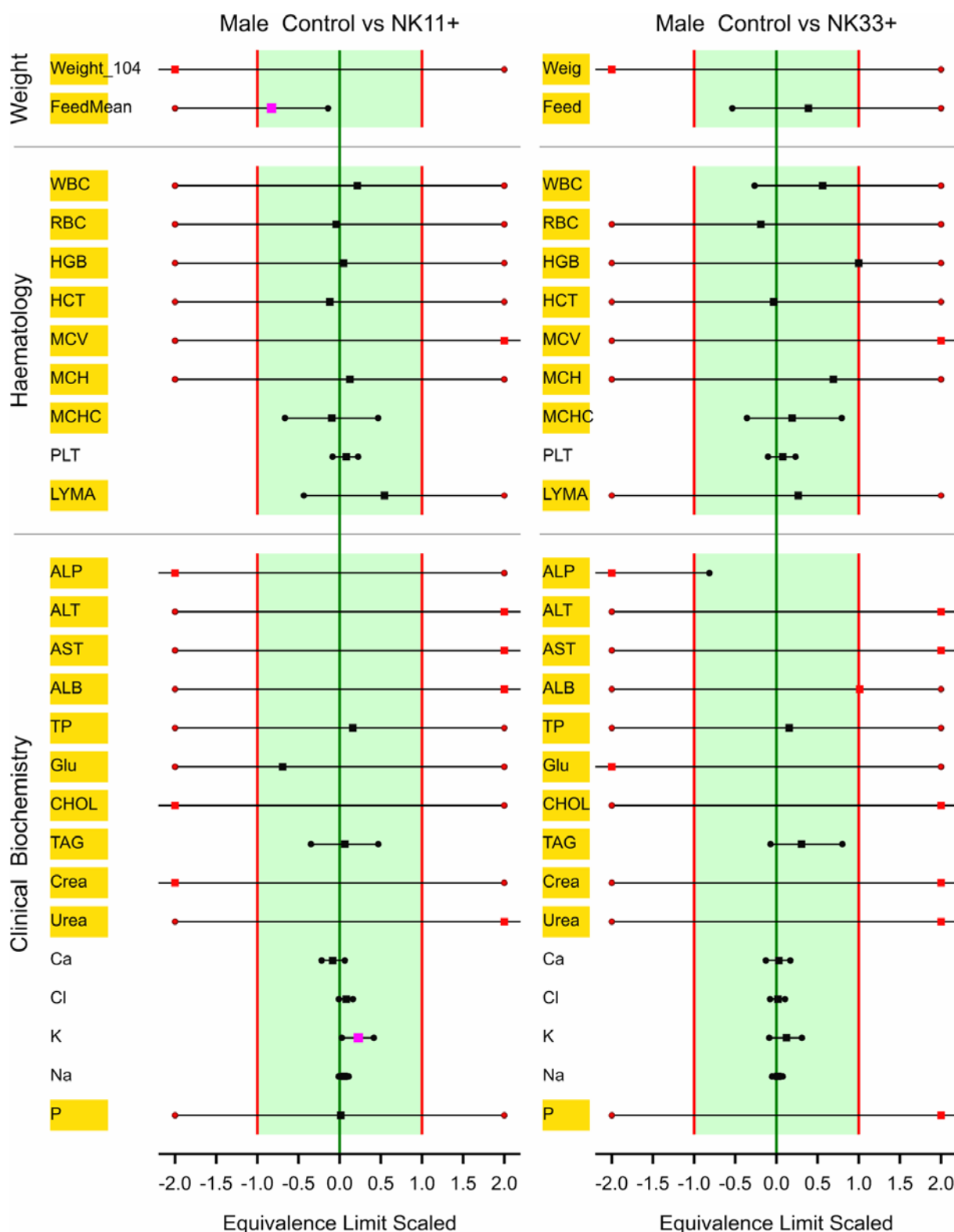


Figure 12 Equivalence testing of NK11+ and NK33+ versus the control feed for males that survived for 24 months. For estimates (square symbols) on the left of zero the GM feed has a smaller mean than the control feed (see also Table 14). Endpoints labelled with a golden background have a large residual variance compared to the historical studies (VR>150%). Fuchsia coloured symbols denote a significant difference.

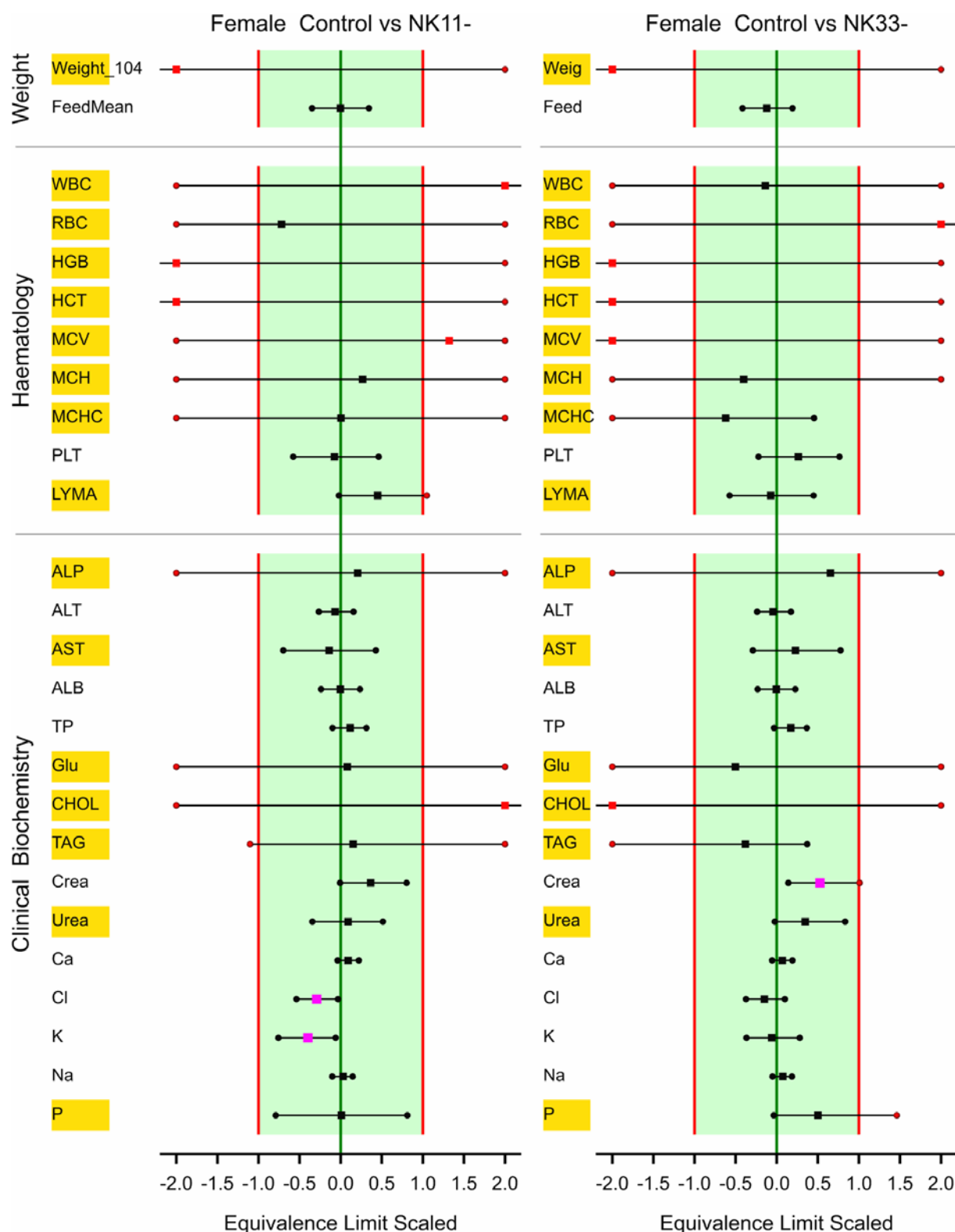


Figure 13 Equivalence testing of NK11- and NK33- versus the control feed for females that survived for 24 months. For estimates (square symbols) on the left of zero the GM feed has a smaller mean than the control feed (see also Table 15). Endpoints labelled with a **golden** background have a large residual variance compared to the historical studies (VR>150%). Fuchsia coloured symbols denote a significant difference.

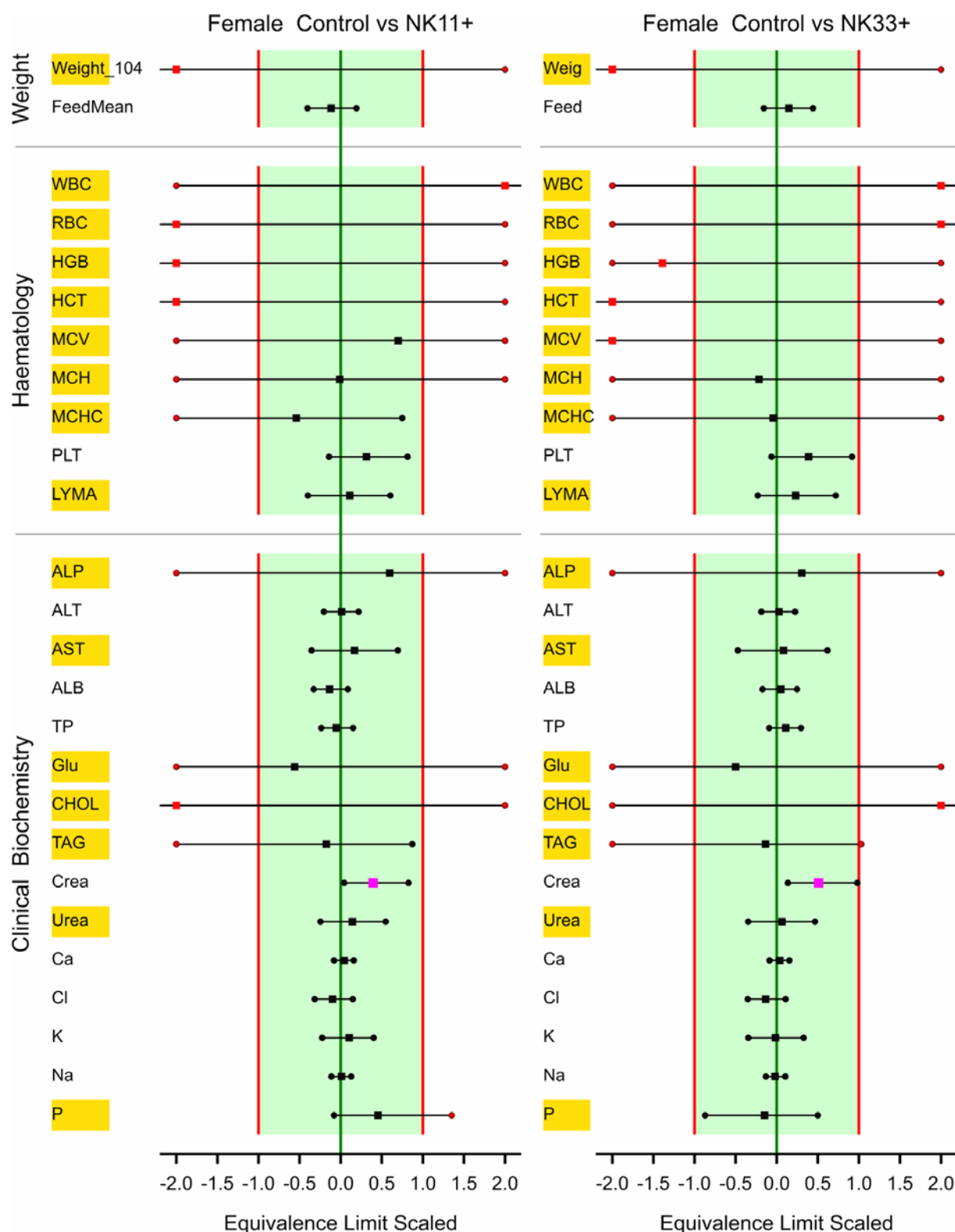


Figure 14 Equivalence testing of NK11+ and NK33+ versus the control feed for females that survived for 24 months. For estimates (square symbols) on the left of zero the GM feed has a smaller mean than the control feed (see also Table 15). Endpoints labelled with a golden background have a large residual variance compared to the historical studies (VR>150%). Fuchsia coloured symbols denote a significant difference.

Table 14 95% Confidence interval plus estimate for the ratio Δ of the GMO feeds versus the Control feed for males that survived for 24 months. 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_104	0.924	1.008	1.099	0.896	0.979	1.070	0.877	0.957	1.045	0.894	0.980	1.074
FeedMean	0.940	0.984	1.029	0.934	0.978	1.024	0.904	0.946	0.990	0.978	1.026	1.077
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	0.845	1.041	1.282	0.748	0.927	1.149	0.864	1.065	1.314	0.943	1.175	1.463
RBC	0.934	0.981	1.031	0.960	1.010	1.063	0.950	0.999	1.049	0.943	0.993	1.046
HGB	0.927	0.973	1.021	0.969	1.019	1.071	0.953	1.001	1.051	0.959	1.010	1.063
HCT	0.958	0.999	1.043	0.964	1.007	1.051	0.951	0.993	1.036	0.955	0.998	1.043
MCV	0.996	1.016	1.036	0.998	1.019	1.039	0.986	1.006	1.026	0.990	1.010	1.031
MCH	0.977	1.003	1.029	0.982	1.009	1.036	0.977	1.002	1.029	0.986	1.014	1.042
MCHC	0.980	0.993	1.006	0.979	0.992	1.006	0.984	0.997	1.011	0.992	1.005	1.019
PLT	0.936	1.027	1.127	0.952	1.048	1.154	0.952	1.046	1.148	0.943	1.044	1.156
LYMR	0.893	1.036	1.201	0.898	1.045	1.217	0.892	1.036	1.204	0.800	0.944	1.114
LYMA	0.880	1.089	1.348	0.872	1.085	1.350	0.931	1.154	1.430	0.847	1.074	1.362
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	0.806	1.040	1.342	0.655	0.853	1.110	0.709	0.917	1.187	0.584	0.764	1.001
ALT	0.887	1.030	1.195	0.874	1.020	1.189	0.878	1.020	1.185	0.894	1.046	1.225
AST	0.953	1.131	1.343	0.878	1.048	1.251	0.882	1.049	1.247	0.883	1.059	1.269
BIL	0.885	1.033	1.204	0.886	1.038	1.217	0.860	1.005	1.174	0.809	0.954	1.126
ALB	0.944	1.000	1.059	0.995	1.055	1.119	0.987	1.045	1.107	0.954	1.014	1.077
TP	0.972	1.006	1.041	0.980	1.016	1.052	0.973	1.008	1.043	0.972	1.008	1.045
Glu	0.839	1.001	1.195	0.853	1.024	1.229	0.815	0.974	1.164	0.743	0.899	1.087
CHOL	0.755	0.925	1.133	0.719	0.887	1.094	0.762	0.935	1.148	0.845	1.047	1.298
TAG	0.992	1.256	1.592	0.843	1.076	1.374	0.823	1.044	1.326	0.952	1.222	1.569
Crea	0.838	1.049	1.312	0.761	0.959	1.209	0.767	0.964	1.213	0.887	1.123	1.423
Urea	1.018	1.177	1.360	0.881	1.023	1.188	0.915	1.061	1.231	0.902	1.053	1.229
CHGB	1.077	1.450	1.952	0.832	1.131	1.537	0.873	1.178	1.590	0.981	1.343	1.838

Ca	0.983	1.004	1.026	0.967	0.988	1.011	0.966	0.988	1.010	0.982	1.004	1.027
Cl	0.989	1.000	1.010	0.991	1.002	1.013	0.999	1.009	1.020	0.991	1.002	1.014
K	0.979	1.026	1.076	0.962	1.011	1.061	1.005	1.055	1.106	0.979	1.029	1.082
Na	0.995	1.003	1.012	0.999	1.008	1.017	0.998	1.007	1.015	0.993	1.002	1.011
P	0.964	1.086	1.223	0.814	0.920	1.040	0.886	1.001	1.130	0.945	1.071	1.213
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	0.825	1.104	1.478	0.623	0.827	1.097	0.772	1.027	1.367	0.749	1.000	1.336
uVolW	0.857	1.132	1.496	0.654	0.856	1.121	0.825	1.085	1.426	0.791	1.043	1.375
uLeu	0.704	0.981	1.368	0.747	1.031	1.423	0.526	0.729	1.009	0.847	1.177	1.637
uOsmoll	0.789	0.962	1.174	0.881	1.068	1.295	0.760	0.923	1.122	0.850	1.035	1.261
uProtein	0.604	1.059	1.857	0.550	0.947	1.632	0.445	0.772	1.338	0.790	1.380	2.408
uHemogl	0.663	1.643	4.070	0.461	1.110	2.674	0.463	1.128	2.745	0.441	1.085	2.669
uKeton	0.683	1.196	2.092	0.751	1.292	2.221	0.707	1.224	2.118	1.011	1.761	3.068
upH	0.816	1.068	1.399	0.757	0.982	1.275	0.799	1.040	1.354	0.907	1.185	1.547

Table 15 95% Confidence interval plus estimate for the ratio Δ of the GMO feeds versus the Control feed for females that survived for 24 months. 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_104	0.857	0.950	1.053	0.840	0.927	1.023	0.860	0.946	1.041	0.891	0.980	1.079
FeedMean	0.958	1.000	1.043	0.945	0.984	1.026	0.946	0.985	1.025	0.980	1.020	1.061
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	0.793	1.105	1.541	0.714	0.989	1.368	0.922	1.256	1.713	0.819	1.113	1.513
RBC	0.935	0.999	1.068	0.947	1.010	1.078	0.920	0.980	1.044	0.956	1.016	1.081
HGB	0.944	0.984	1.025	0.938	0.976	1.016	0.949	0.986	1.025	0.954	0.991	1.030
HCT	0.932	0.975	1.020	0.928	0.969	1.012	0.946	0.987	1.029	0.947	0.987	1.028
MCV	0.983	1.007	1.032	0.963	0.987	1.012	0.982	1.005	1.029	0.969	0.991	1.014
MCH	0.972	1.006	1.042	0.958	0.991	1.024	0.968	1.000	1.032	0.963	0.995	1.027
MCHC	0.984	1.000	1.017	0.973	0.989	1.005	0.975	0.991	1.006	0.984	0.999	1.015

PLT	0.846	0.978	1.131	0.938	1.080	1.243	0.957	1.096	1.255	0.979	1.120	1.281
LYMR	0.850	0.979	1.127	0.860	0.990	1.139	0.885	1.014	1.162	0.883	1.007	1.148
LYMA	0.981	1.211	1.496	0.786	0.969	1.194	0.856	1.049	1.285	0.910	1.103	1.338
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	0.868	1.031	1.225	0.934	1.102	1.300	0.932	1.093	1.282	0.892	1.046	1.227
ALT	0.846	0.963	1.096	0.861	0.975	1.104	0.892	1.007	1.136	0.902	1.016	1.146
AST	0.802	0.954	1.136	0.911	1.078	1.275	0.898	1.057	1.244	0.874	1.027	1.207
BIL	0.879	0.993	1.123	0.884	0.996	1.122	0.850	0.954	1.070	0.897	1.005	1.126
ALB	0.953	0.999	1.048	0.954	0.999	1.046	0.932	0.974	1.018	0.966	1.010	1.056
TP	0.982	1.021	1.061	0.993	1.031	1.070	0.955	0.990	1.027	0.984	1.020	1.057
Glu	0.862	1.013	1.190	0.792	0.928	1.087	0.791	0.920	1.069	0.799	0.928	1.077
CHOL	0.836	1.036	1.283	0.766	0.941	1.155	0.724	0.885	1.080	0.846	1.031	1.257
TAG	0.772	1.074	1.494	0.610	0.837	1.150	0.678	0.922	1.255	0.692	0.938	1.273
Crea	0.993	1.100	1.219	1.039	1.146	1.265	1.008	1.109	1.221	1.038	1.141	1.255
Urea	0.924	1.023	1.133	0.990	1.091	1.203	0.943	1.037	1.140	0.925	1.017	1.117
cHGB	0.650	0.909	1.269	0.672	0.926	1.278	0.653	0.892	1.219	0.712	0.970	1.322
Ca	0.993	1.015	1.037	0.990	1.011	1.033	0.987	1.007	1.028	0.986	1.006	1.027
Cl	0.967	0.982	0.999	0.976	0.991	1.007	0.979	0.994	1.009	0.977	0.992	1.007
K	0.850	0.917	0.990	0.917	0.987	1.062	0.953	1.023	1.098	0.929	0.997	1.070
Na	0.993	1.002	1.011	0.996	1.005	1.013	0.993	1.001	1.009	0.991	0.999	1.007
P	0.889	1.002	1.130	0.987	1.108	1.243	0.982	1.098	1.228	0.868	0.970	1.084
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	0.758	1.018	1.368	0.802	1.066	1.416	0.702	0.924	1.215	0.869	1.162	1.554
uVolW	0.800	1.058	1.398	0.836	1.093	1.430	0.736	0.954	1.236	0.877	1.155	1.520
uLeu	0.478	1.225	3.140	0.391	0.969	2.400	0.542	1.298	3.110	0.329	0.833	2.106
uOsmoll	0.766	0.931	1.131	0.771	0.930	1.121	0.825	0.988	1.184	0.740	0.897	1.087
uProtein	0.789	1.988	5.006	0.660	1.605	3.908	0.681	1.605	3.783	0.451	1.122	2.788
uHemogl	0.289	0.694	1.669	0.411	0.957	2.228	0.494	1.116	2.518	0.291	0.691	1.641
uKeton	0.421	0.764	1.387	0.496	0.880	1.563	0.700	1.218	2.118	0.420	0.757	1.362
upH	0.890	1.337	2.007	1.041	1.540	2.278	0.839	1.223	1.784	0.793	1.184	1.767

3.4 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 15 for males and in Figure 16 for females. Note that these are 90% intervals, rather than the 95% intervals in Table 14 and Table 15. For the variables Weight_104, WBC and LYMA the null hypotheses of non-equivalence could not be rejected in all cases (Table 16). However in all cases the estimated effect is within the equivalence limits indicating that, in the terminology of EFSA (2011a), equivalence is still more likely than lack of equivalence.

Table 16 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_104	0.006	0.030	0.083	0.035	0.149	0.275	0.151	0.040
WBC	0.018	0.005	0.031	0.180	0.166	0.049	0.413	0.158
LYMA	0.051	0.052	0.136	0.057	0.253	0.003	0.019	0.047
ALP	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Crea	0.001	0.000	0.000	0.009	0.000	0.000	0.000	0.000
Urea	0.001	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

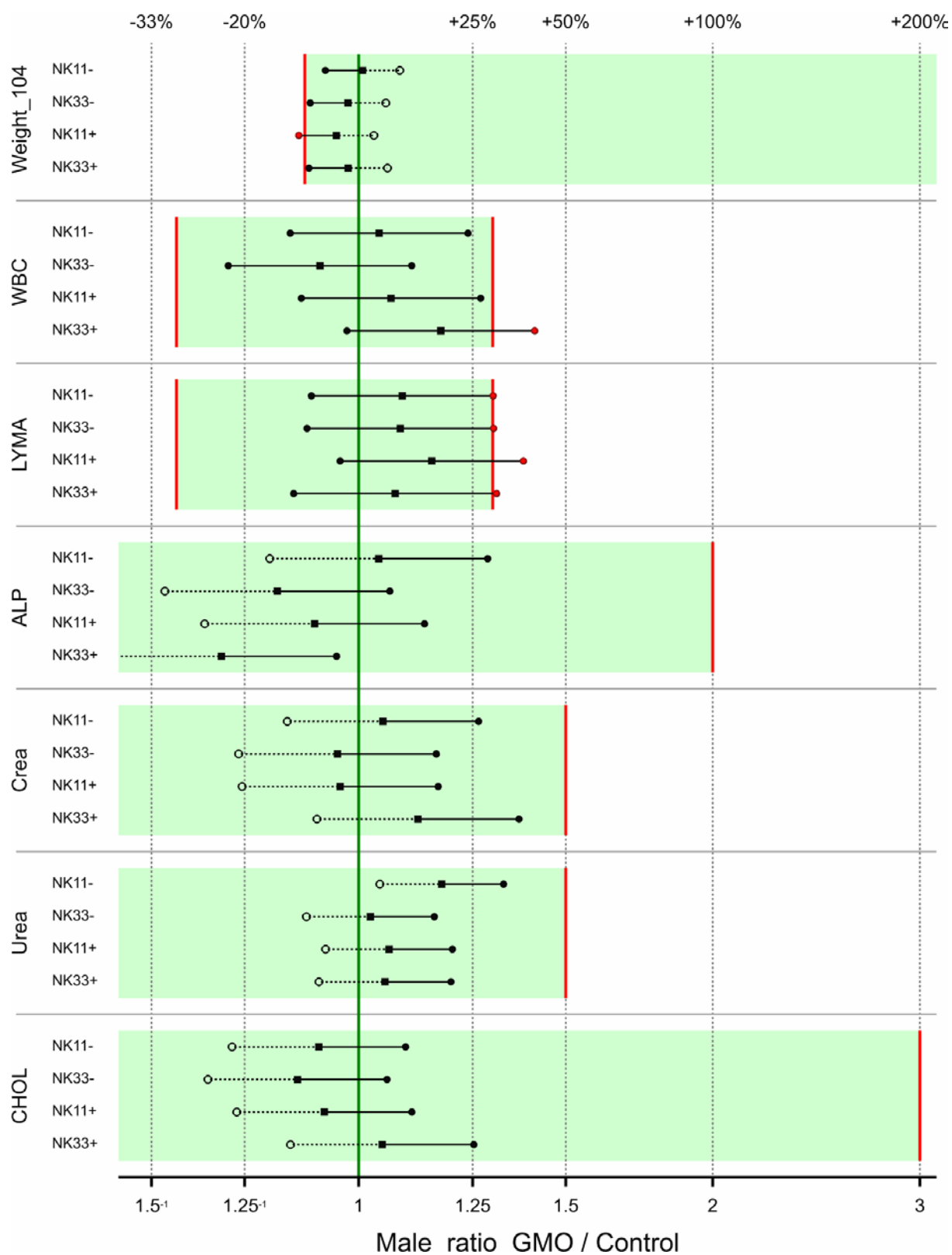


Figure 15 90% confidence intervals for the ratio of the mean of the GMO feed and the control feed for selected variables for males that survived for 24 months, along with equivalence intervals defined by targeted effect sizes of Hong *et al.* (2017).

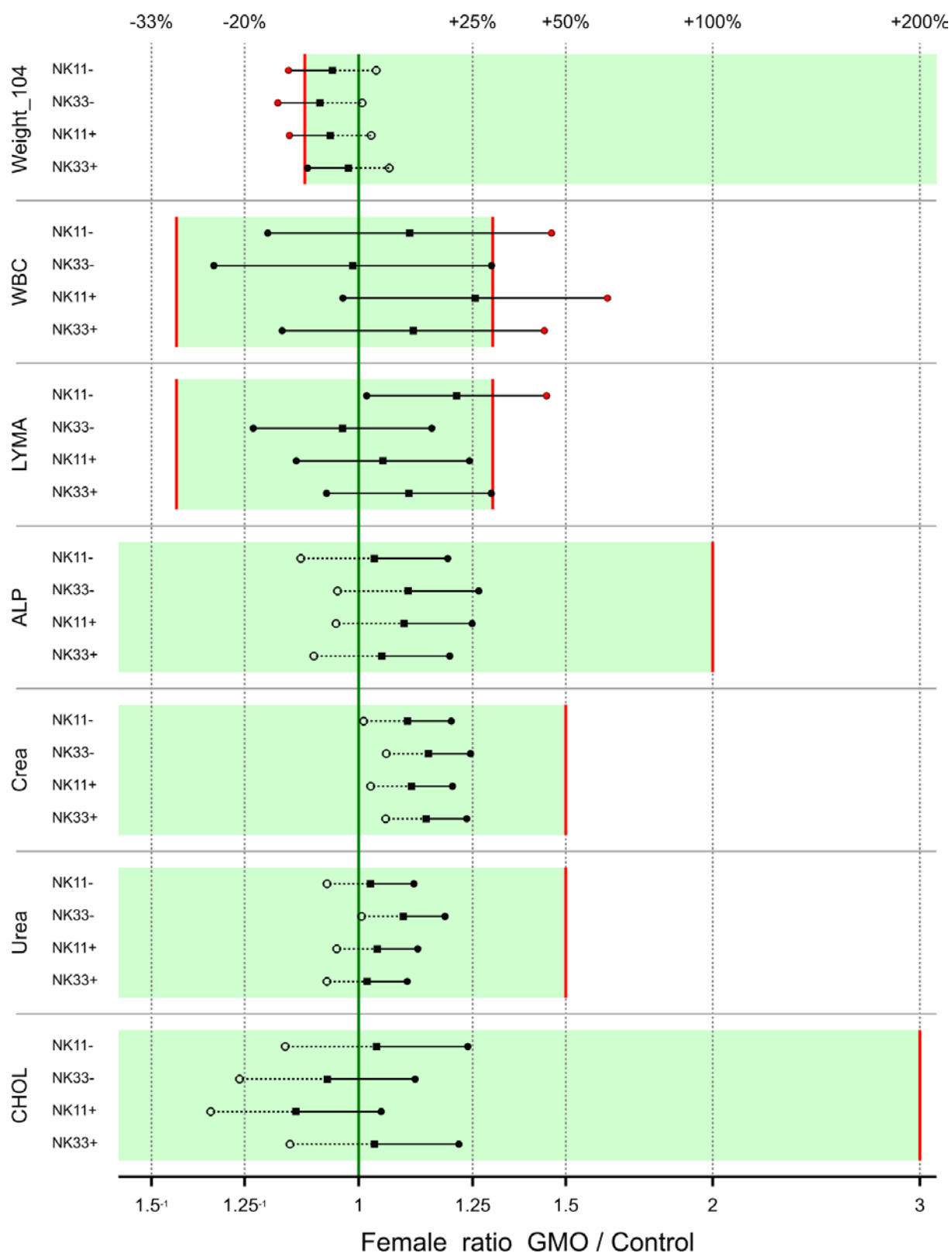


Figure 16 90% confidence intervals for the ratio of the mean of the GMO feed and the control feed for selected variables for females that survived for 24 months, along with equivalence intervals defined by targeted effect sizes of Hong *et al.* (2017).

3.5 Classical statistical analysis

A classical analysis of variance was performed on the cage means after log transforming the data. 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 17 (males) and Table 18 (females) present the results of the t-tests, of Dunnett's tests and of Wilcoxon tests for the 37 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 14 (males) and Table 15 (females). For comparison an analysis on the data at the animal level is reported in Appendix 12; it is concluded that there is little difference between t-tests on the cage and on the animal level.

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 17 and Table 18) that the relative precision of variables ranges from high to low precision. For example CVs smaller than 5% are observed for most haematology variables, while CVs larger than 50% are found for Monocytes, Eosinophils, cHGB, uLeu and uKeton. For some variables there is a difference in precision for males and females, e.g. growthRate for males has a CV in the range 10-13%, while for females the range equals 42-61%.

In 14 cases (4.7% of the 296 comparisons) a difference was significant in at least one of the tests at the 5% level. On their own, Dunnett's test resulted in 2 significant differences (0.7%), the t-test resulted in 11 significant differences (3.7%), and Wilcoxon's test resulted in 7 significant differences (2.4%). Note that cells coloured red in Table 14 and Table 15, with 95% confidence intervals for ratios, correspond to cells coloured red in Table 17 and Table 18 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 9 variables (Weight_104, PLT, ALB, Crea, Ca, P, uLeu, uOsmoll, uProtein) and for females for 6 variables (WBC, HGB, TAG, uVol, uVolW, uHemogl). Levene's test is significant for 4 male variables (Weight_104, uLeu, uOsmoll, uProtein), and for 3 females variables (P, uVol, uHemogl). This implies that the important assumption of homogeneity of variance is not always fulfilled. For these significant cases, one might resort to Wilcoxon's test which is, for these variables, only significant for uVol in females (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.

3.6 Standardized effect sizes

SES intervals were calculated for all 37 variables. Results for the four treatment groups, separately for males and females, are given in Figure 17 to Figure 20. The number of intervals that extend outside the ± 1 SD limits equals 72 out of 296 (24%).

Table 17 Means and coefficient of variation (CV) for male rats that survived for 24 months. 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_104	655.8	15.9	658.7	11.5		644.0	9.2		634.0	13.4		653.5	19.3	
FeedMean	19.11	6.1	18.83	8.3		18.89	8.5		18.23	8.1	t	19.66	10.7	
Haematology	Control		NK11-			NK33-			NK11+			NK33+		
Males	Mean	CV	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig
WBC	9.43	37.8	9.89	48.7		8.62	34.5		9.78	34.6		11.18	51.0	
RBC	7.894	5.3	7.758	8.1		7.956	6.2		7.864	8.7		7.879	7.8	
HGB	15.36	5.8	14.95	8.9		15.61	5.8		15.31	8.3		15.51	7.5	
HCT	44.15	5.7	44.20	6.1		44.52	4.4		43.93	7.4		44.23	7.5	
MCV	55.61	3.8	56.46	2.8		56.65	3.7		55.97	2.8		56.19	3.3	
MCH	19.46	3.9	19.48	3.7		19.64	4.6		19.49	4.4		19.72	4.9	
MCHC	34.91	2.2	34.63	1.9		34.68	2.5		34.79	2.2		35.08	2.4	
PLT	827.0	14.3	849.8	10.2		880.8	21.3		867.3	22.2		859.0	17.0	
LYMR	58.40	23.2	61.54	22.9		61.03	19.7		61.05	19.3		56.92	24.5	
LYMA	4.679	39.3	5.139	30.9		5.036	40.3		5.314	28.3		4.750	32.4	
ClinChem	Control		NK11-			NK33-			NK11+			NK33+		
Males	Mean	CV	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig
ALP	1.093	40.6	1.181	47.3		0.951	37.1		1.005	31.5		0.841	27.0	
ALT	0.832	20.3	0.897	33.6		0.876	29.2		0.880	26.8		0.904	30.3	
AST	2.599	25.4	3.045	31.0		2.730	24.3		2.851	33.3		2.796	29.5	
BIL	7.417	37.0	7.711	36.5		7.700	33.4		7.235	31.5		6.781	28.6	
ALB	35.76	9.6	36.07	11.2		37.66	5.7		37.23	11.1		36.05	8.6	
TP	71.29	5.2	71.75	6.7		72.43	4.3		71.70	6.4		71.71	5.2	
Glu	4.179	26.2	4.263	25.4		4.359	26.4		4.075	27.6		3.942	32.0	
CHOL	4.592	34.8	4.307	46.6		4.030	28.3		4.311	45.9		4.719	39.7	
TAG	2.075	45.8	2.622	48.2	w	2.250	39.2		2.405	63.4		2.516	58.5	
Crea	30.44	22.6	35.19	64.1		31.05	41.5		30.67	30.1		41.88	79.8	

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Urea	4.028	17.8	4.997	38.4	t	4.324	25.9		4.415	20.5		4.354	27.0	
cHGB	106.5	75.9	142.8	53.4	tw	110.6	42.1		115.4	57.9		135.1	83.1	
Ca	2.530	3.4	2.536	4.9		2.506	3.2		2.492	2.2		2.539	4.3	
Cl	101.8	1.8	101.7	1.6		101.8	1.5		102.6	2.1		102.0	2.4	
K	4.612	8.7	4.720	10.3		4.605	6.0		4.846	8.8	tw	4.692	8.7	
Na	142.7	1.0	143.3	1.6		143.8	1.0	w	143.7	1.5		143.2	1.6	
P	1.666	21.5	1.807	22.7		1.522	16.9		1.640	18.5		1.826	33.8	
Urine	Control		NK11-			NK33-			NK11+			NK33+		
Males	Mean	CV	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig
uVol	12.03	37.0	12.58	34.6		9.37	26.7		12.43	42.0		12.50	34.5	
uVolW	1.796	35.4	2.057	41.7		1.464	28.3		1.950	40.8		1.942	39.5	
uLeu	487.5	10.3	475.7	14.9		489.5	9.4		412.5	40.8		489.5	9.4	
uOsmoll	738.8	20.8	713.4	24.2		798.2	14.6		711.2	33.3		755.4	31.6	
uProtein	3.758	37.6	3.750	41.8		3.678	47.0		3.600	57.2		4.046	37.0	
uHemogl	39.38	190.7	37.50	176.7		30.66	214.3		33.38	236.9		44.74	184.9	
uKeton	0.375	133.3	0.500	109.8		0.645	83.1		0.475	132.2		0.829	82.3	t
upH	6.156	6.8	6.278	8.7		6.211	7.0		6.225	6.4		6.329	4.6	

Table 18 Means and coefficient of variation (CV) for female rats that survived for 24 months. 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_104	418.4	15.0	397.7	15.4		397.6	15.0		404.7	13.6		417.6	17.0	
FeedMean	14.11	6.5	14.07	7.2		13.98	5.8		14.00	6.8		14.51	7.2	
Haematology	Control		NK11-			NK33-			NK11+			NK33+		
Females	Mean	CV	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig
WBC	7.84	75.0	7.80	33.7		6.87	50.1		10.38	97.8		8.15	44.0	
RBC	7.188	8.0	7.153	6.3		7.187	9.4		7.076	10.9		7.260	6.9	
HGB	15.16	3.7	14.95	5.6		14.82	5.9		15.00	7.3		15.08	4.4	
HCT	42.58	6.1	42.02	6.7		41.35	6.9		42.18	6.7		42.11	4.2	
MCV	58.23	3.3	58.76	3.6		57.64	4.0		58.54	3.0		57.70	2.9	
MCH	20.87	3.9	20.93	4.2		20.76	6.0		20.85	5.7		20.79	4.8	
MCHC	35.85	1.6	35.61	2.5		35.46	2.9		35.47	2.6		35.82	2.0	
PLT	784.1	13.0	762.6	21.7		836.8	20.0		842.2	23.6		888.8	21.3	
LYMR	56.77	16.0	55.17	18.8		56.51	16.6		57.49	18.4		56.80	17.3	
LYMA	3.466	37.1	4.106	38.5		3.231	27.4		3.439	25.1		3.723	36.4	
ClinChem	Control		NK11-			NK33-			NK11+			NK33+		
Females	Mean	CV	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig
ALP	0.582	31.2	0.563	30.6		0.602	29.6		0.592	21.0		0.547	21.2	
ALT	0.852	26.5	0.802	20.6		0.812	18.2		0.831	18.2		0.835	19.6	
AST	3.150	31.2	2.921	26.1		3.271	20.7		3.214	26.8		3.097	22.1	
BIL	6.197	14.5	5.900	16.2		6.011	14.7		5.905	25.0		6.152	17.1	
ALB	39.96	7.1	39.51	5.7		39.60	6.3		38.76	6.3		40.08	6.0	
TP	73.77	6.2	74.76	5.3		75.59	4.7		73.00	5.1		74.89	4.6	
Glu	4.965	17.4	5.190	23.1		4.754	21.3		4.805	24.1		4.577	19.0	
CHOL	3.194	23.8	3.294	52.7		2.975	29.2		2.756	29.1		3.311	34.3	
TAG	1.320	35.3	1.475	43.8		1.183	39.9		1.391	49.9		1.596	98.8	
Crea	32.41	12.8	35.19	10.4		37.46	16.7	dT	35.68	14.7	t	36.55	14.7	dTw

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Urea	4.670	13.0	4.823	17.3		4.975	13.5		4.927	15.9		4.670	16.0	
cHGB	87.48	87.5	74.82	36.7		79.20	54.8		78.89	53.6		92.98	80.6	
Ca	2.506	2.6	2.541	3.7		2.528	3.1		2.510	2.2		2.515	3.4	
Cl	97.32	2.4	96.21	2.6	tw	97.12	3.0		97.07	2.7		96.59	2.6	
K	4.338	7.9	3.985	9.9	t	4.305	11.4		4.427	11.4		4.320	10.3	
Na	141.9	1.4	142.2	1.9		142.7	1.4		141.7	1.5		141.3	1.3	
P	1.534	14.4	1.499	19.2		1.706	24.3		1.625	13.4		1.478	16.9	
Urine	Control		NK11-			NK33-			NK11+			NK33+		
Females	Mean	CV	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig
uVol	11.71	26.4	12.27	52.2		12.00	32.4		10.67	42.3		13.21	24.4	w
uVolW	2.791	22.3	3.120	47.4		2.928	32.1		2.678	44.7		3.283	34.2	
uLeu	241.9	85.8	275.0	73.9		268.1	72.5		303.5	70.6		283.1	79.6	
uOsmoll	671.4	26.1	640.6	46.8		647.5	25.0		694.2	24.9		594.6	19.1	
uProtein	0.640	105.4	1.608	102.6		1.625	112.4		1.583	126.1		1.360	124.9	
uHemogl	36.76	233.2	8.33	387.3		23.89	278.7		37.78	220.0		15.44	267.8	
uKeton	0.971	120.1	0.583	108.3		0.861	100.7		0.917	60.6		0.618	89.5	
upH	5.824	8.6	6.167	9.5		6.250	6.3	t	5.944	11.0		6.000	8.1	

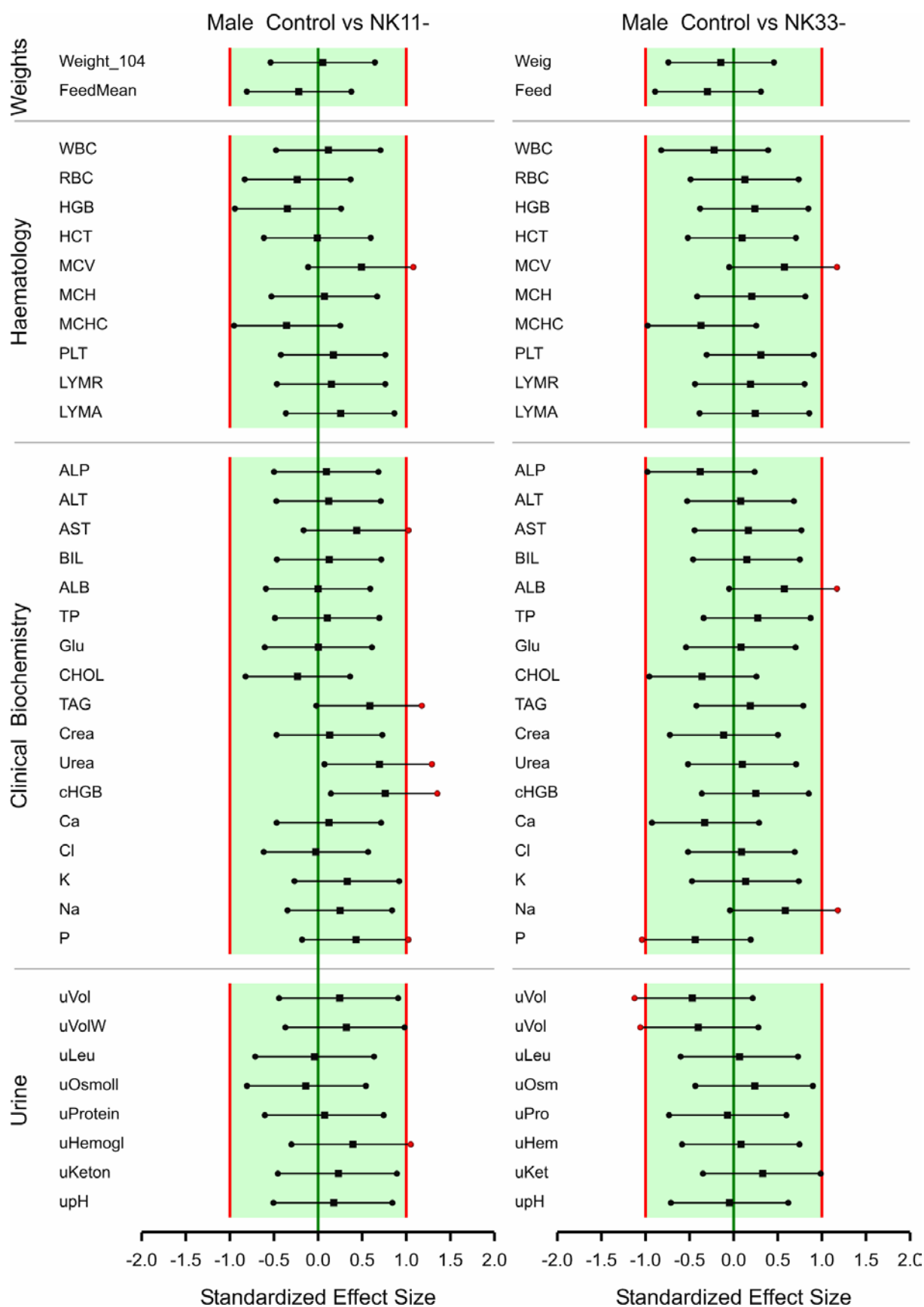


Figure 17 Confidence intervals for Standardized Effect Sized (SES) for male rats that survived for 24 months for GMO feeds NK11- and NK33- versus the control feed.

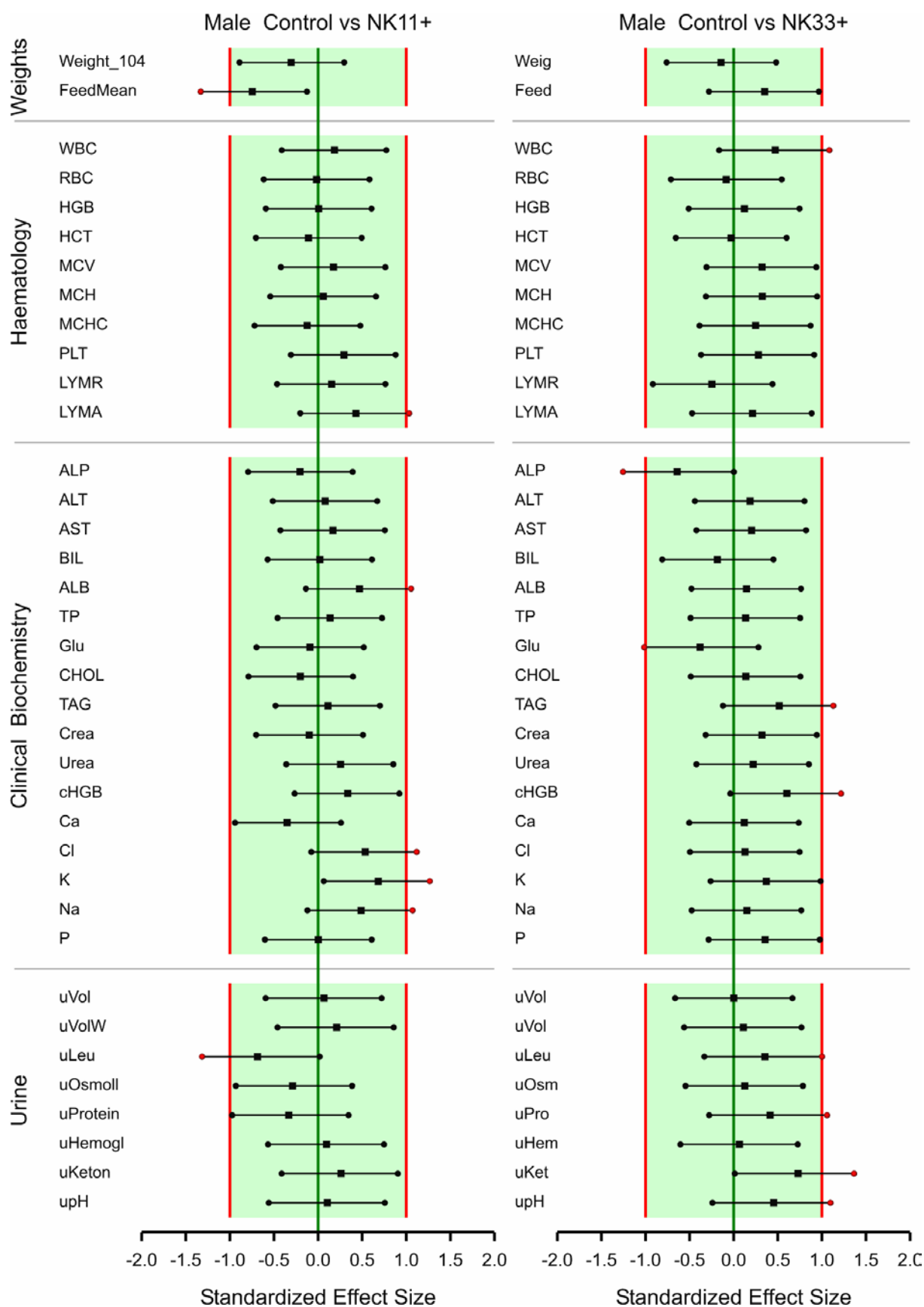


Figure 18 Confidence intervals for Standardized Effect Sized (SES) for male rats that survived for 24 months for GMO feeds NK11+ and NK33+ versus the control feed.

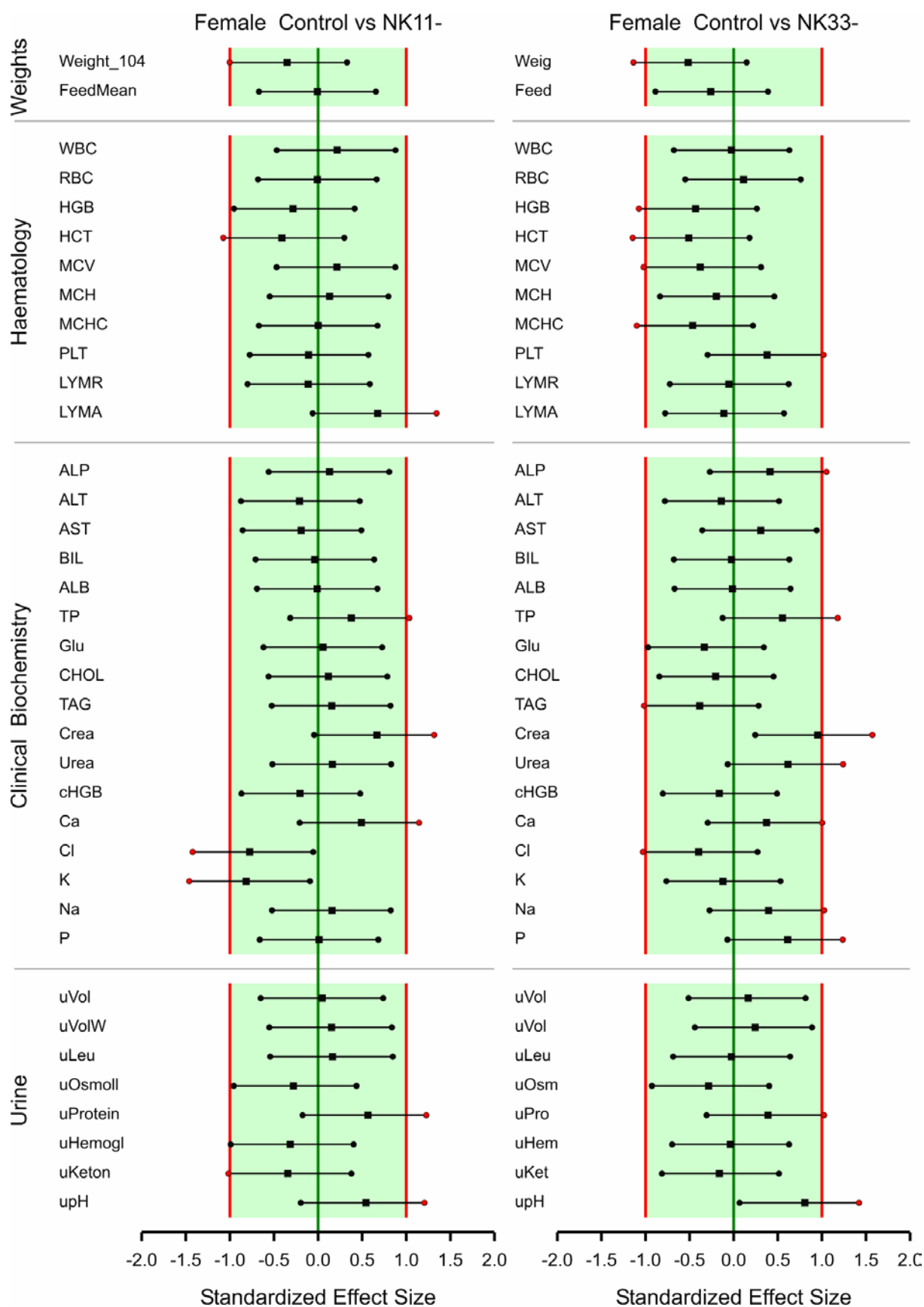


Figure 19 Confidence intervals for Standardized Effect Sized (SES) for female rats that survived for 24 months for GMO feeds NK11- and NK33- versus the control feed.

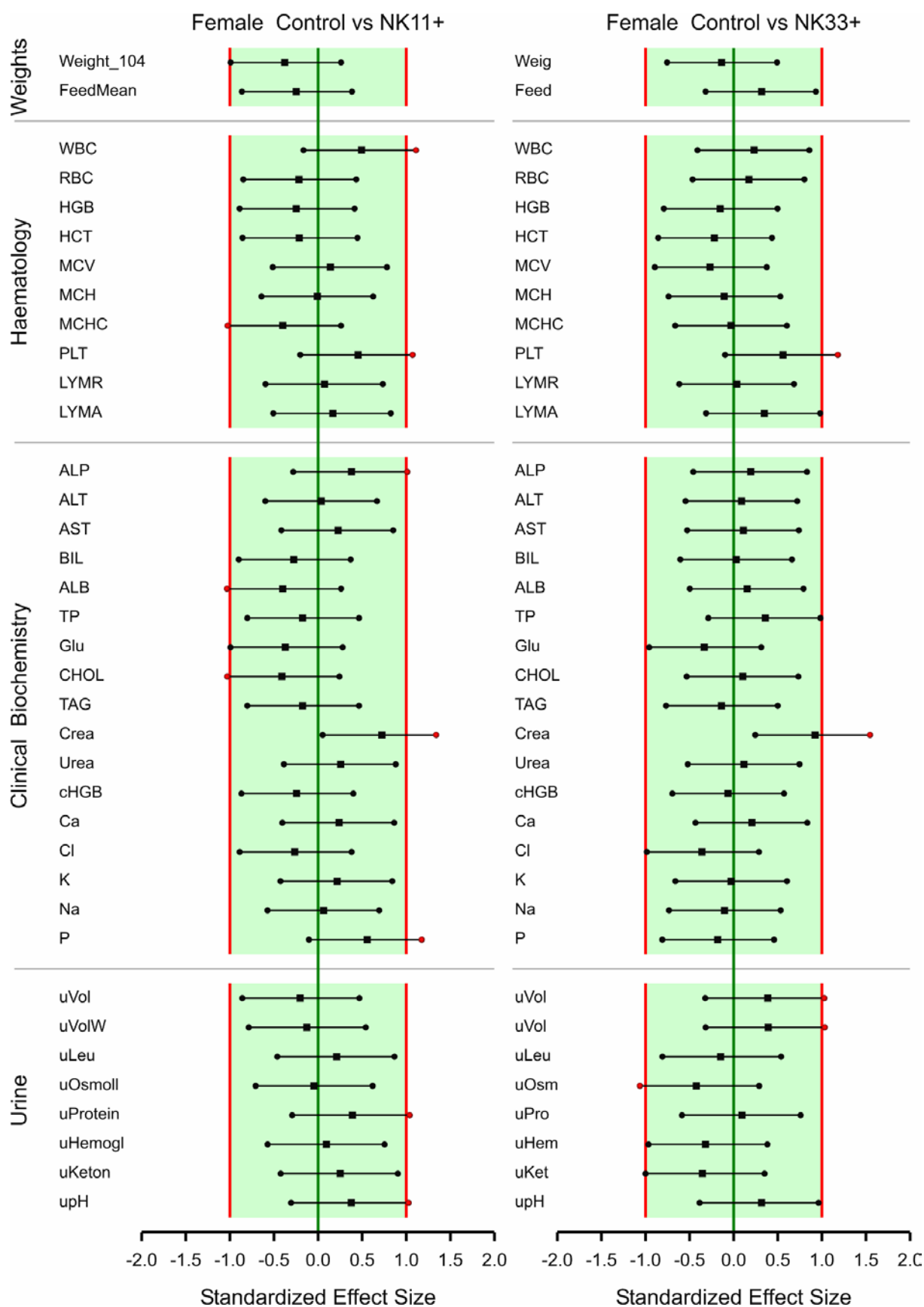


Figure 20 Confidence intervals for Standardized Effect Sized (SES) for female rats that survived for 24 months for GMO feeds NK11+ and NK33+ versus the control feed.

3.7 Factorial analysis

The significance results from fitting the factorial model to the 37 variables are given in Table 19. The ratios for the significant cases are shown in Table 20 and Table 21.

As an example, consider the results for P which has a significant interaction both in males and females. In males the effect of GM inclusion rate is negative for GM feeds without Roundup (from 1.00 to 0.85 which is -15%), while it was positive for GM feeds with Roundup (from 0.92 to 0.99 which is +8%). However, for females it is the other way around: a positive GM inclusion rate effect for GM feeds without Roundup (from 1.00 to 1.11 which is +11%) and a negative effect without Roundup (from 1.10 to 0.97 which equals -12%). The only main significant GM inclusion rate effect larger than 10% was observed for AST in females. None of the significant Roundup main effects was larger than 10%.

The p-values in Table 19 can be summarized as follows. In 1 out of 74 cases (1.4%) there was a significant difference at the 5% level between the mean of the GM feeds and the non-GM feed (Crea in females with a 12% increase for the GM feeds). In 6 cases (8.1%) 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 68 cases, i.e. where the interaction is not significant, there were 3 cases (4.4%) with a significant differences between GM inclusion rates, and no cases with a significant difference between the GM feeds with and without roundup.

Table 19 P values for significance of effects obtained with the factorial model for animals that survived for 24 months. 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_104	0.596	0.901	0.381	0.418	0.214	0.785	0.418	0.381
FeedMean	0.324	0.030	0.948	0.010	0.873	0.375	0.412	0.081
Haematology	GMO	InclRate	Roundup	Interact	GMO	InclRate	Roundup	Interact
WBC	0.593	0.868	0.114	0.167	0.384	0.282	0.258	0.964
RBC	0.821	0.483	0.917	0.337	0.945	0.252	0.776	0.566
HGB	0.975	0.107	0.524	0.293	0.358	0.960	0.488	0.607
HCT	0.957	0.677	0.616	0.955	0.262	0.842	0.290	0.841
MCV	0.118	0.605	0.194	0.886	0.782	0.044	0.926	0.699
MCH	0.537	0.372	0.831	0.768	0.850	0.392	0.933	0.623
MCHC	0.522	0.431	0.067	0.390	0.442	0.999	0.879	0.078
PLT	0.298	0.767	0.806	0.748	0.212	0.251	0.120	0.418
LYMR	0.750	0.492	0.427	0.362	0.977	0.984	0.581	0.846
LYMA	0.270	0.655	0.712	0.673	0.327	0.320	0.964	0.053
ClinChem	GMO	InclRate	Roundup	Interact	GMO	InclRate	Roundup	Interact
ALP	0.288	0.042	0.203	0.932	0.326	0.930	0.993	0.315
ALT	0.643	0.893	0.906	0.745	0.884	0.792	0.304	0.970
AST	0.316	0.576	0.555	0.495	0.656	0.510	0.682	0.187
BIL	0.881	0.702	0.352	0.616	0.777	0.445	0.707	0.536
ALB	0.240	0.528	0.777	0.048	0.795	0.187	0.673	0.233
TP	0.519	0.695	0.839	0.706	0.342	0.108	0.117	0.442
Glu	0.750	0.673	0.246	0.418	0.350	0.529	0.376	0.361
CHOL	0.491	0.652	0.273	0.302	0.713	0.529	0.701	0.075
TAG	0.159	0.963	0.615	0.076	0.603	0.355	0.906	0.215
Crea	0.816	0.745	0.733	0.145	0.004	0.308	0.963	0.853

Urea	0.196	0.138	0.404	0.222	0.317	0.605	0.347	0.204
cHGB	0.050	0.546	0.741	0.086	0.555	0.608	0.884	0.765
Ca	0.679	0.955	0.821	0.045	0.263	0.764	0.370	0.850
Cl	0.465	0.536	0.145	0.248	0.126	0.628	0.258	0.310
K	0.126	0.256	0.179	0.794	0.592	0.473	0.022	0.046
Na	0.140	0.968	0.758	0.136	0.689	0.960	0.185	0.386
P	0.701	0.201	0.545	0.009	0.389	0.520	0.496	0.005
Urine	GMO	InclRate	Roundup	Interact	GMO	InclRate	Roundup	Interact
uVol	0.829	0.117	0.548	0.181	0.827	0.169	0.988	0.366
uVolW	0.902	0.097	0.407	0.200	0.648	0.233	0.847	0.411
uLeu	0.785	0.020	0.449	0.057	0.808	0.294	0.862	0.745
uOsmoll	0.985	0.106	0.582	0.939	0.419	0.449	0.900	0.476
uProtein	0.970	0.211	0.881	0.069	0.207	0.368	0.351	0.819
uHemogl	0.600	0.488	0.505	0.561	0.677	0.746	0.885	0.187
uKeton	0.186	0.242	0.373	0.444	0.696	0.379	0.509	0.135
upH	0.580	0.789	0.375	0.237	0.089	0.723	0.186	0.534

Table 20 Ratios for significant variables at the 5% level in the factorial analysis for males that survived for 24 months. 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	FeedMean	-	-	-	1.00	0.99	0.96	1.04
ClinChem	ALP	-	0.83	-	-	-	-	-
ClinChem	ALB	-	-	-	1.00	1.06	1.05	1.01
ClinChem	Ca	-	-	-	1.00	0.98	0.98	1.00
ClinChem	P	-	-	-	1.00	0.85	0.92	0.99
Urine	uLeu	-	1.30	-	-	-	-	-

Table 21 Ratios for significant variables at the 5% level in the factorial analysis for females that survived for 24 months. 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+
Haematology	MCV	-	0.98	-	-	-	-	-
ClinChem	Crea	1.12	-	-	-	-	-	-
ClinChem	K	-	-	-	1.00	1.08	1.12	1.09
ClinChem	P	-	-	-	1.00	1.11	1.10	0.97

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- Table 21 Ratios for significant variables at the 5% level in the factorial analysis for females that survived for 24 months. 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.

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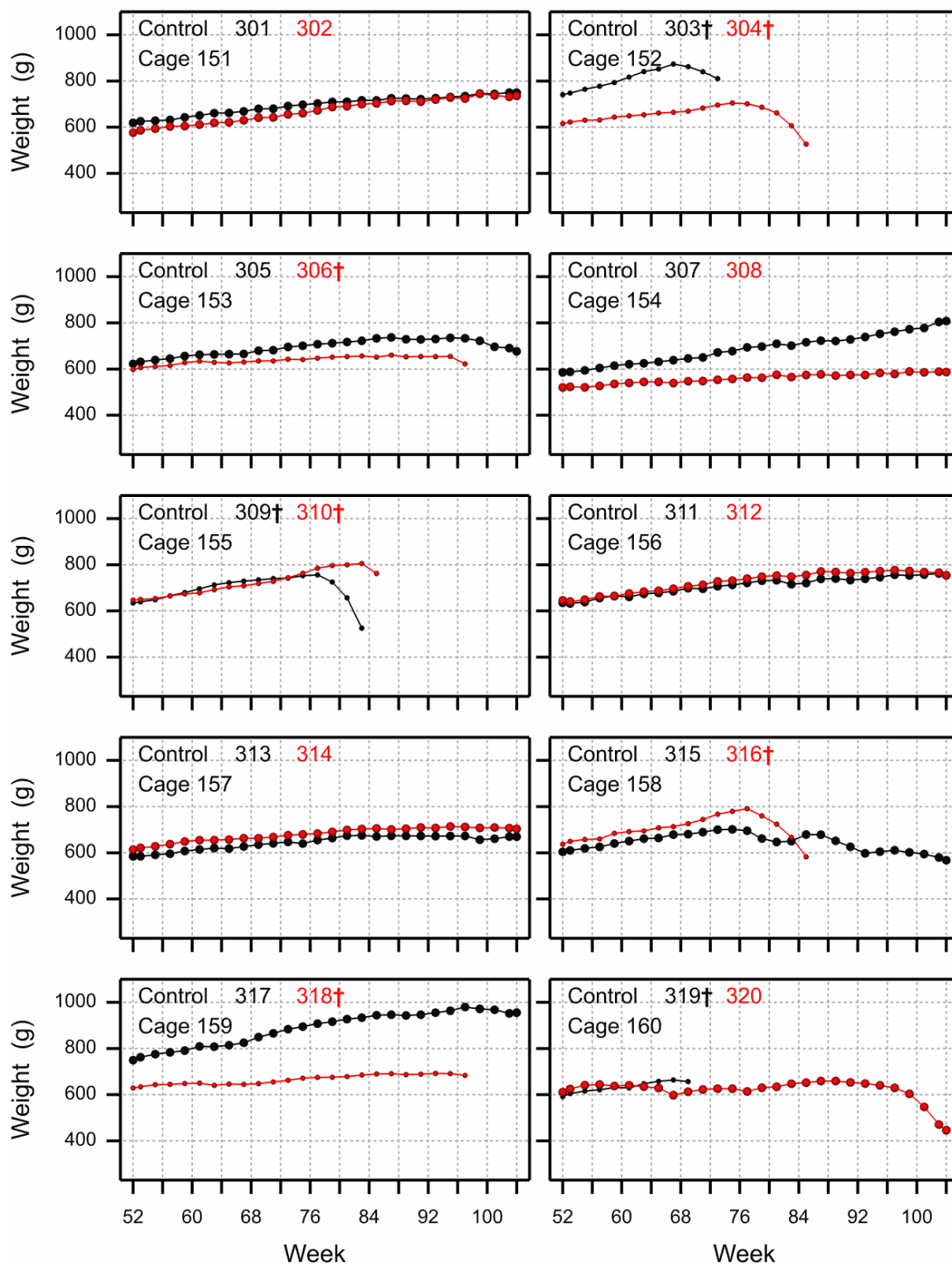
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Appendix 1. Growth curves per animal pair

The feed group and animal numbers are given in the left top corner of the graph. Large symbols are used for those animals that survived for 24 months.

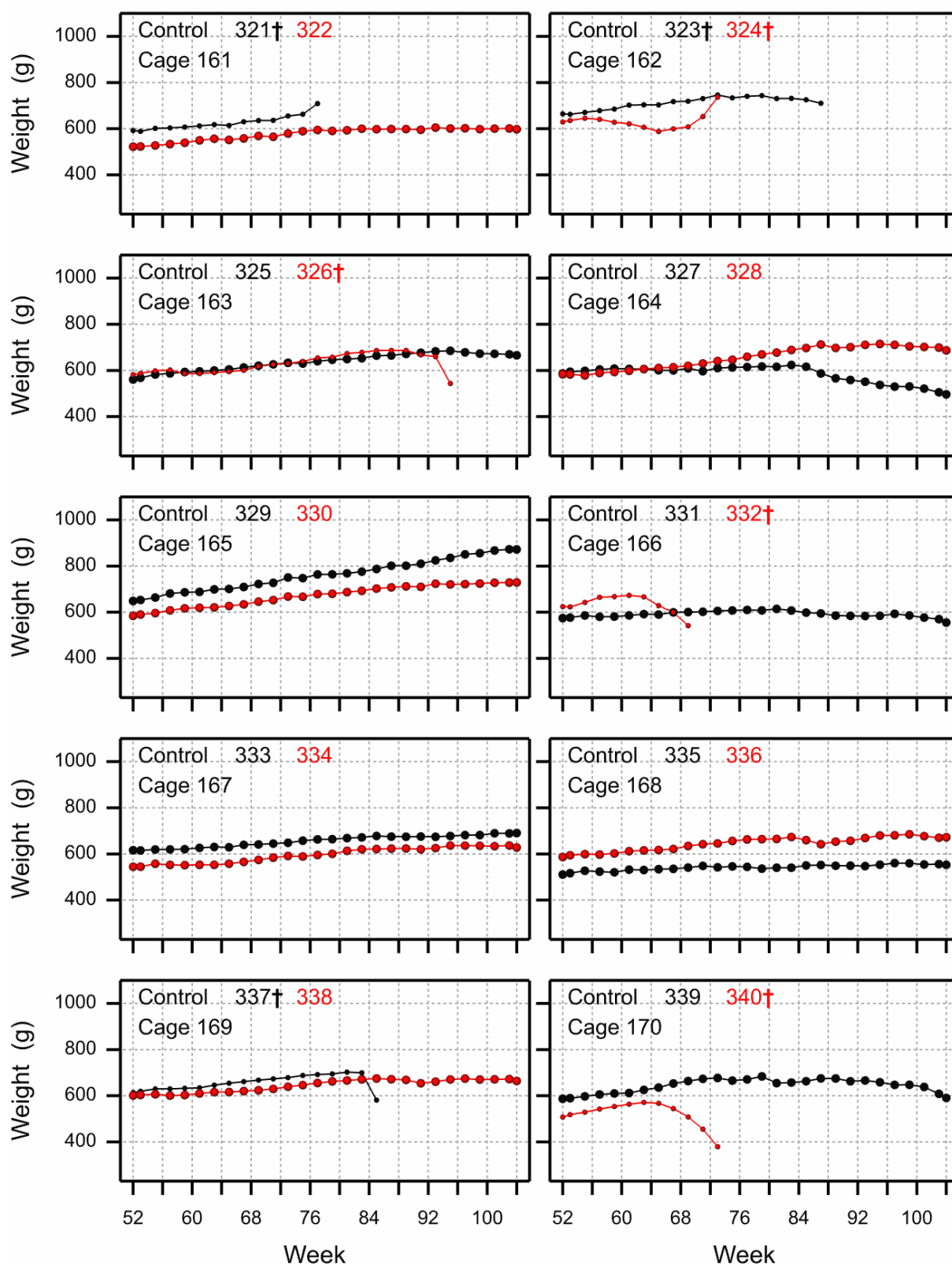
Study A - Weights weeks 52 - 104 Male



Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph. Large symbols are used for those animals that survived for 24 months.

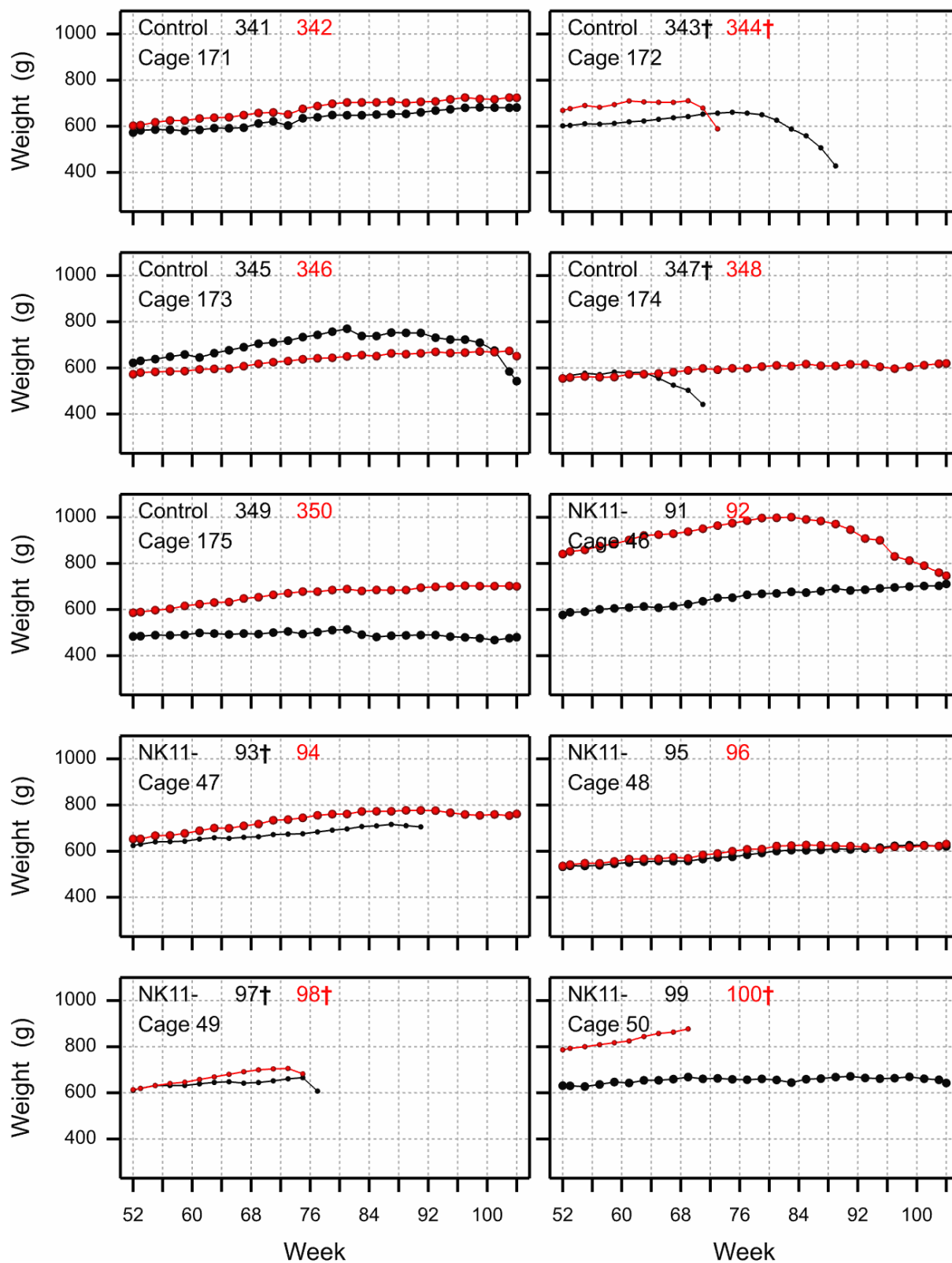
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Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph. Large symbols are used for those animals that survived for 24 months.

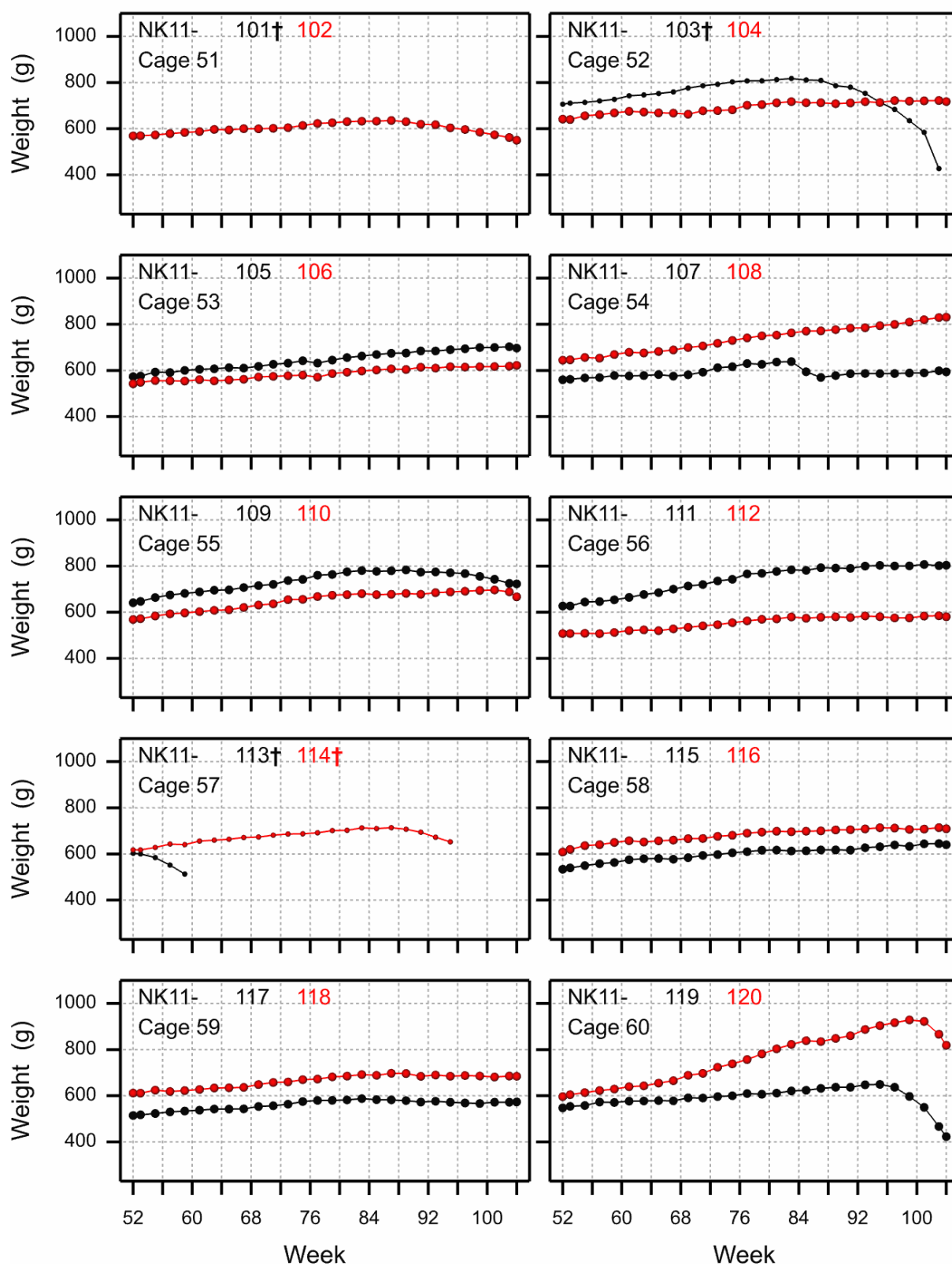
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Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph. Large symbols are used for those animals that survived for 24 months.

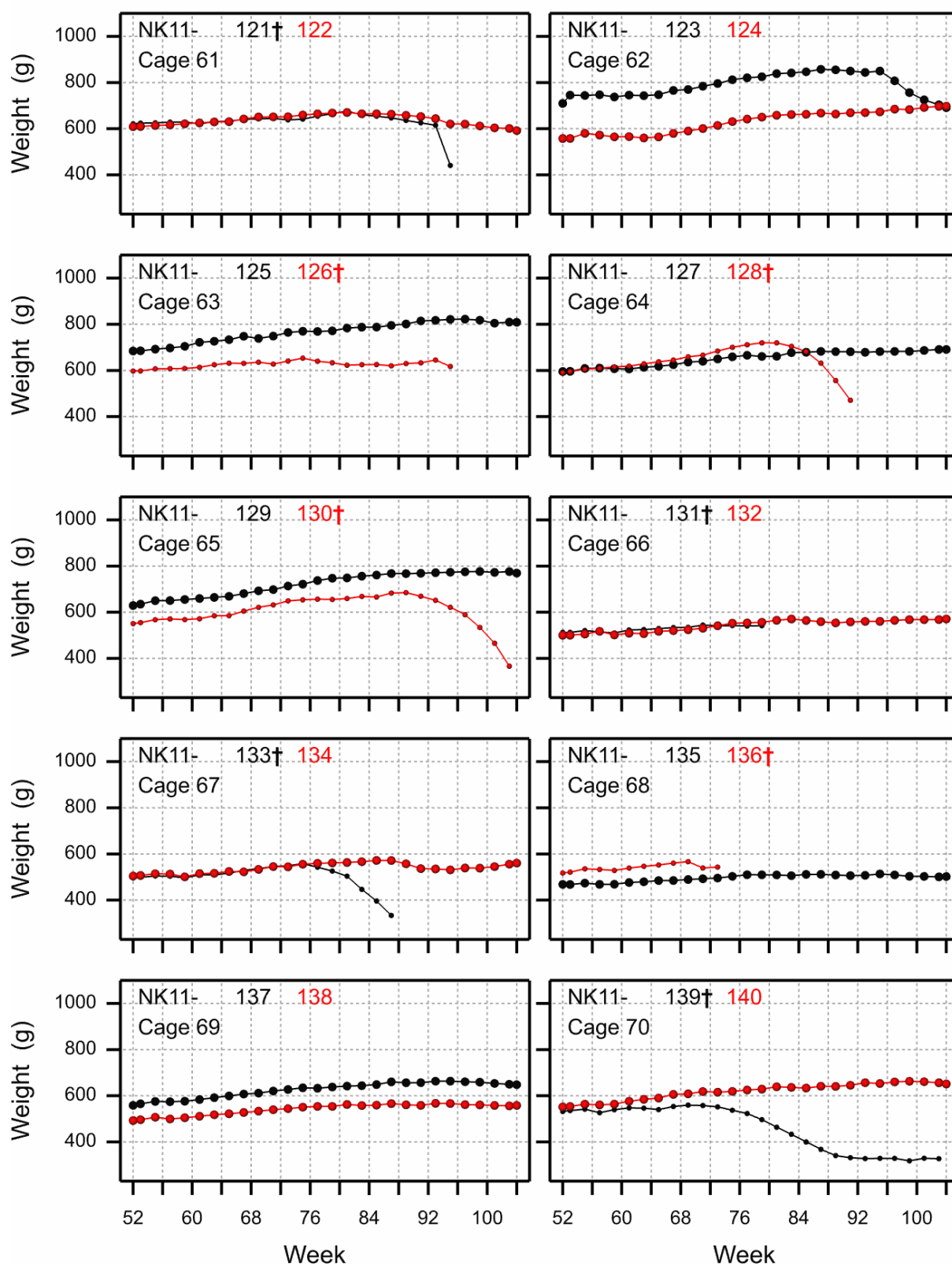
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Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph. Large symbols are used for those animals that survived for 24 months.

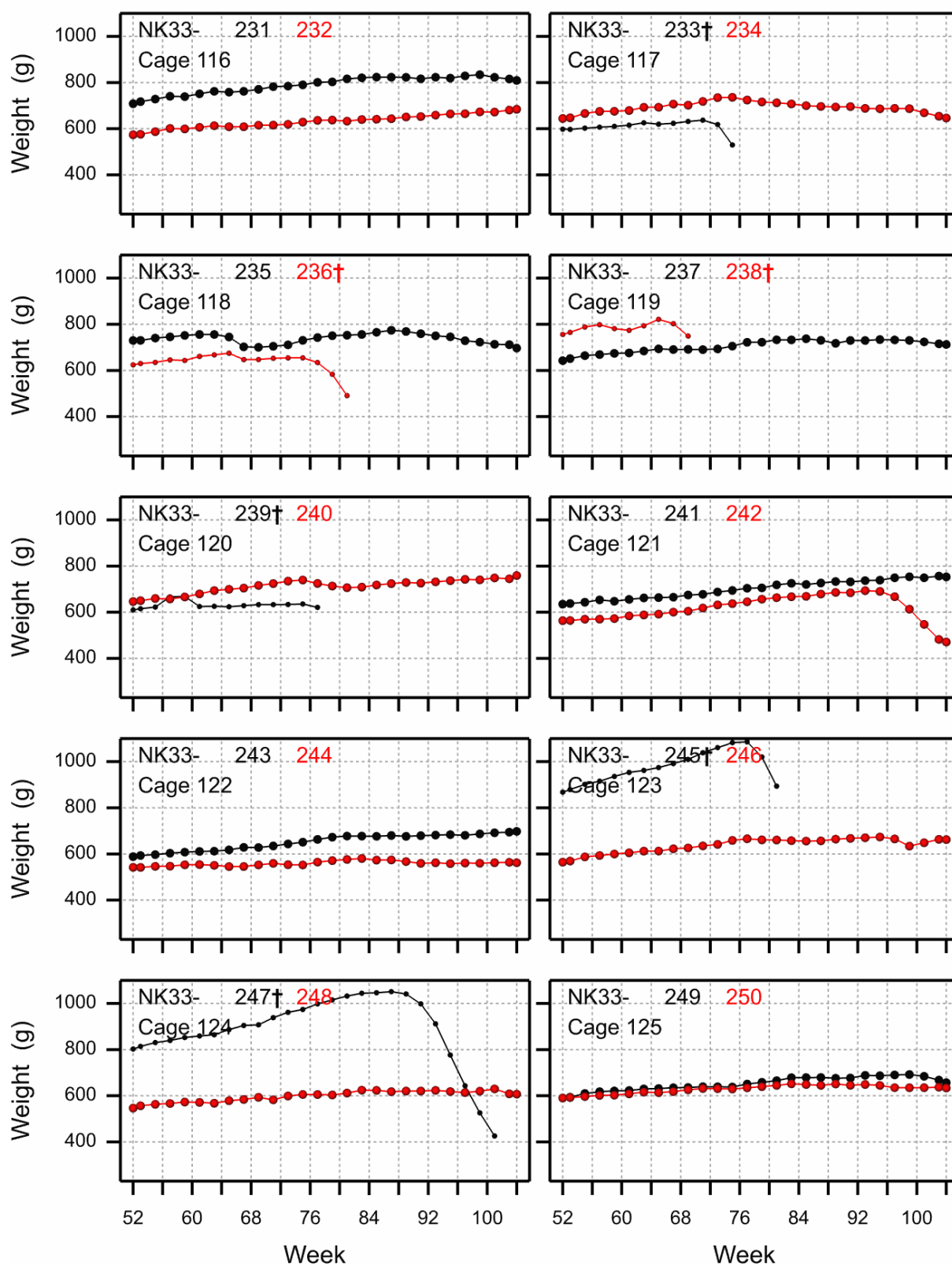
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Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph. Large symbols are used for those animals that survived for 24 months.

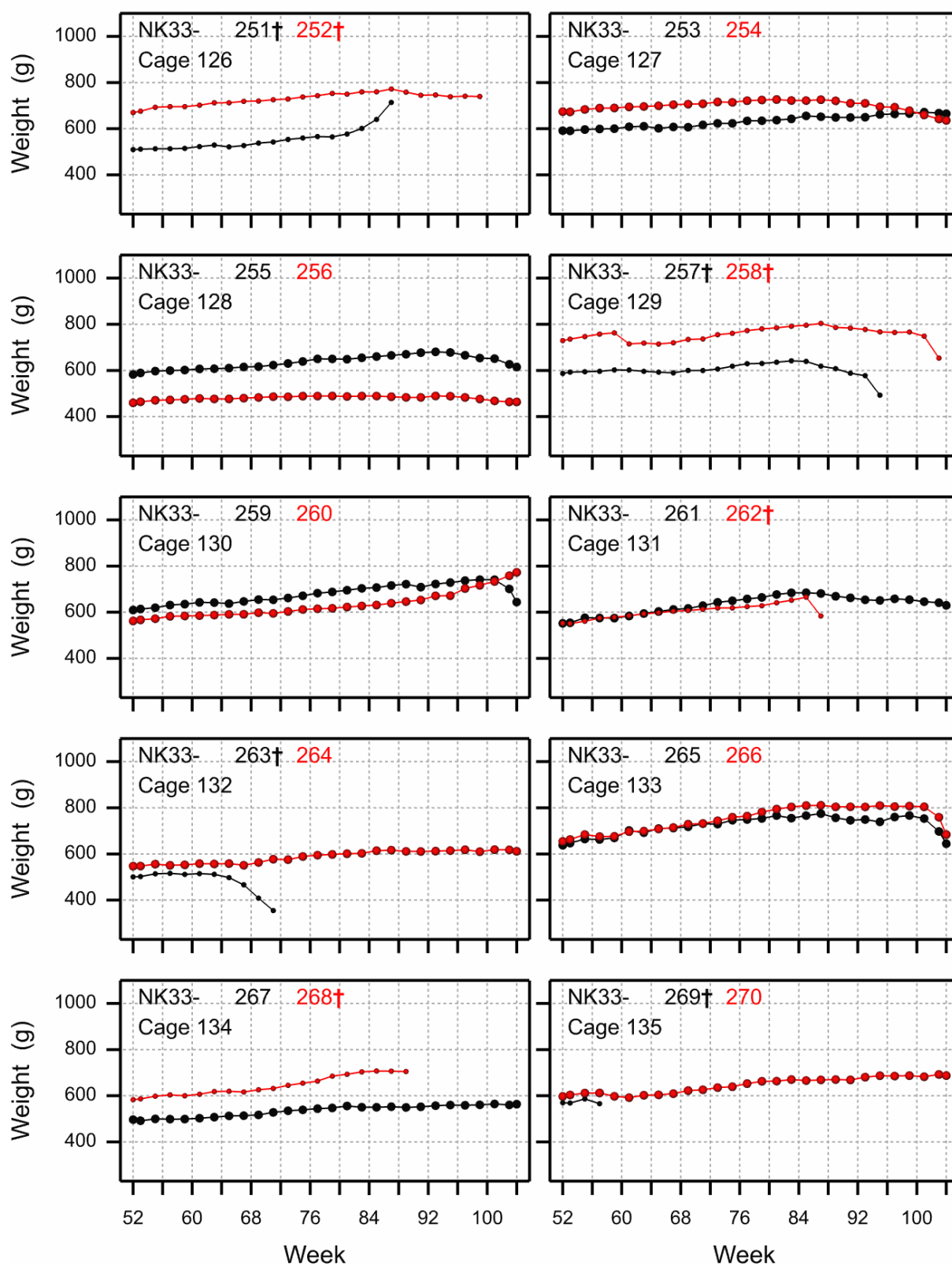
Study A - Weights weeks 52 - 104 Male



Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph. Large symbols are used for those animals that survived for 24 months.

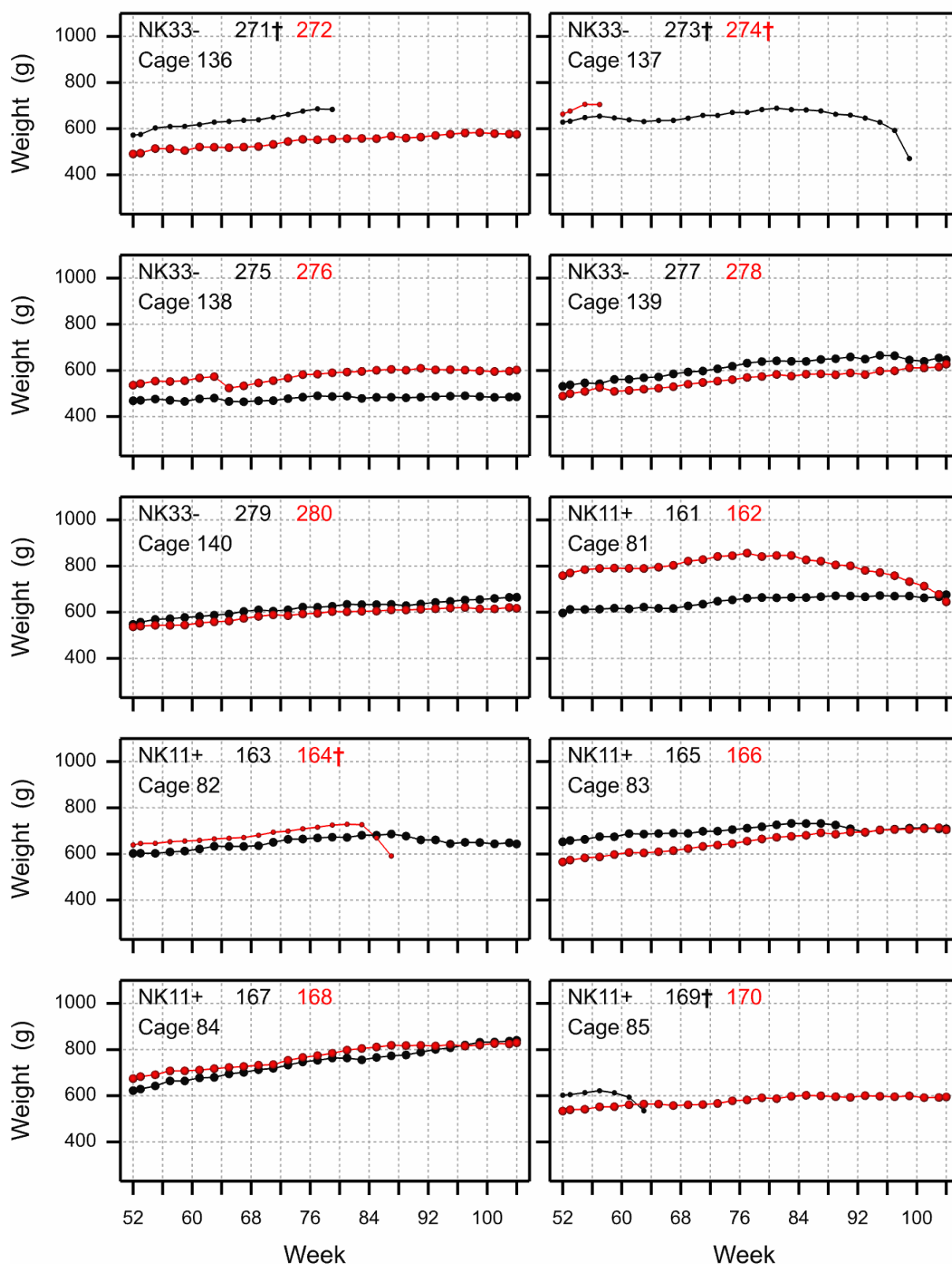
Study A - Weights weeks 52 - 104 Male



Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph. Large symbols are used for those animals that survived for 24 months.

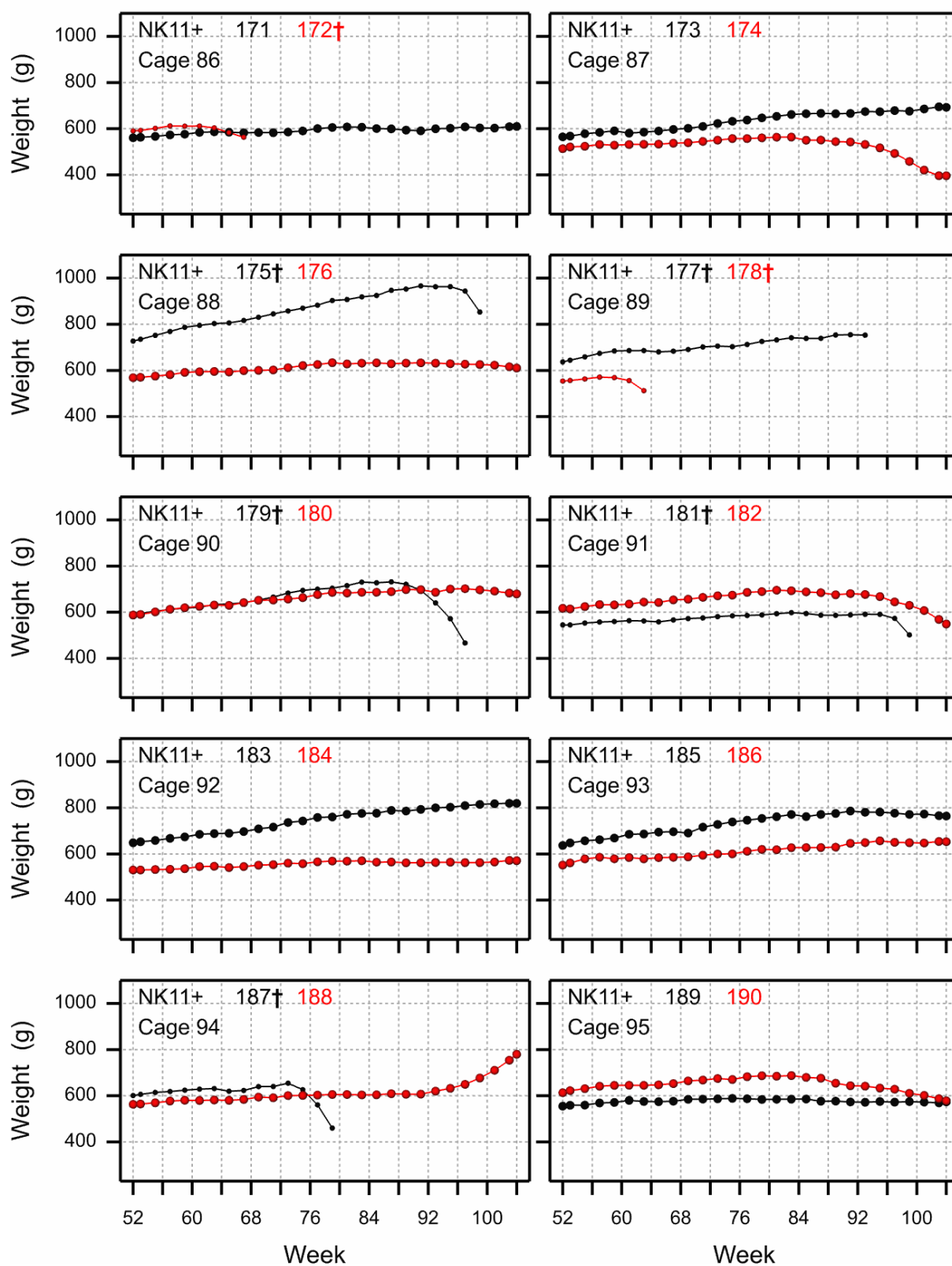
Study A - Weights weeks 52 - 104 Male



Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph. Large symbols are used for those animals that survived for 24 months.

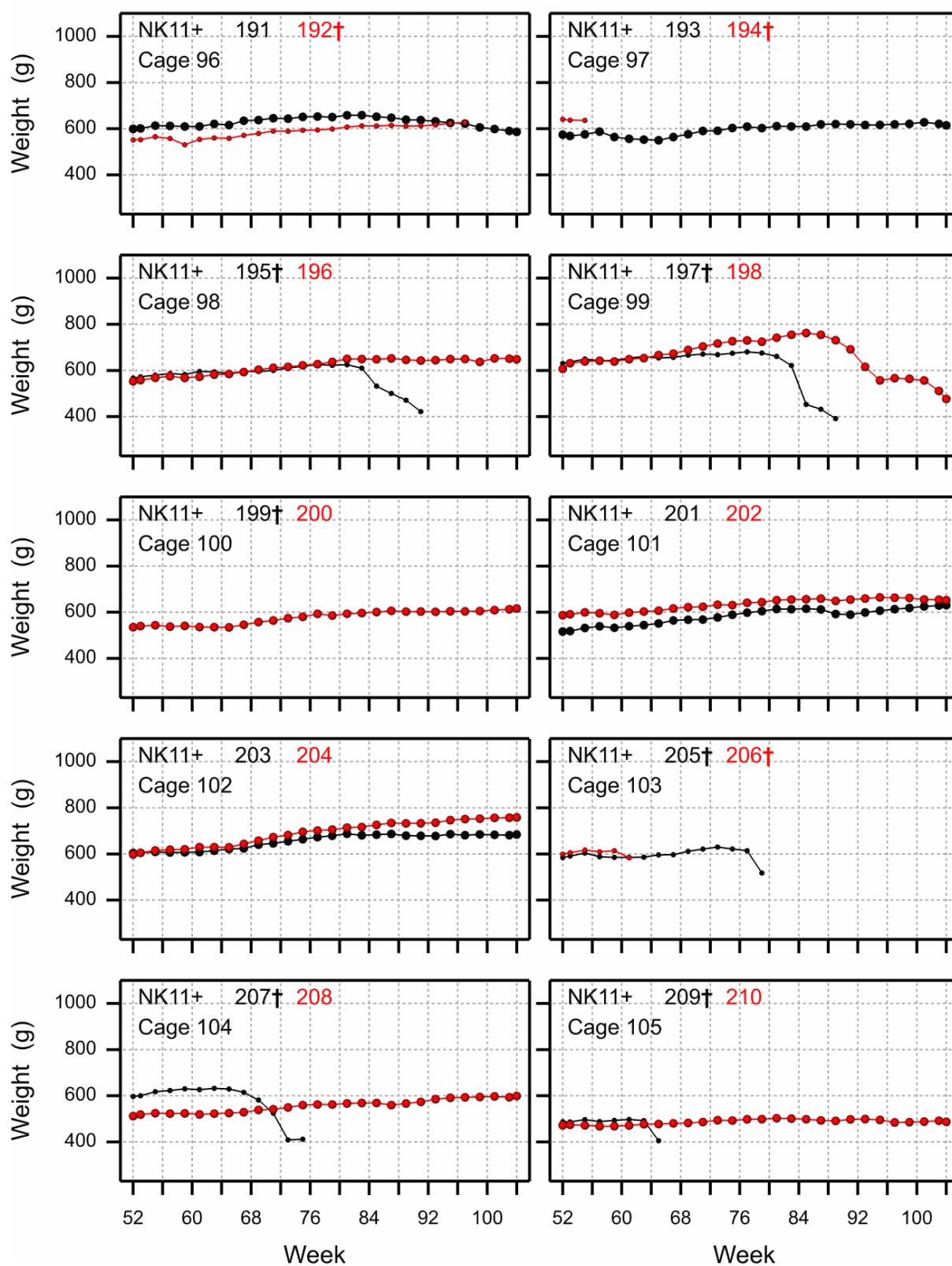
Study A - Weights weeks 52 - 104 Male



Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph. Large symbols are used for those animals that survived for 24 months.

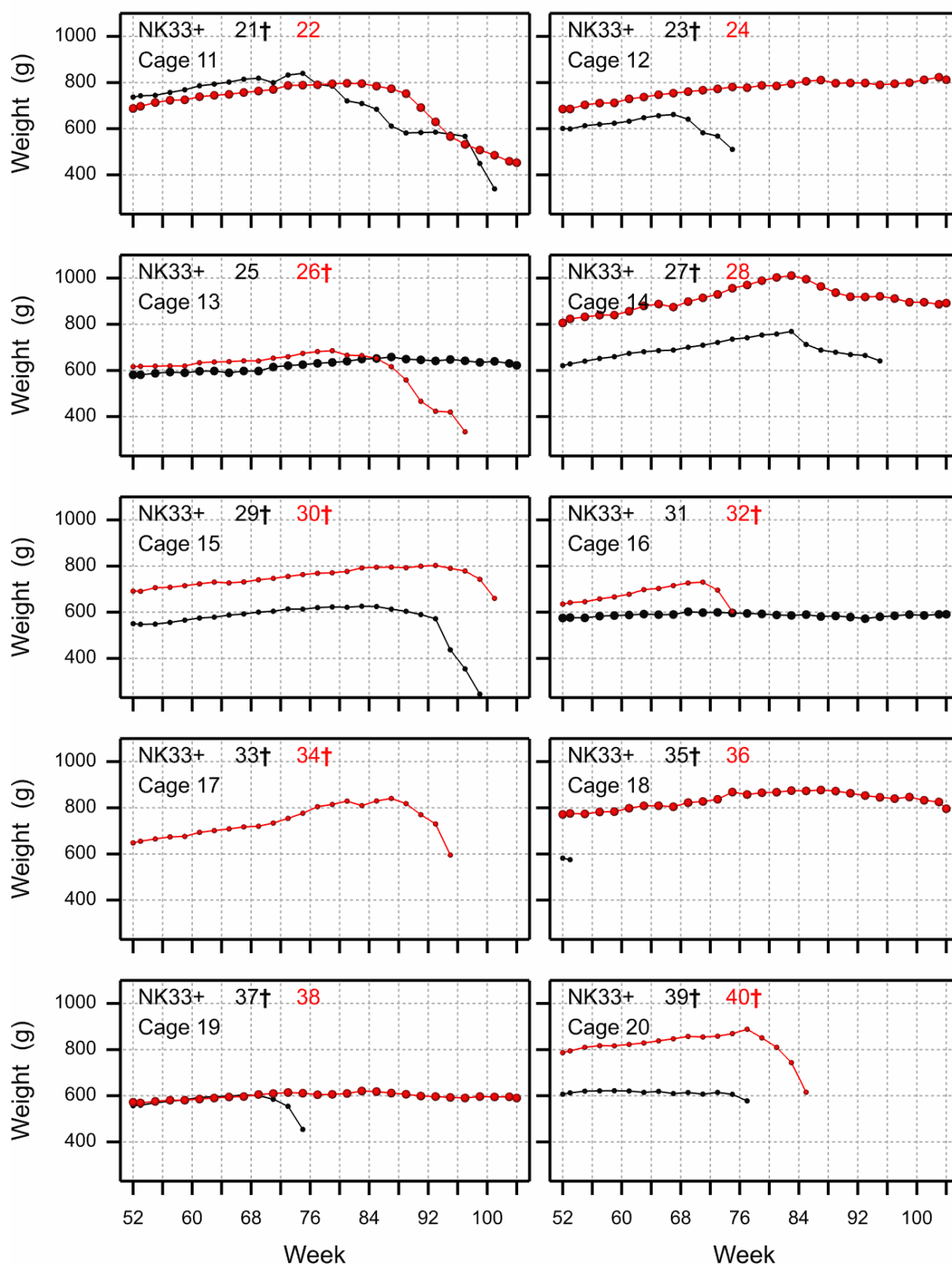
Study A - Weights weeks 52 - 104 Male



Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph. Large symbols are used for those animals that survived for 24 months.

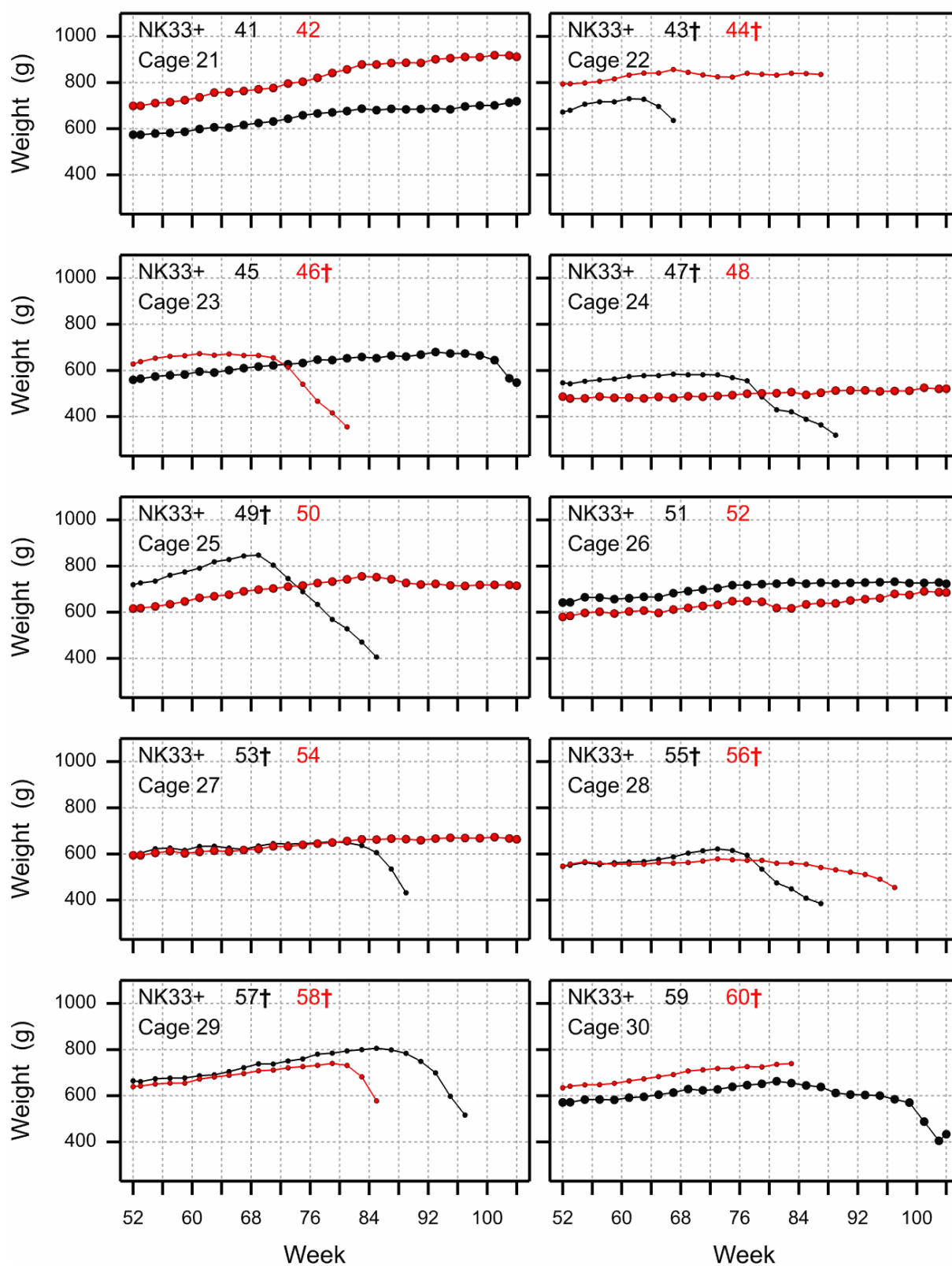
Study A - Weights weeks 52 - 104 Male



Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph. Large symbols are used for those animals that survived for 24 months.

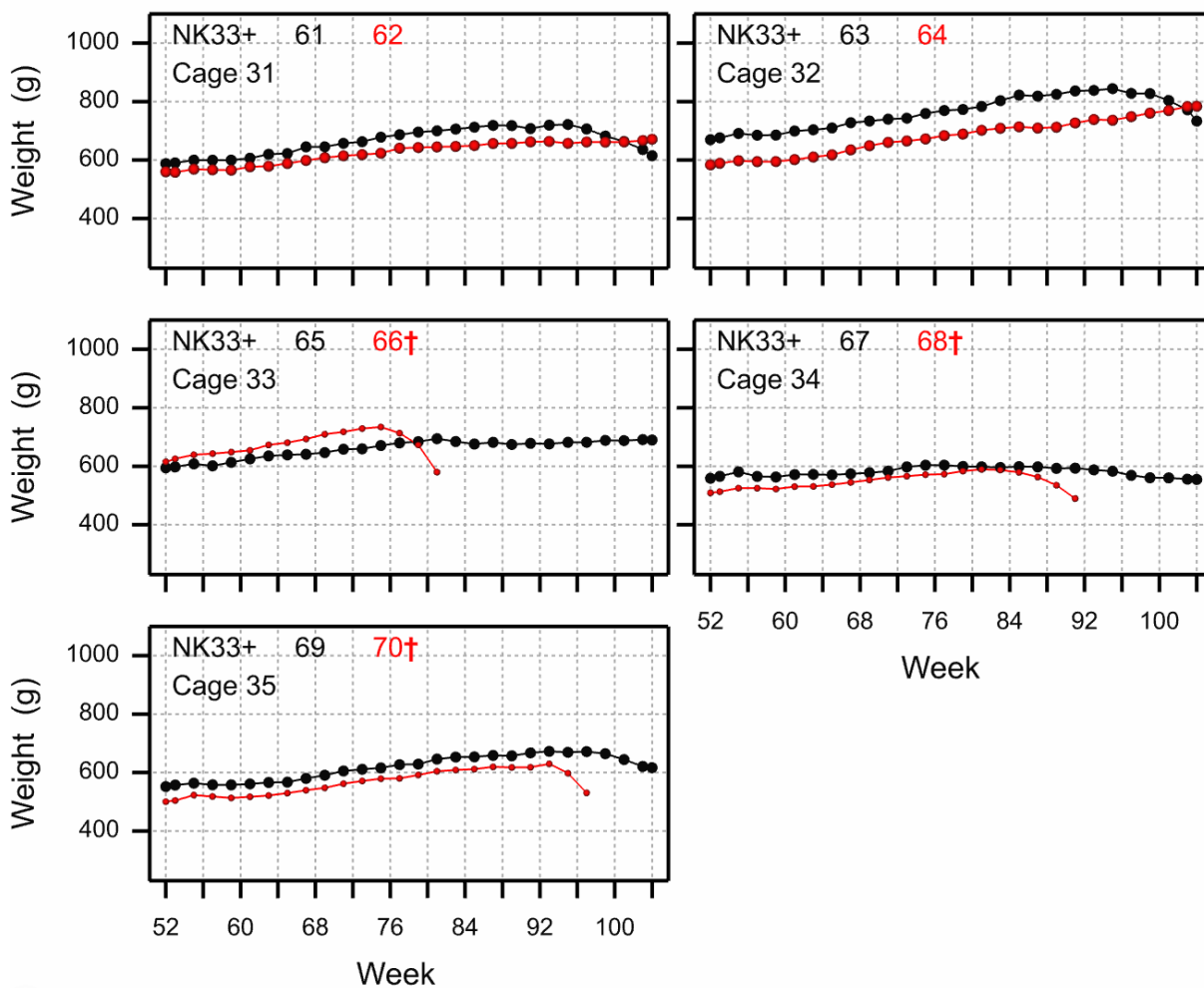
Study A - Weights weeks 52 - 104 Male



Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph. Large symbols are used for those animals that survived for 24 months.

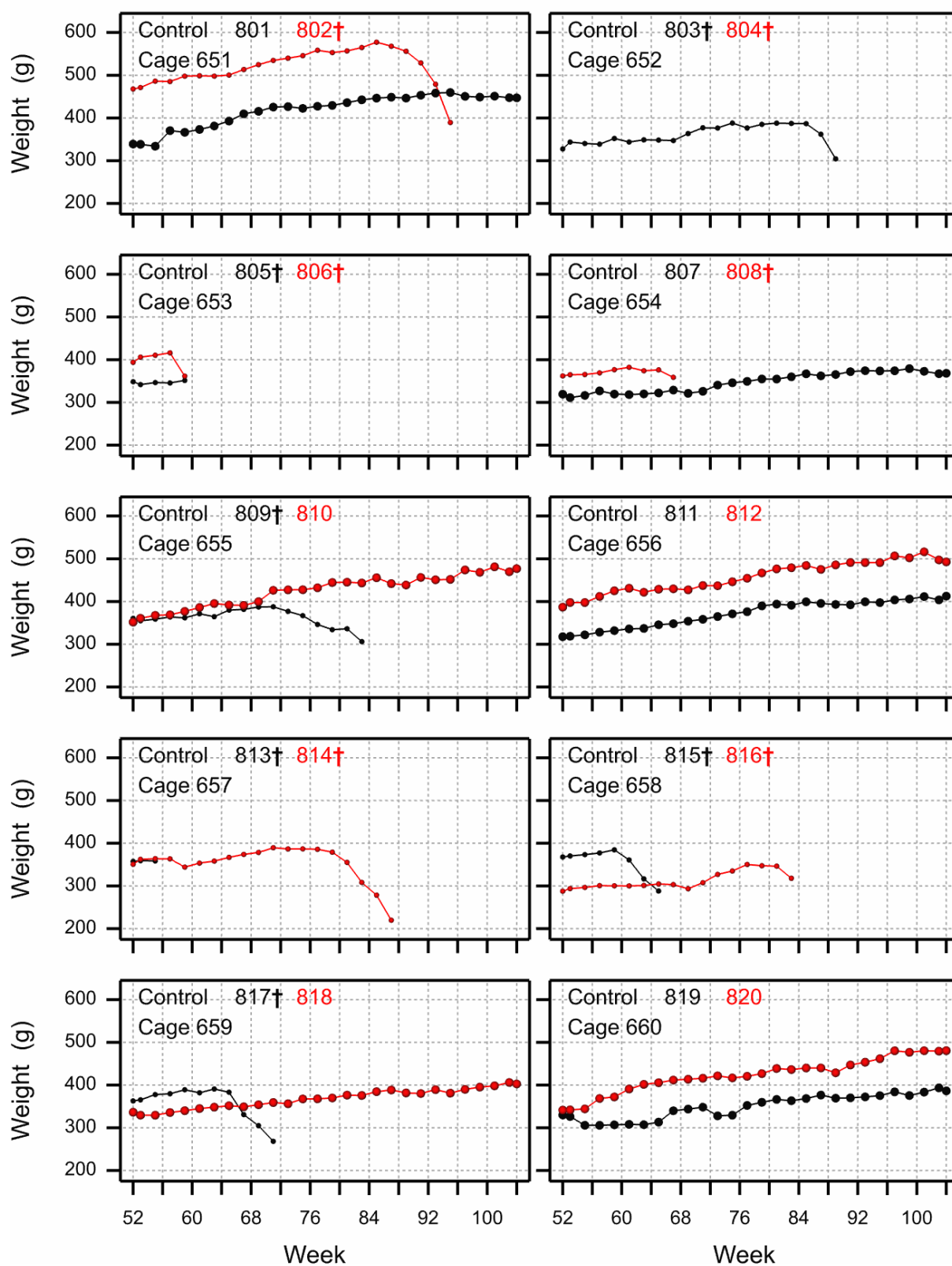
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Appendix 1. Growth curves per animal pair (continued)

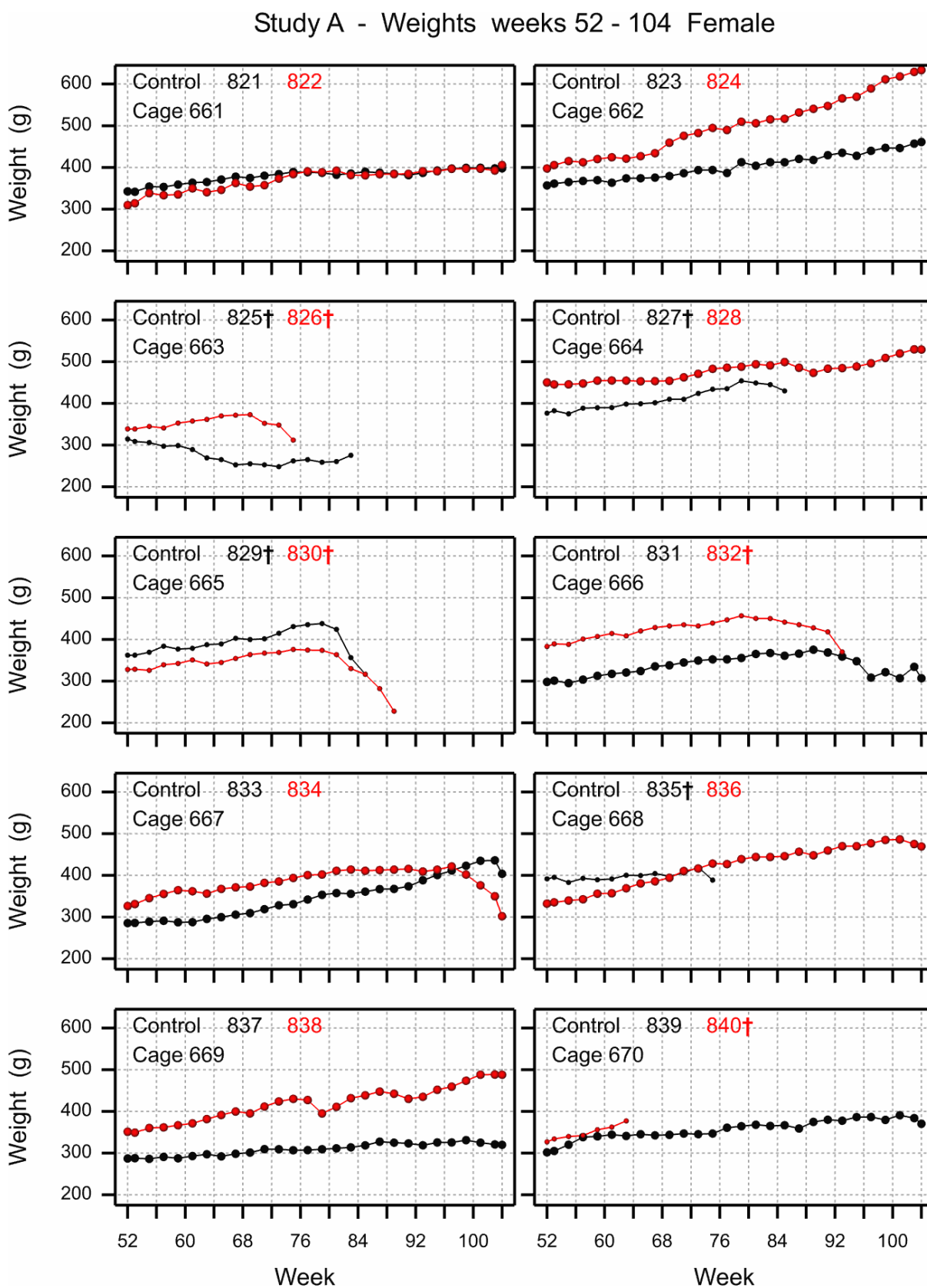
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Appendix 1. Growth curves per animal pair (continued)

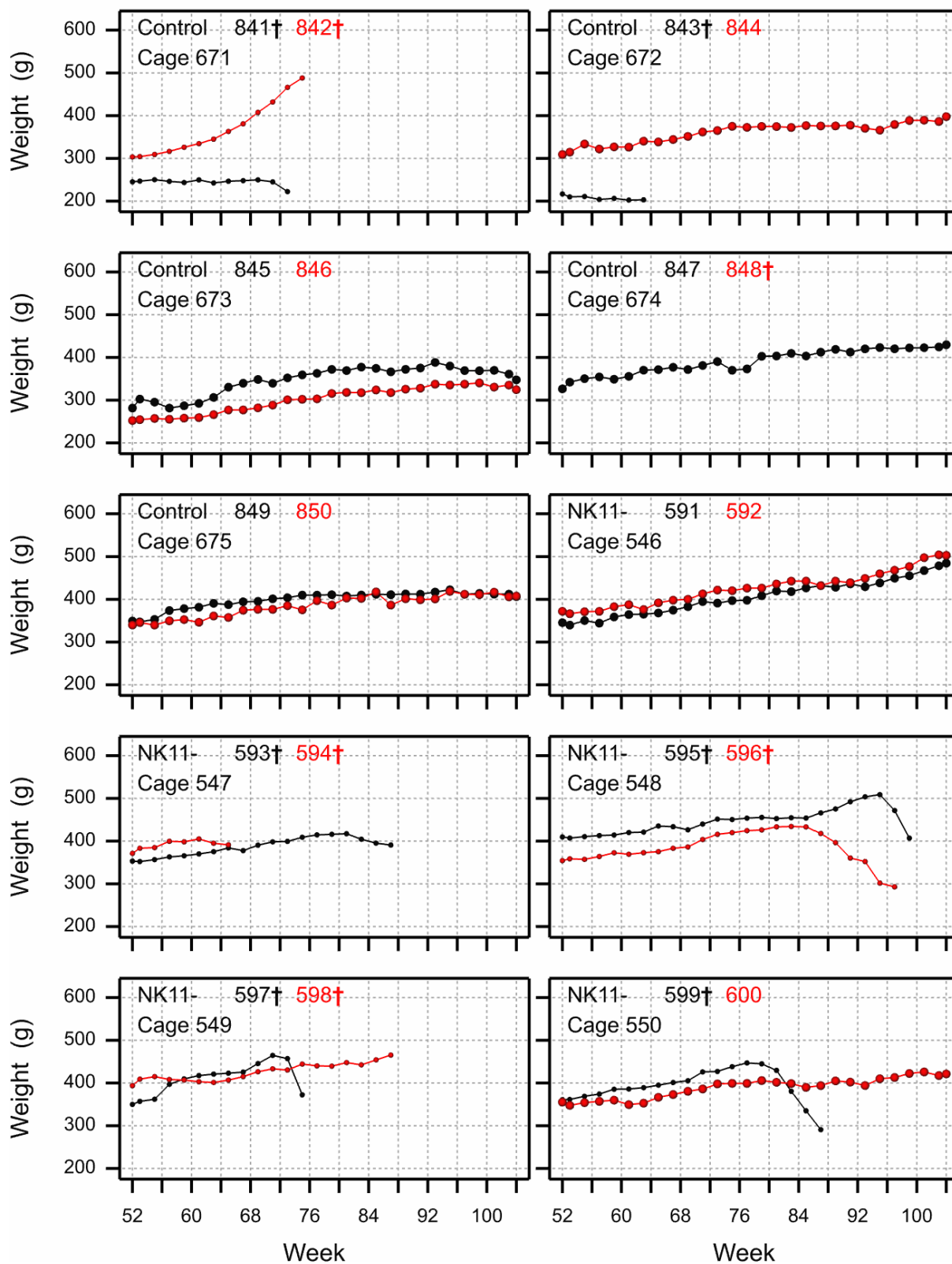
The feed group and animal numbers are given in the left top corner of the graph. Large symbols are used for those animals that survived for 24 months.



Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph. Large symbols are used for those animals that survived for 24 months.

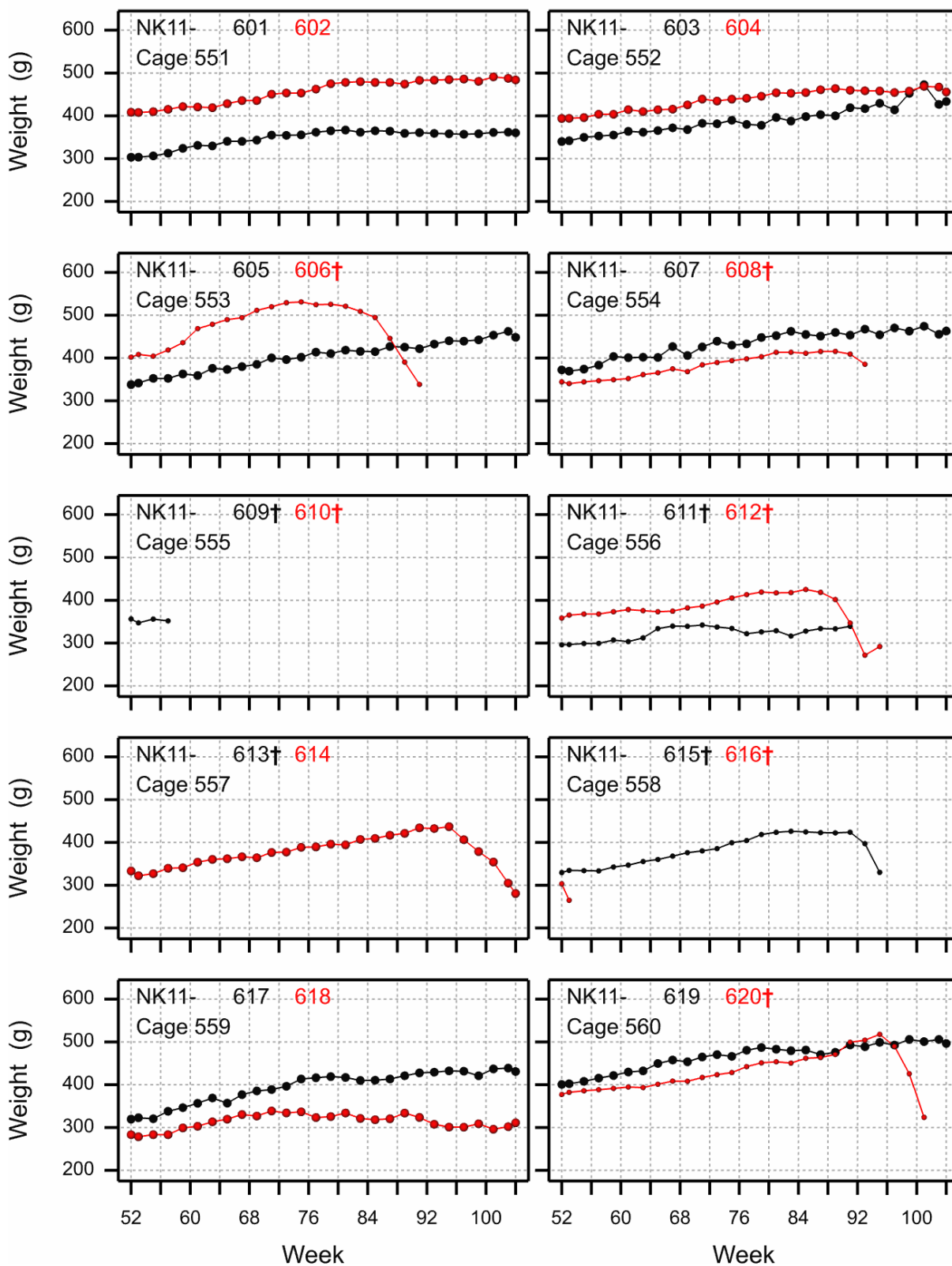
Study A - Weights weeks 52 - 104 Female



Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph. Large symbols are used for those animals that survived for 24 months.

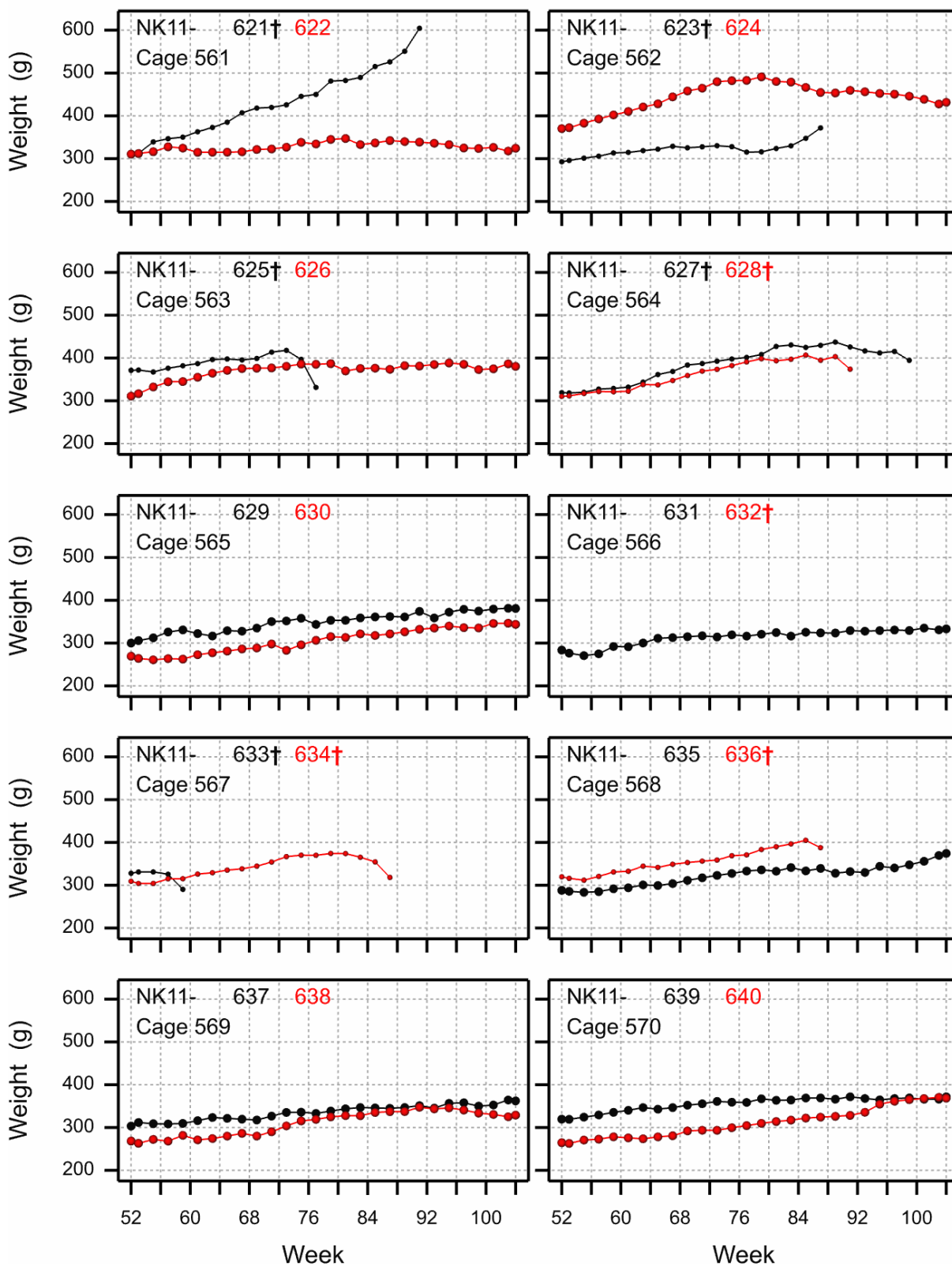
Study A - Weights weeks 52 - 104 Female



Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph. Large symbols are used for those animals that survived for 24 months.

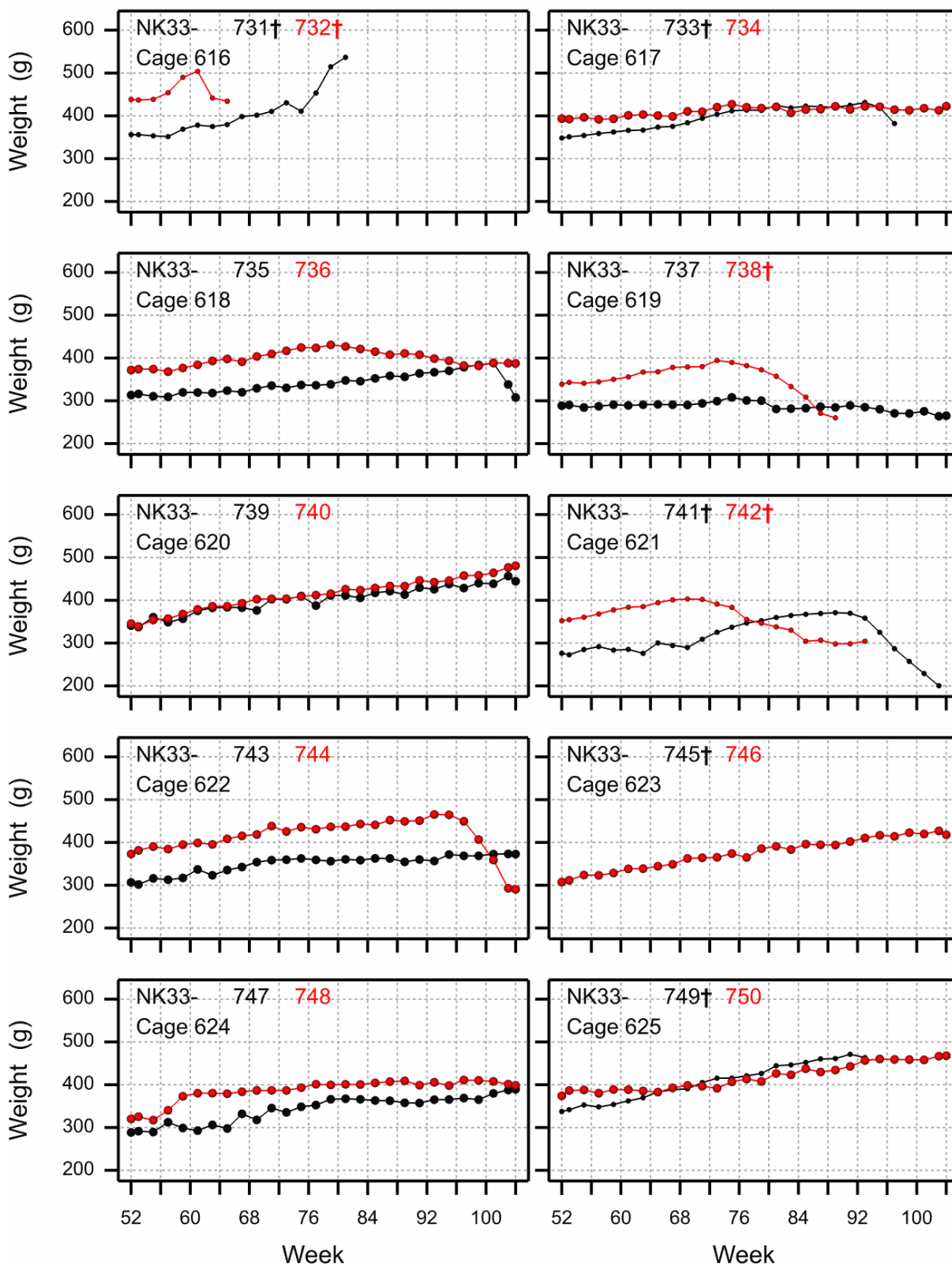
Study A - Weights weeks 52 - 104 Female



Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph. Large symbols are used for those animals that survived for 24 months.

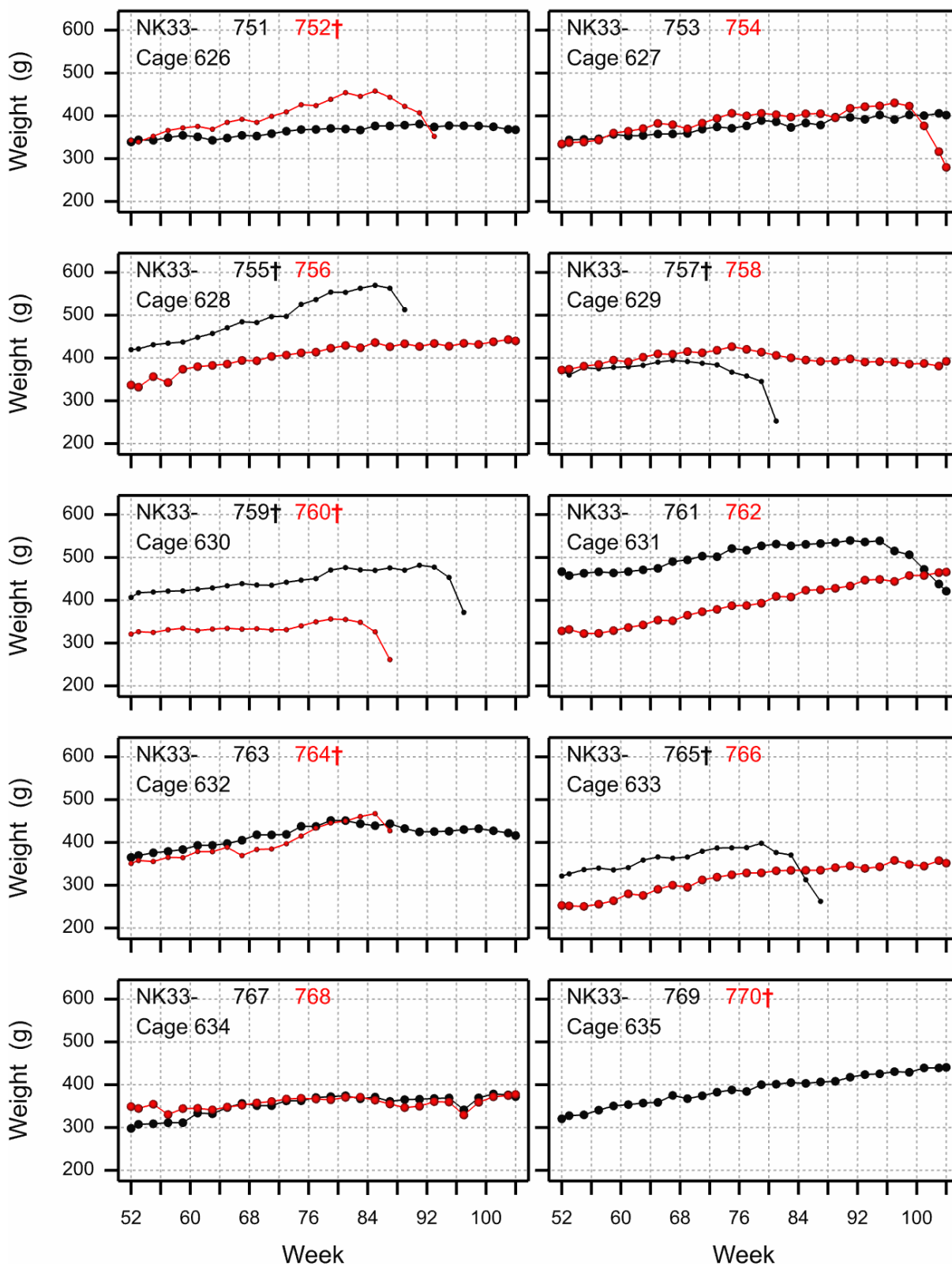
Study A - Weights weeks 52 - 104 Female



Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph. Large symbols are used for those animals that survived for 24 months.

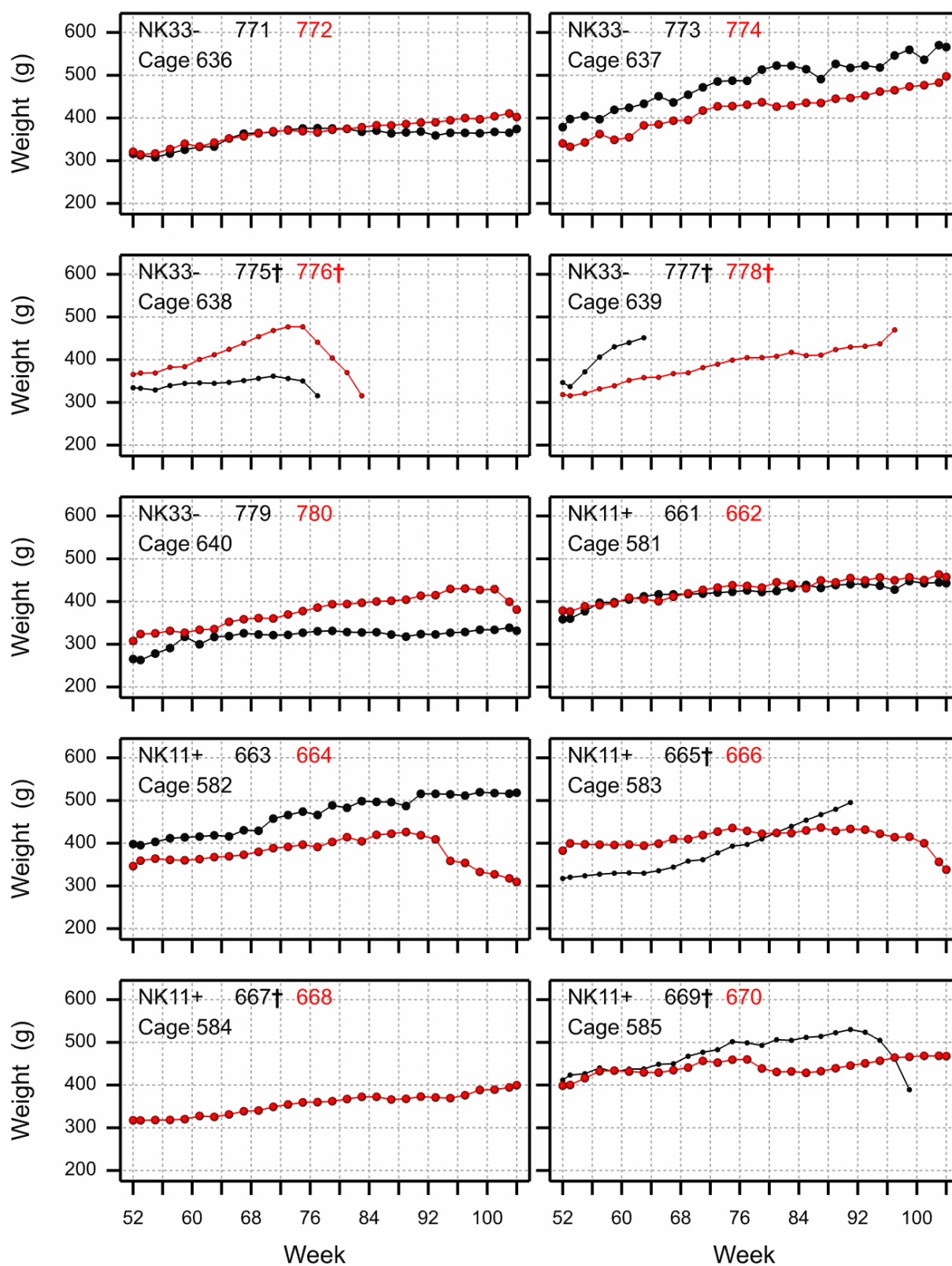
Study A - Weights weeks 52 - 104 Female



Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph. Large symbols are used for those animals that survived for 24 months.

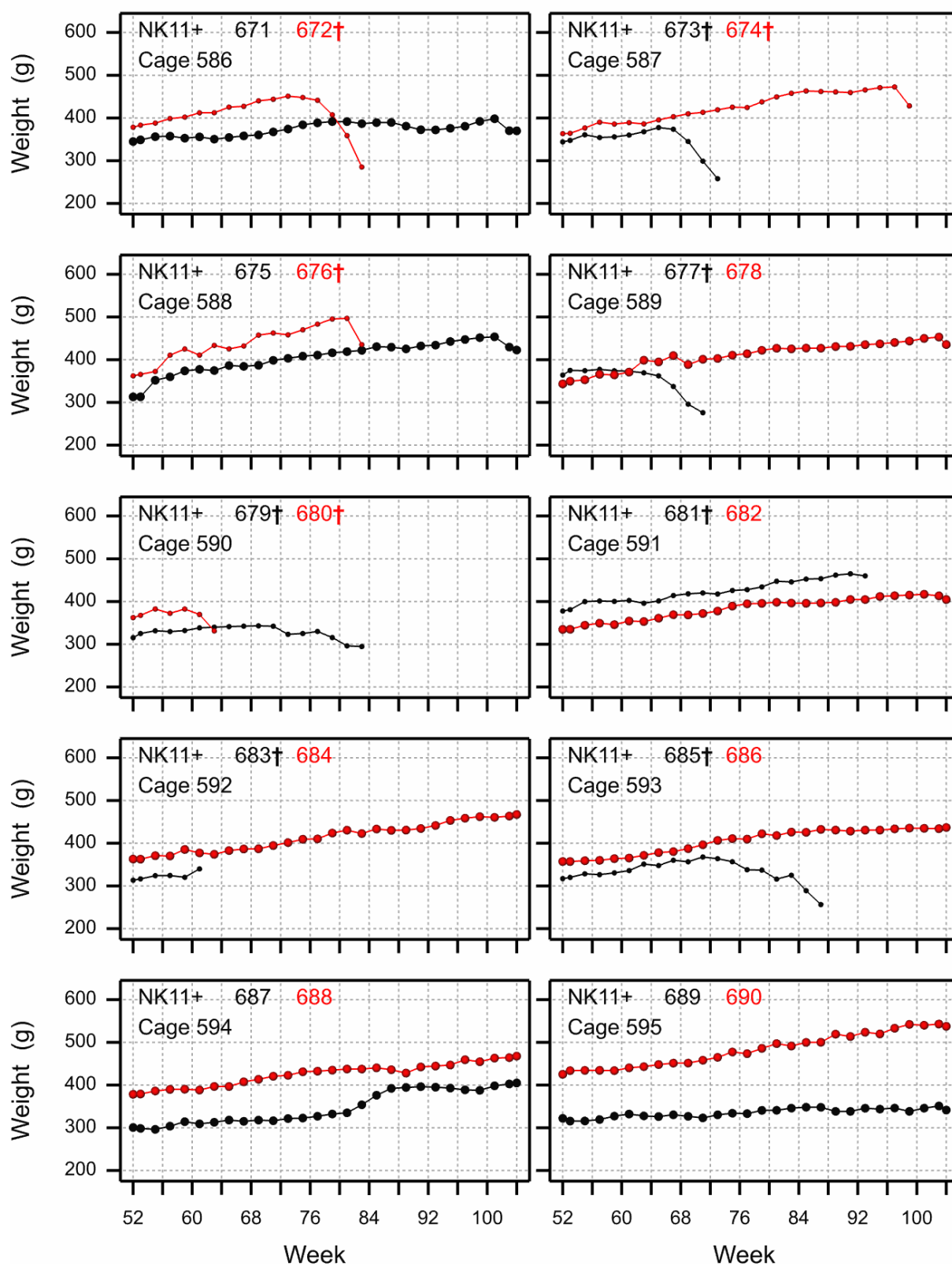
Study A - Weights weeks 52 - 104 Female



Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph. Large symbols are used for those animals that survived for 24 months.

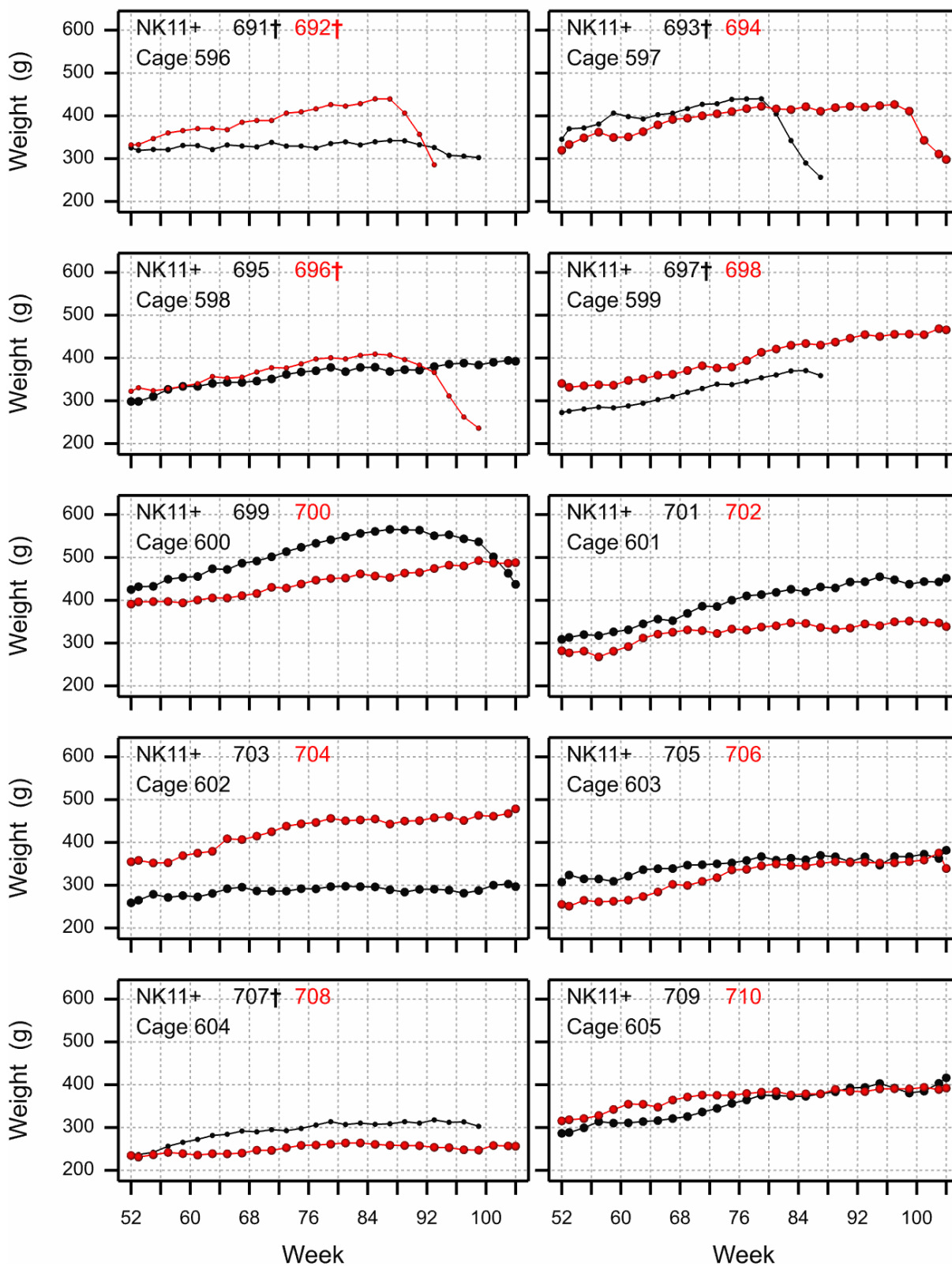
Study A - Weights weeks 52 - 104 Female



Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph. Large symbols are used for those animals that survived for 24 months.

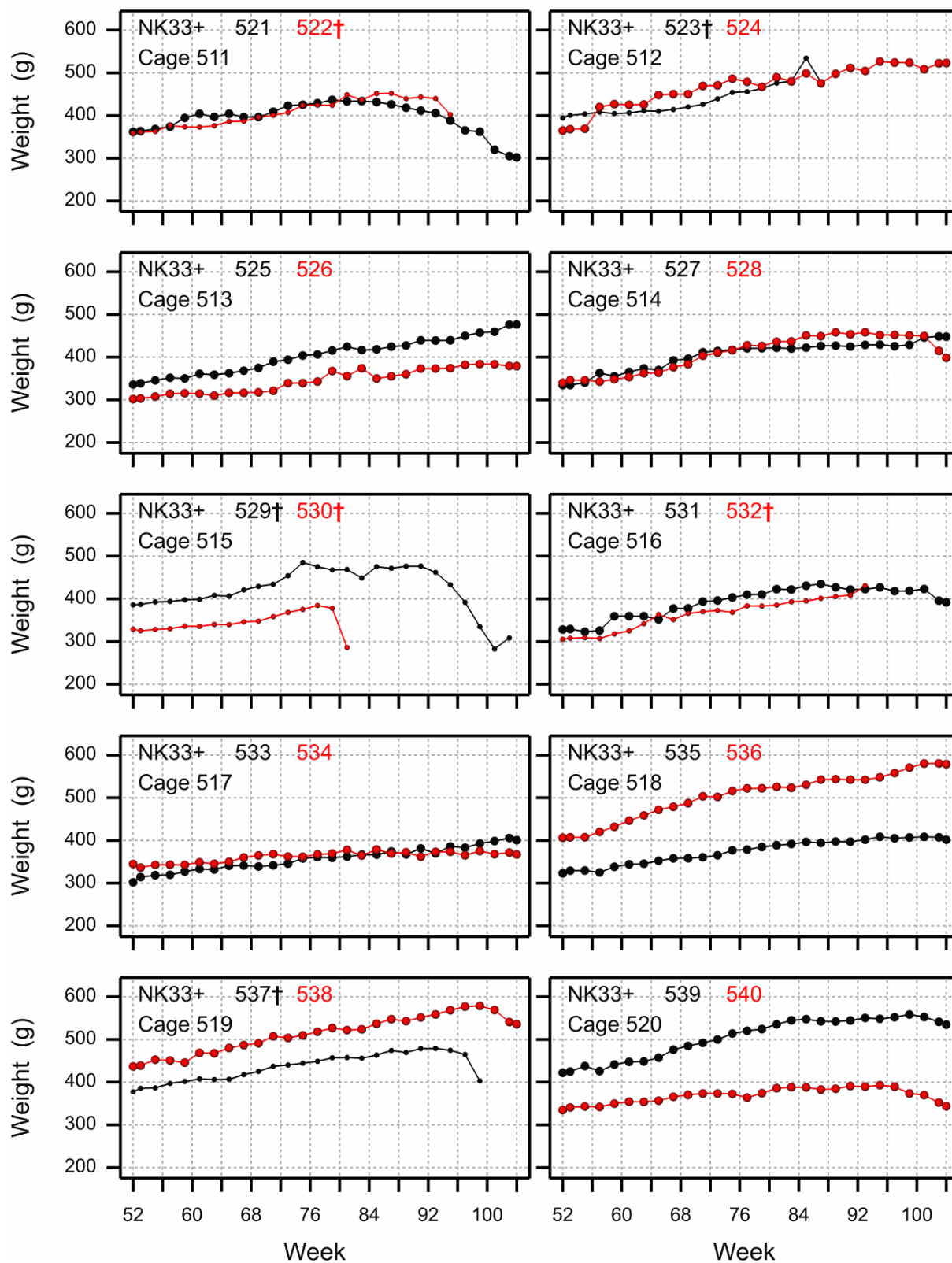
Study A - Weights weeks 52 - 104 Female



Appendix 1. Growth curves per animal pair (continued)

The feed group and animal numbers are given in the left top corner of the graph. Large symbols are used for those animals that survived for 24 months.

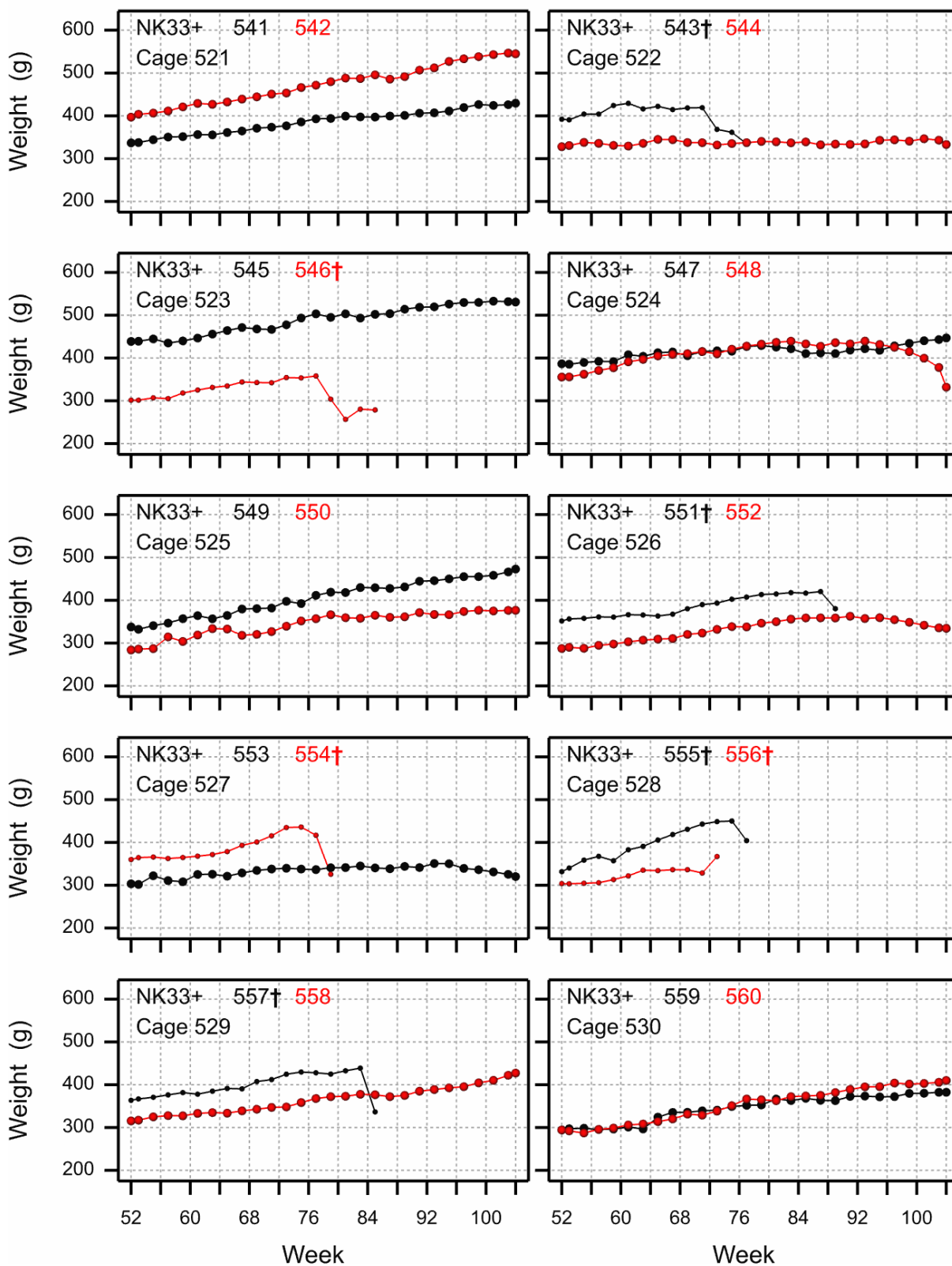
Study A - Weights weeks 52 - 104 Female



Appendix 1. Growth curves per animal pair (continued)

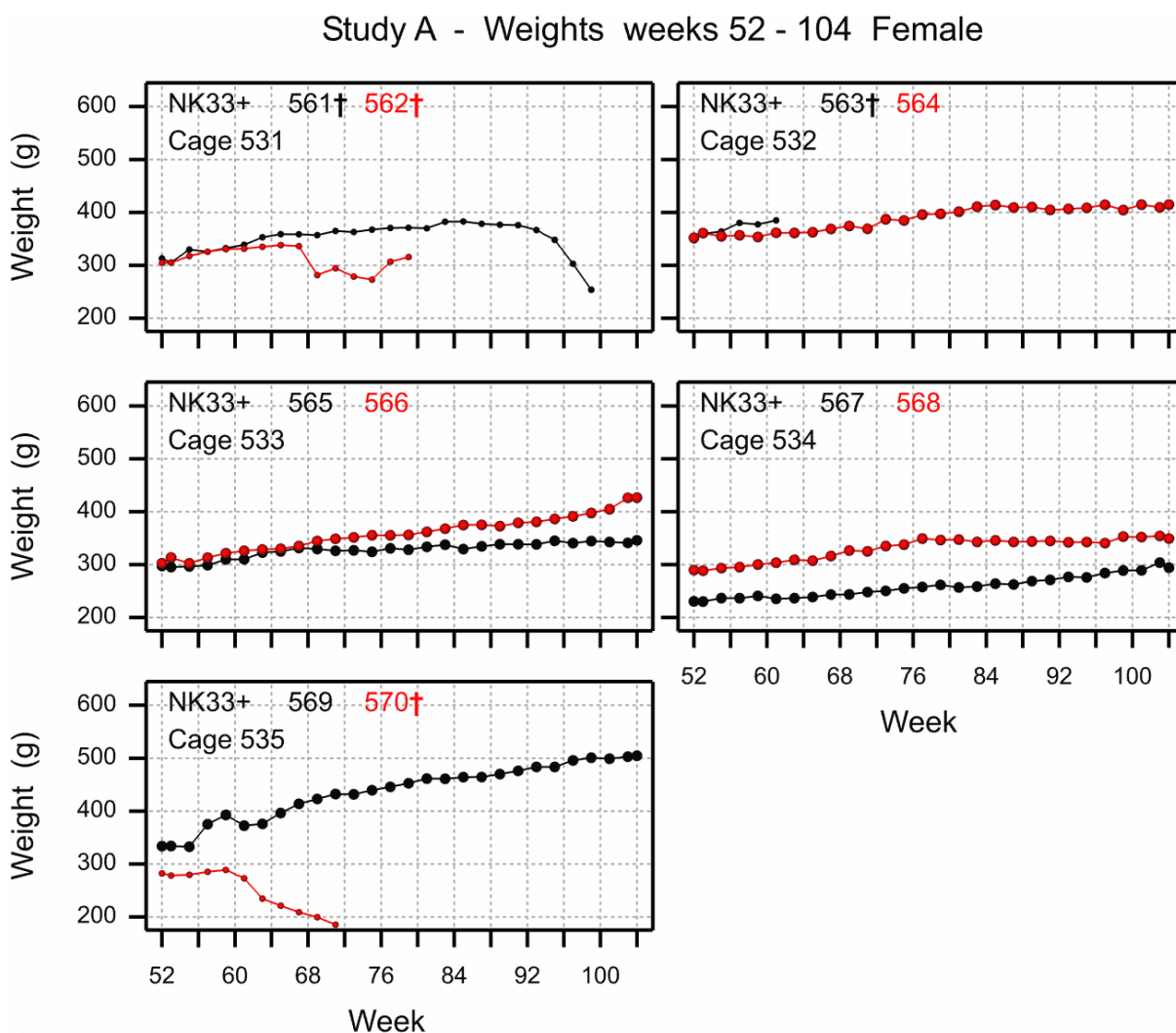
The feed group and animal numbers are given in the left top corner of the graph. Large symbols are used for those animals that survived for 24 months.

Study A - Weights weeks 52 - 104 Female



Appendix 1. Growth curves per animal pair (continued)

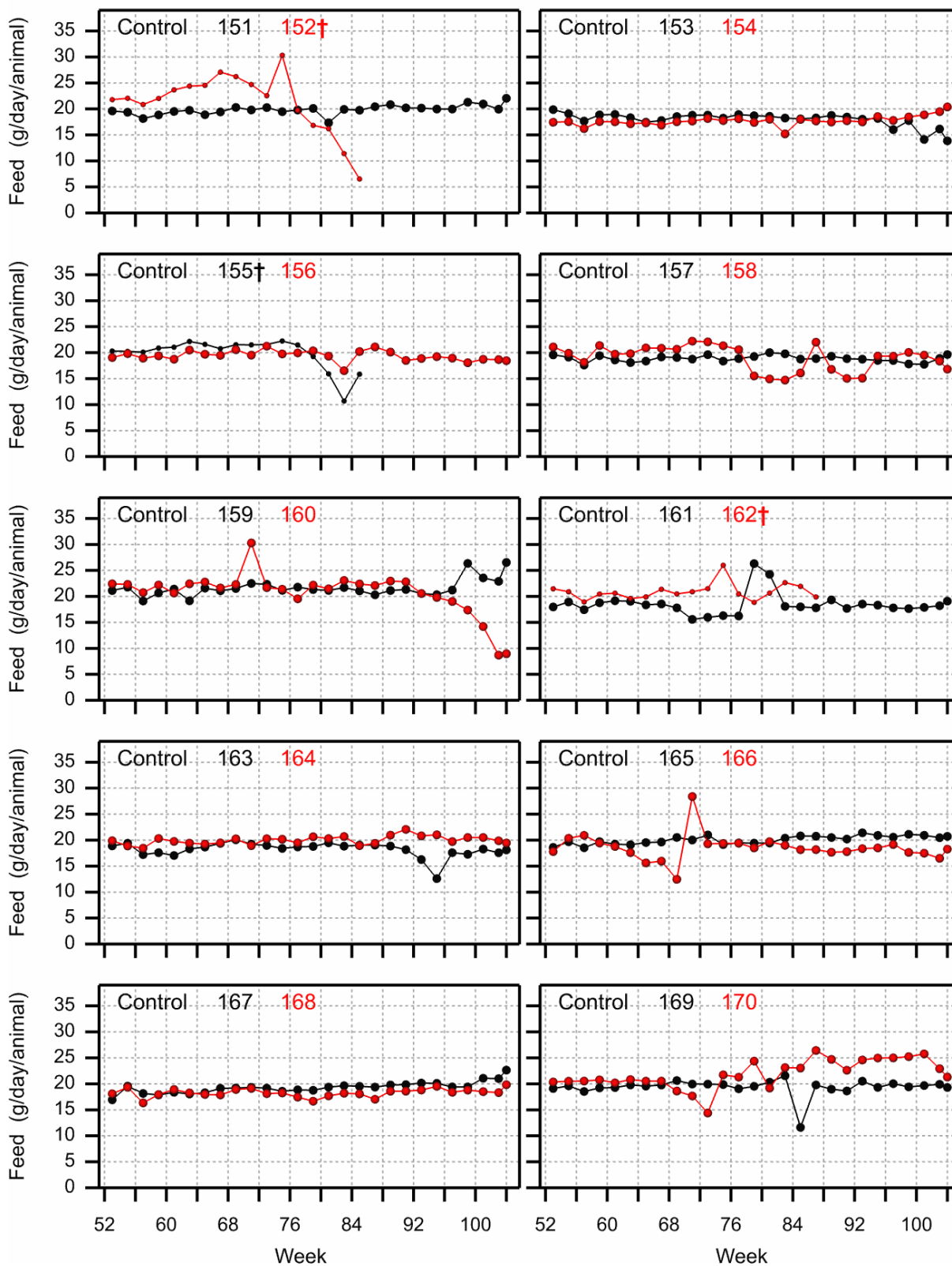
The feed group and animal numbers are given in the left top corner of the graph. Large symbols are used for those animals that survived for 24 months.



Appendix 2. Feed consumption per cage

The feed group and cage numbers are given in the left top corner of the graph. Large symbols are used for those cages in which one or two animals that survived for 24 months.

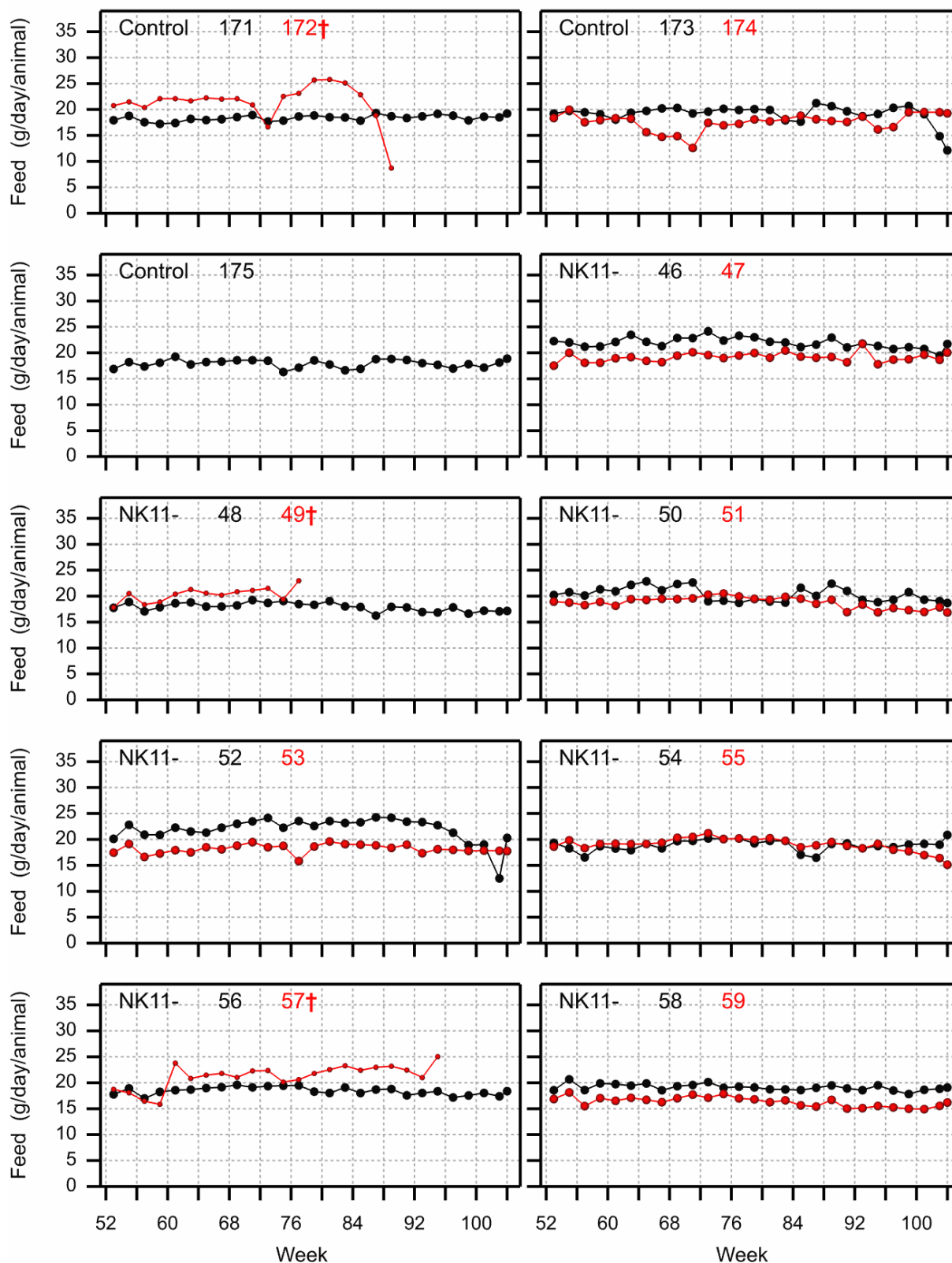
Study A - Feed Consumption weeks 52 - 104 Male



Appendix 2. Feed consumption per cage (continued)

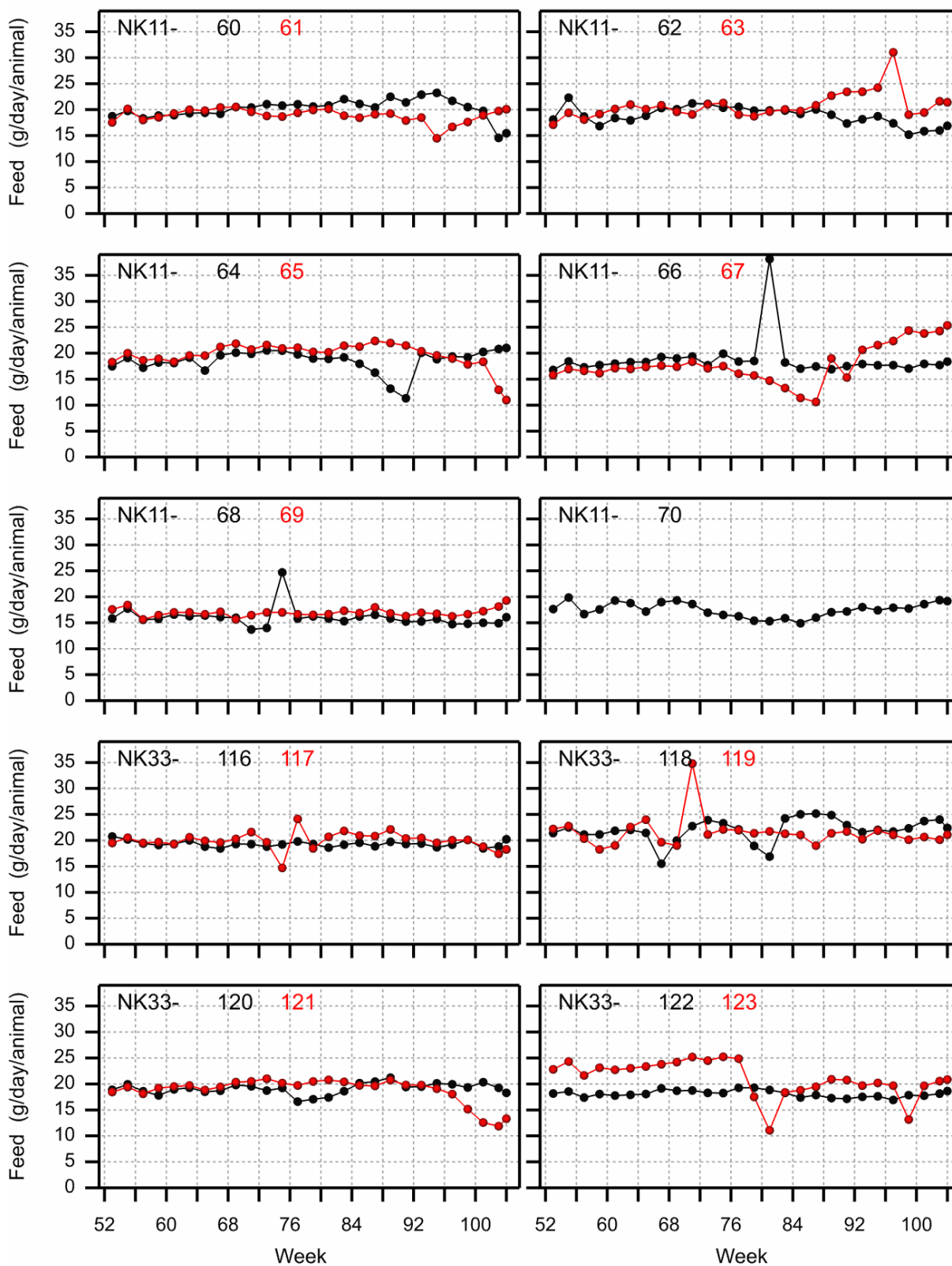
The feed group and cage numbers are given in the left top corner of the graph. Large symbols are used for those cages in which one or two animals that survived for 24 months.

Study A - Feed Consumption weeks 52 - 104 Male



Appendix 2. Feed consumption per cage (continued)

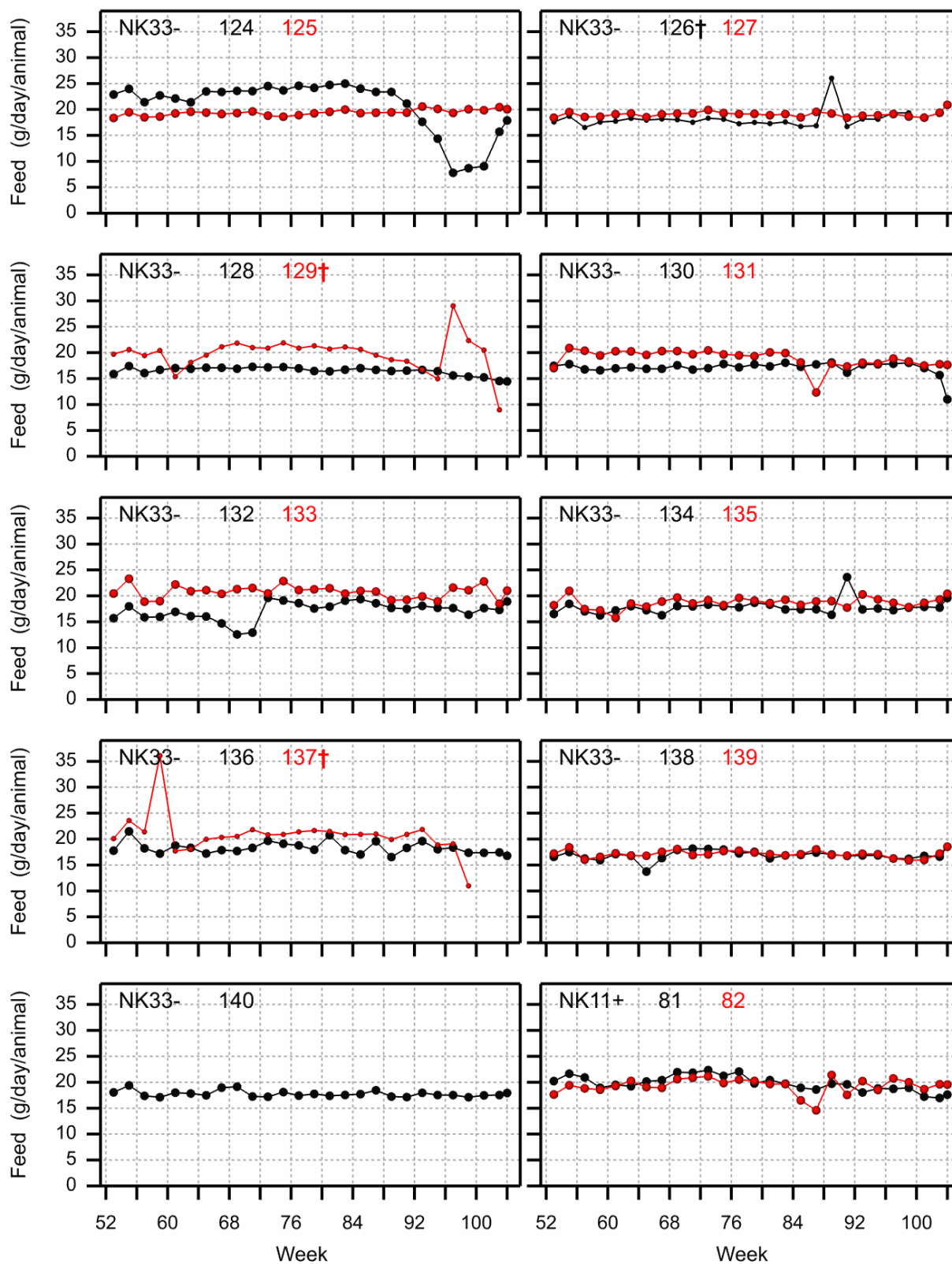
The feed group and cage numbers are given in the left top corner of the graph. Large symbols are used for those cages in which one or two animals that survived for 24 months.

Study A - Feed Consumption weeks 52 - 104 Male

Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph. Large symbols are used for those cages in which one or two animals that survived for 24 months.

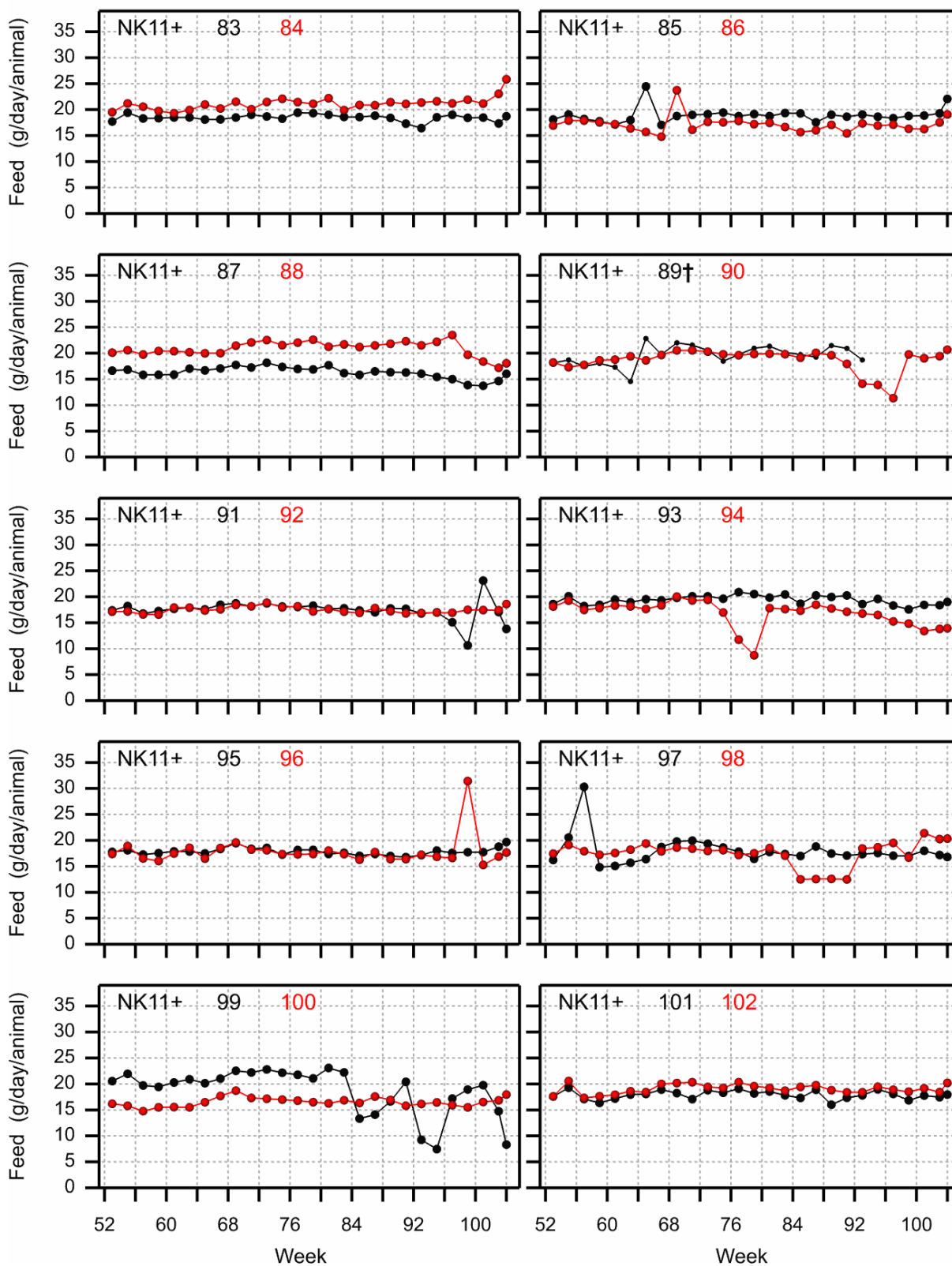
Study A - Feed Consumption weeks 52 - 104 Male



Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph. Large symbols are used for those cages in which one or two animals that survived for 24 months.

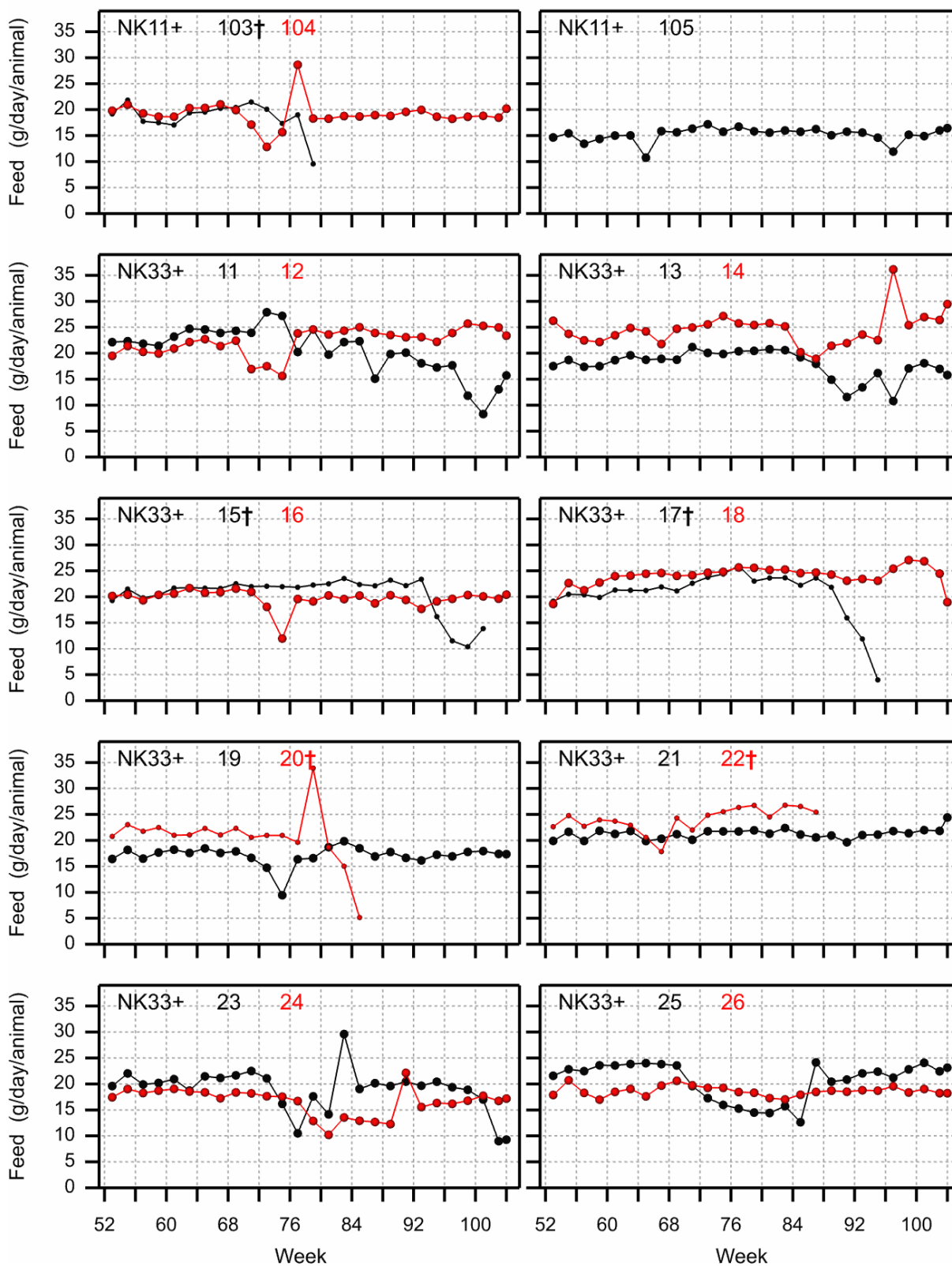
Study A - Feed Consumption weeks 52 - 104 Male



Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph. Large symbols are used for those cages in which one or two animals that survived for 24 months.

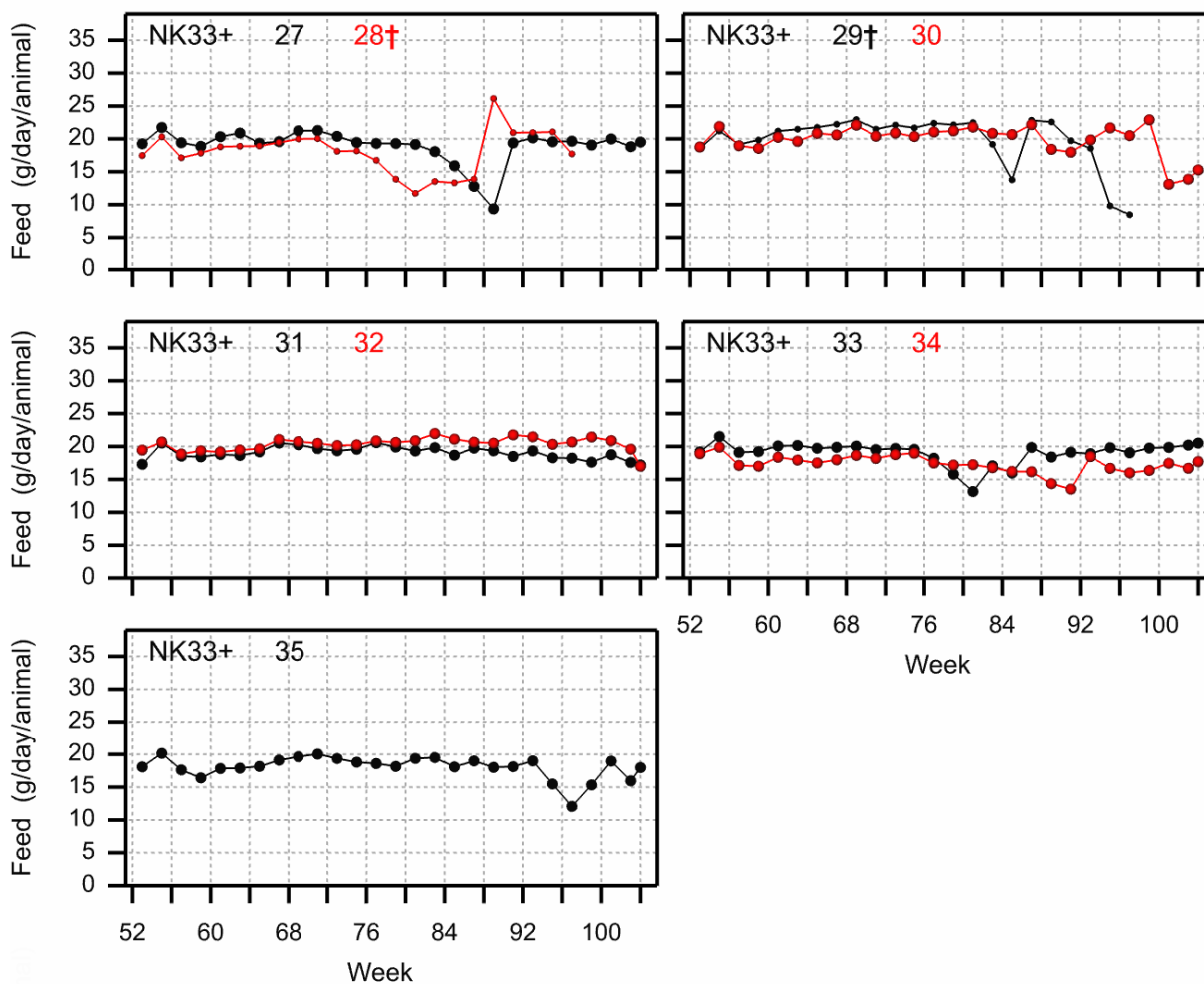
Study A - Feed Consumption weeks 52 - 104 Male



Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph. Large symbols are used for those cages in which one or two animals that survived for 24 months.

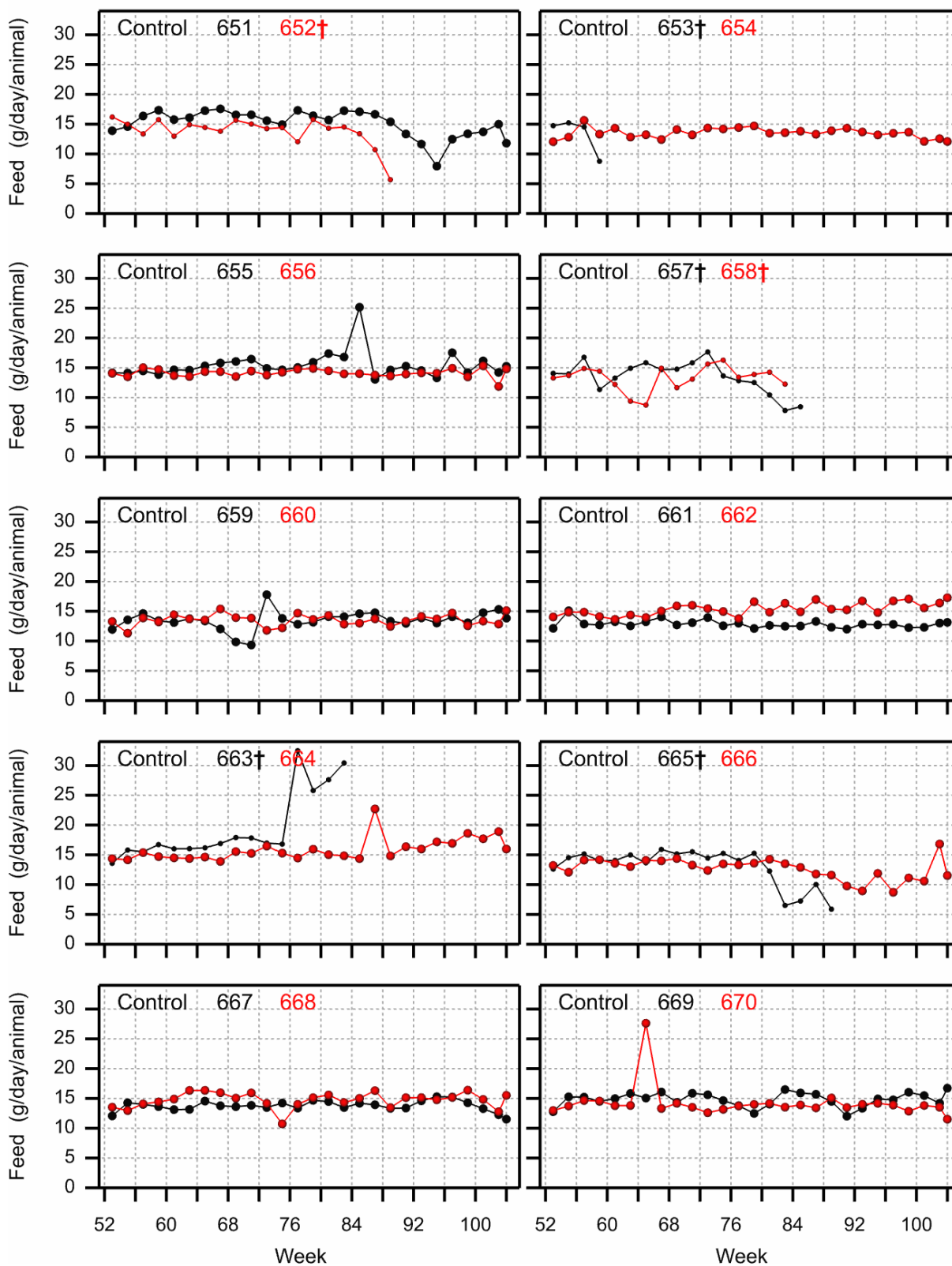
Study A - Feed Consumption weeks 52 - 104 Male



Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph. Large symbols are used for those cages in which one or two animals that survived for 24 months.

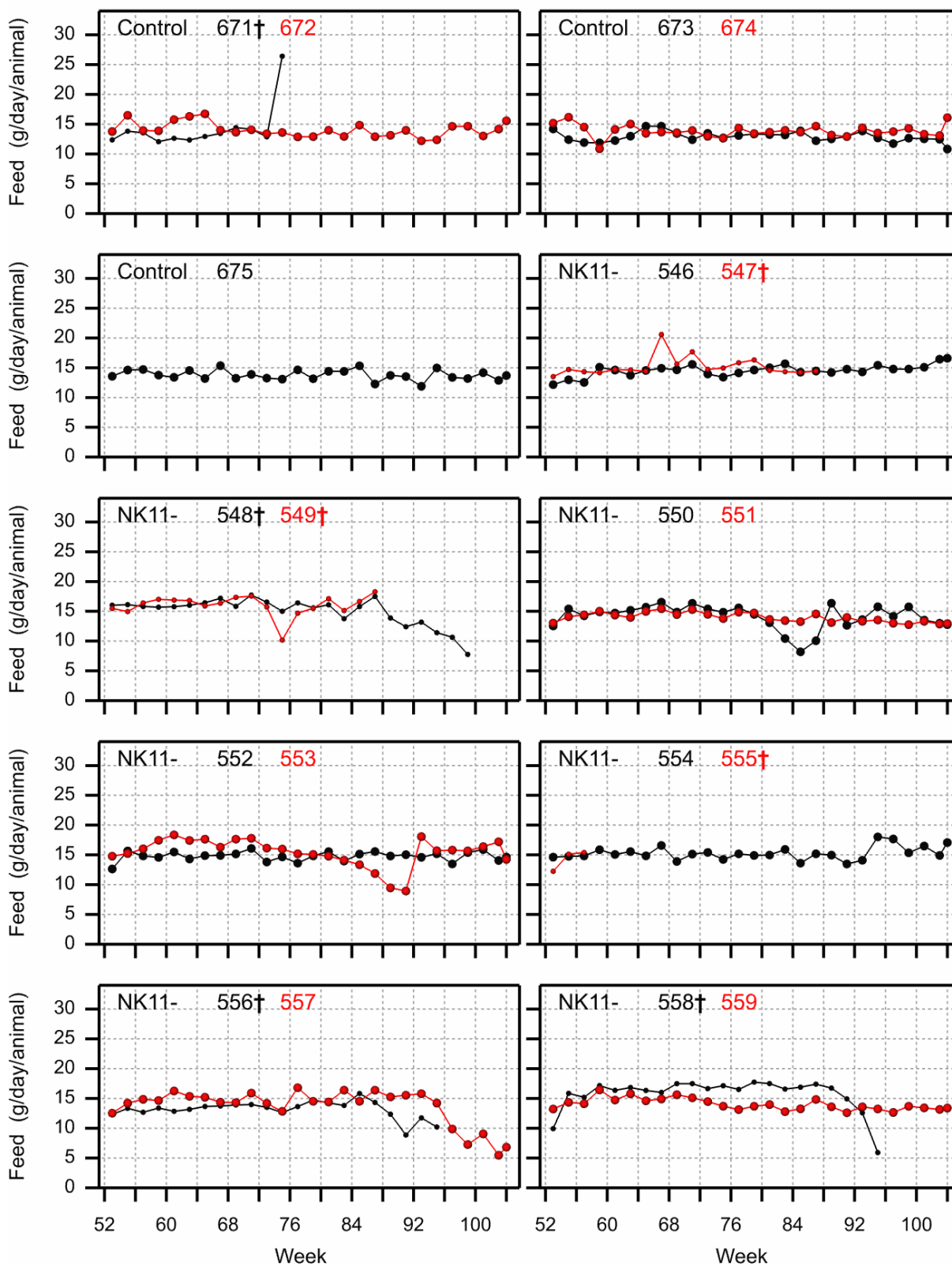
Study A - Feed Consumption weeks 52 - 104 Female



Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph. Large symbols are used for those cages in which one or two animals that survived for 24 months.

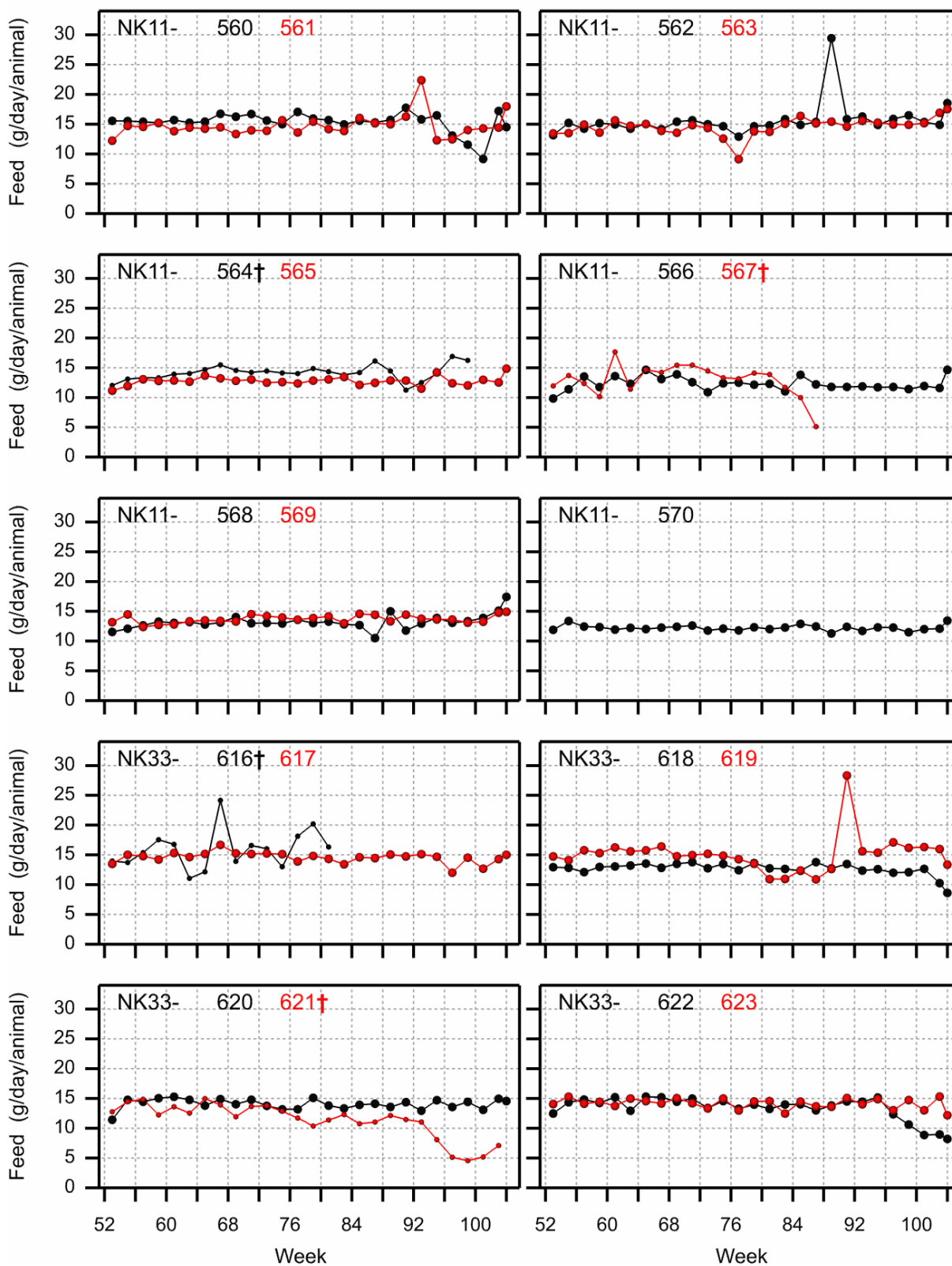
Study A - Feed Consumption weeks 52 - 104 Female



Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph. Large symbols are used for those cages in which one or two animals that survived for 24 months.

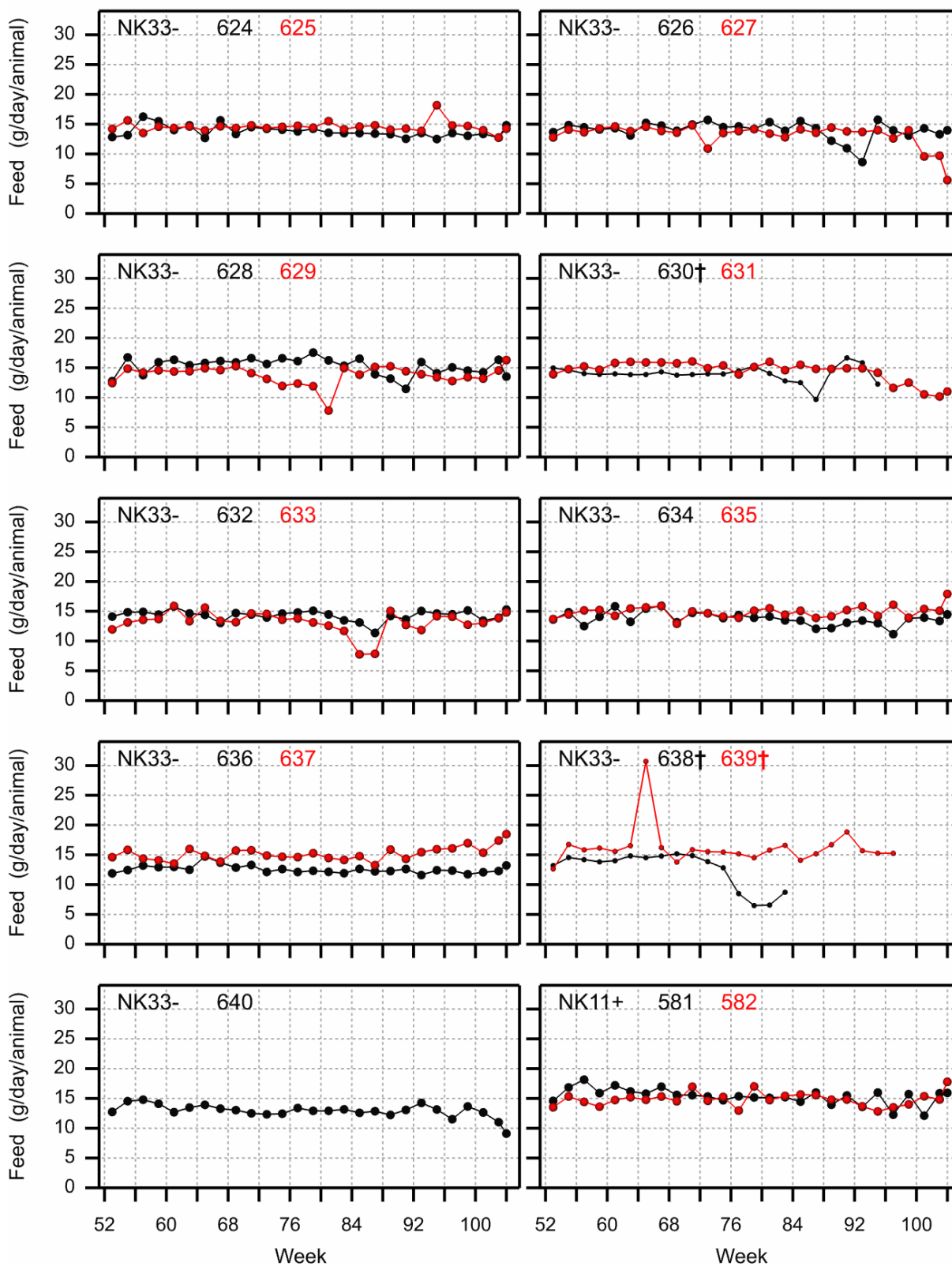
Study A - Feed Consumption weeks 52 - 104 Female



Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph. Large symbols are used for those cages in which one or two animals that survived for 24 months.

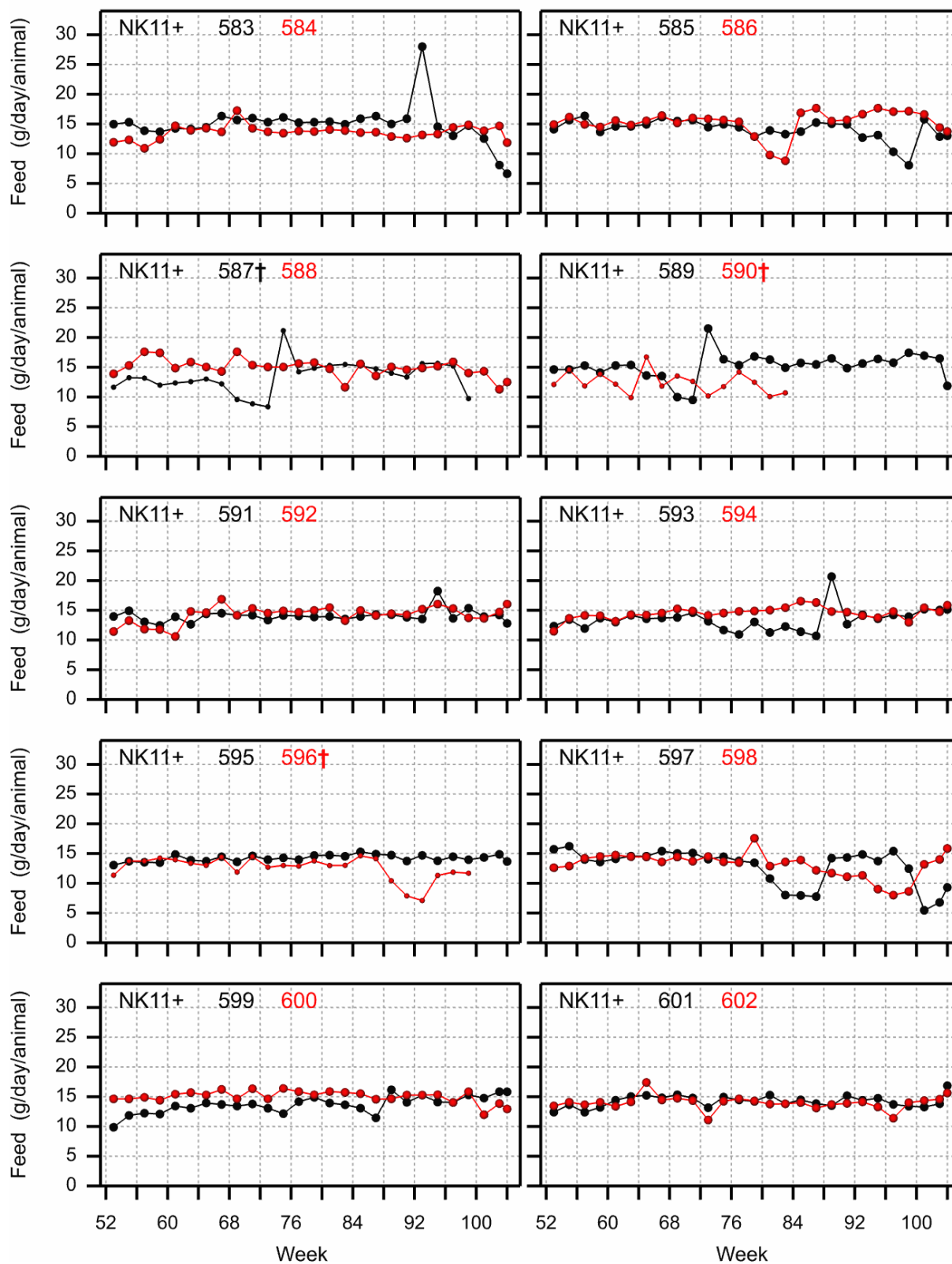
Study A - Feed Consumption weeks 52 - 104 Female



Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph. Large symbols are used for those cages in which one or two animals that survived for 24 months.

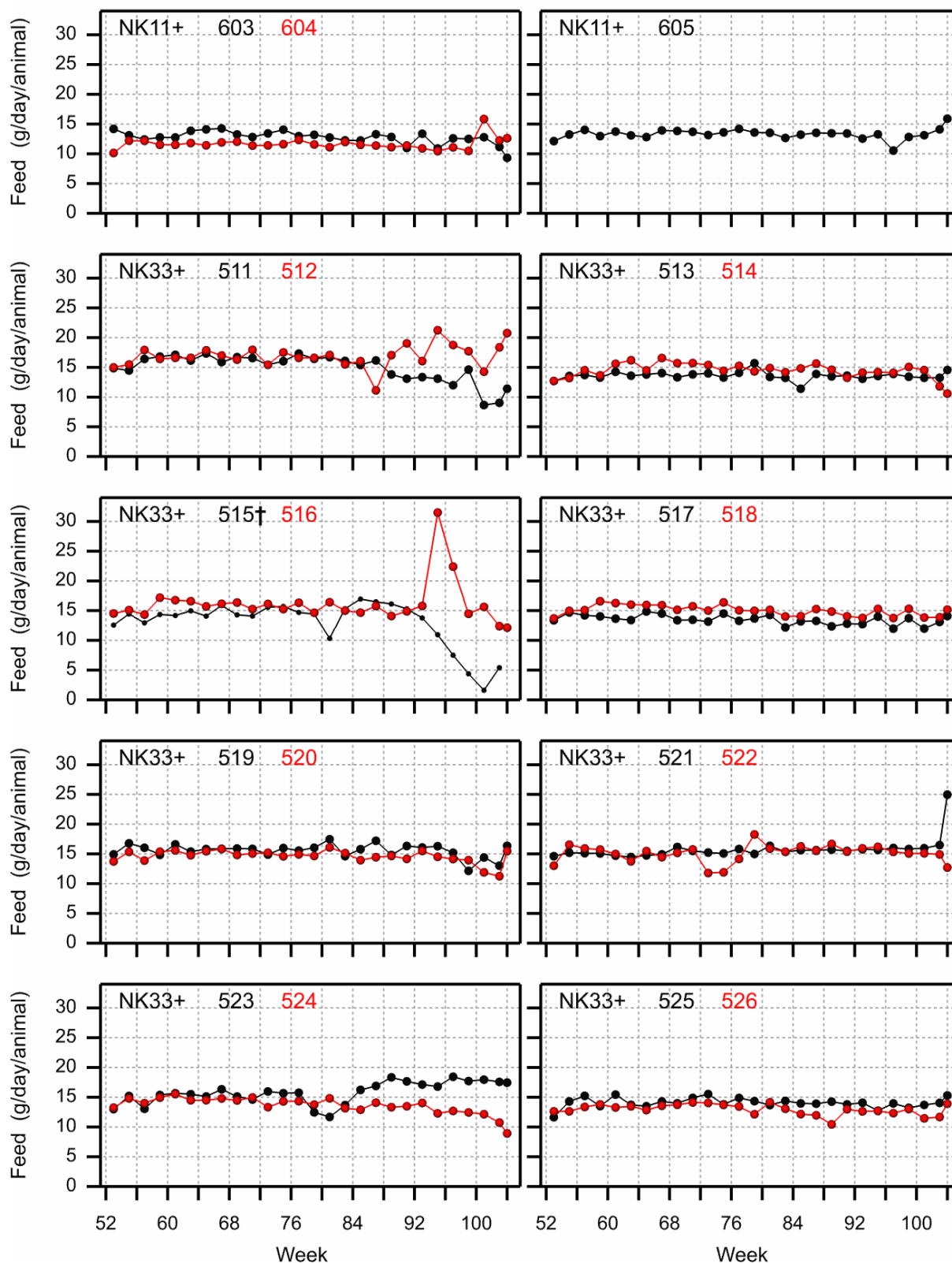
Study A - Feed Consumption weeks 52 - 104 Female



Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph. Large symbols are used for those cages in which one or two animals that survived for 24 months.

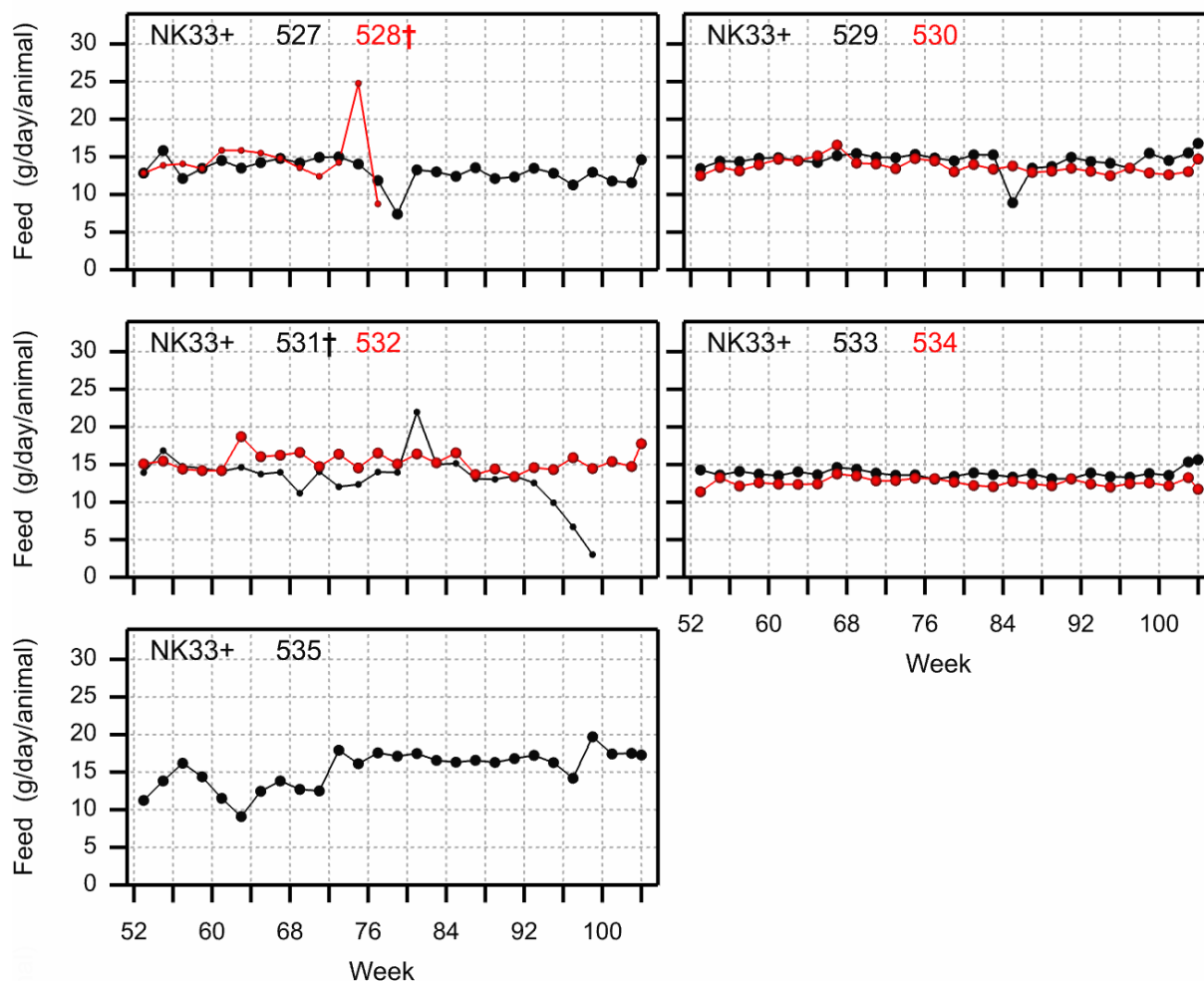
Study A - Feed Consumption weeks 52 - 104 Female



Appendix 2. Feed consumption per cage (continued)

The feed group and cage numbers are given in the left top corner of the graph. Large symbols are used for those cages in which one or two animals that survived for 24 months.

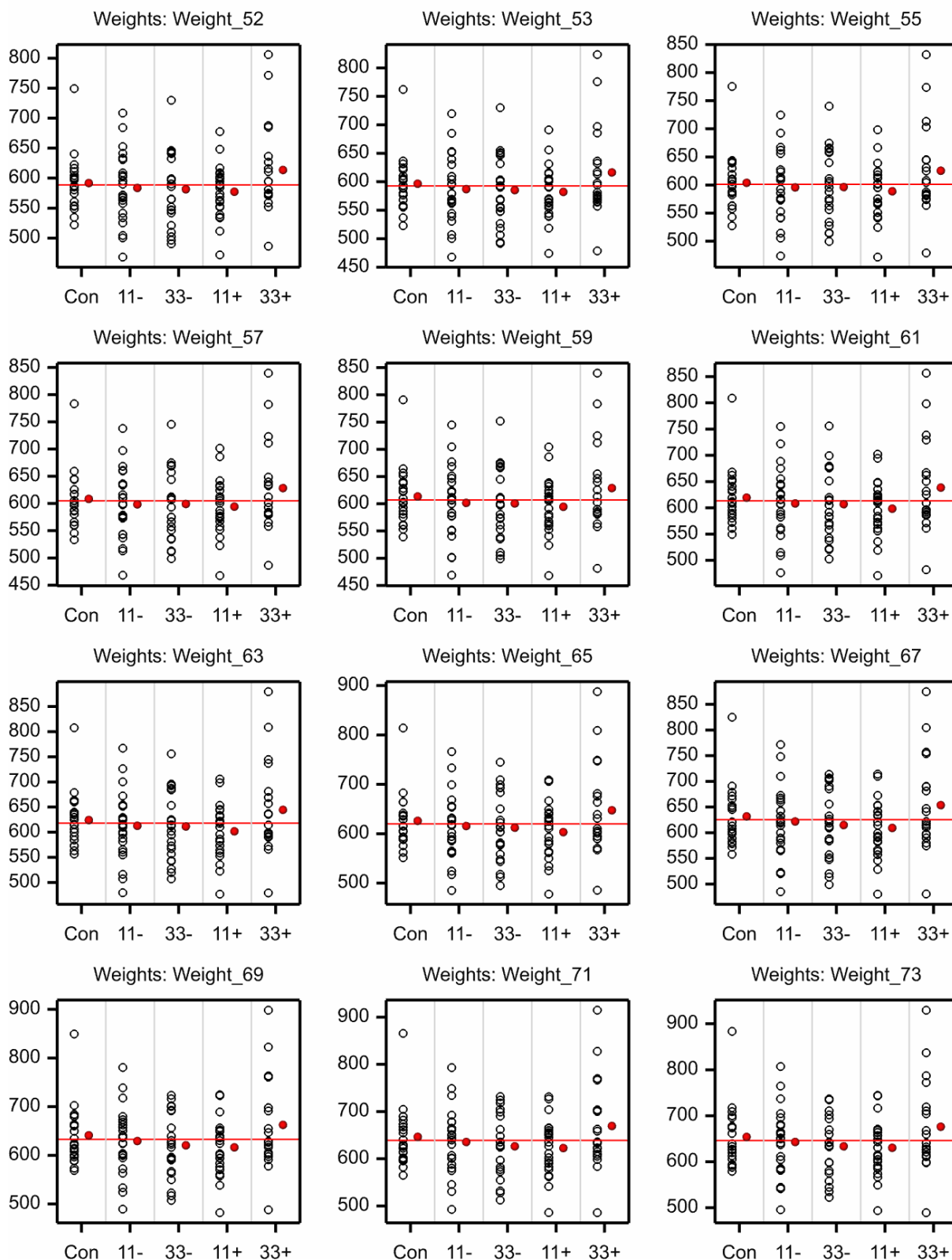
Study A - Feed Consumption weeks 52 - 104 Female



Appendix 3. Graphs of cage means on the original scale

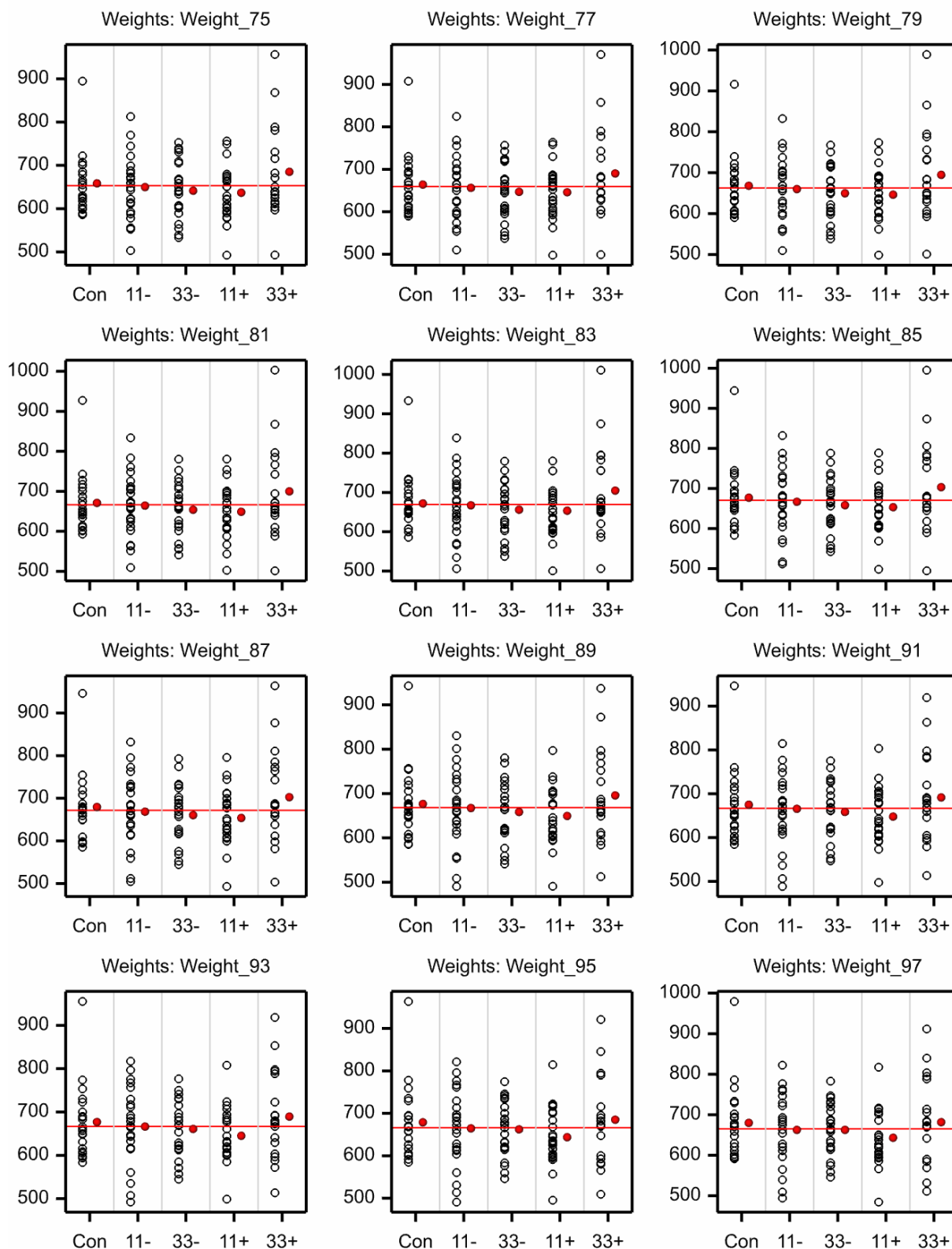
Red symbols denote means for feeding groups while the red line denotes the overall mean.

Study A month 24 - Cage Means Original Scale Male



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

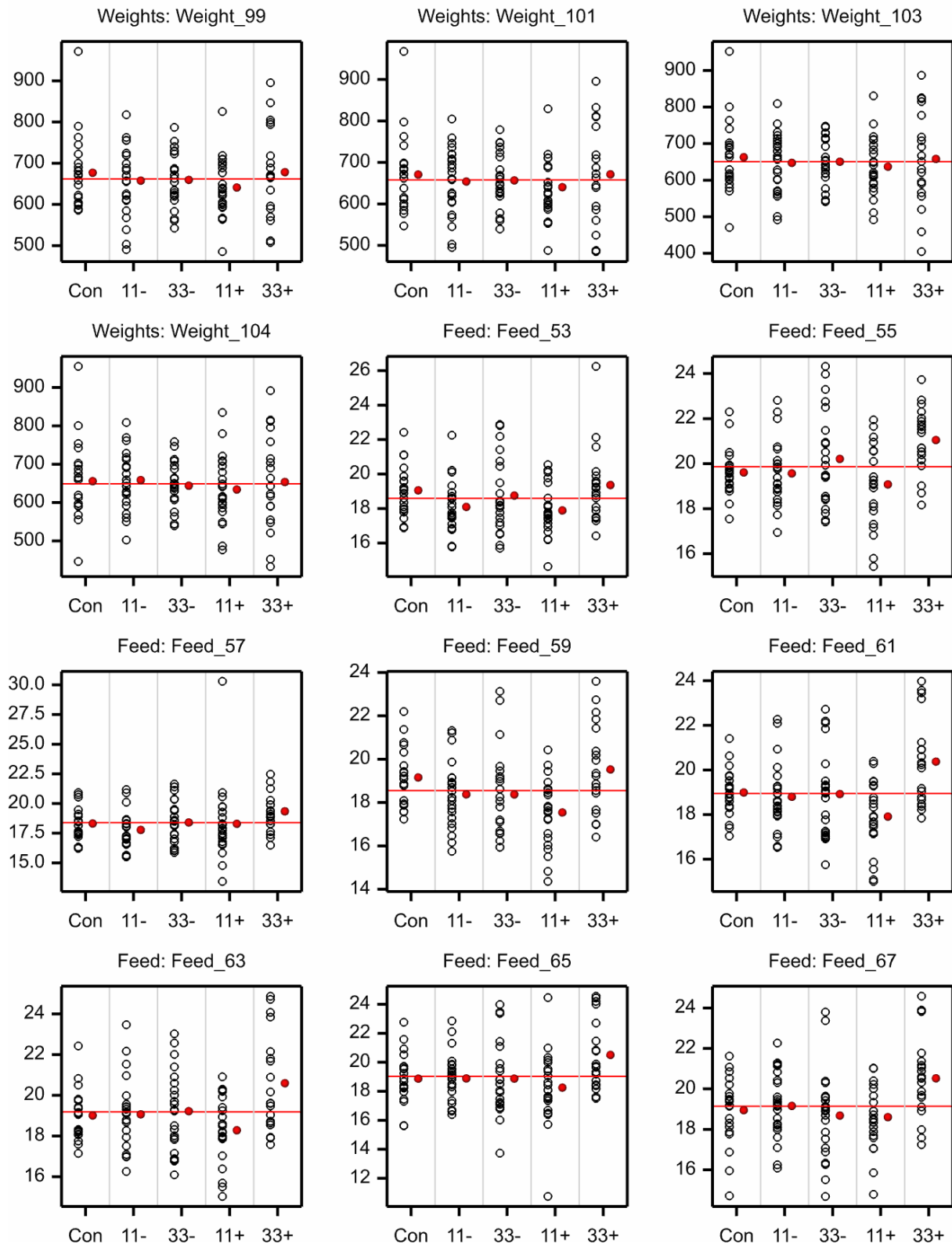
Red symbols denote means for feeding groups while the red line denotes the overall mean.

Study A month 24 - Cage Means Original Scale Male

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

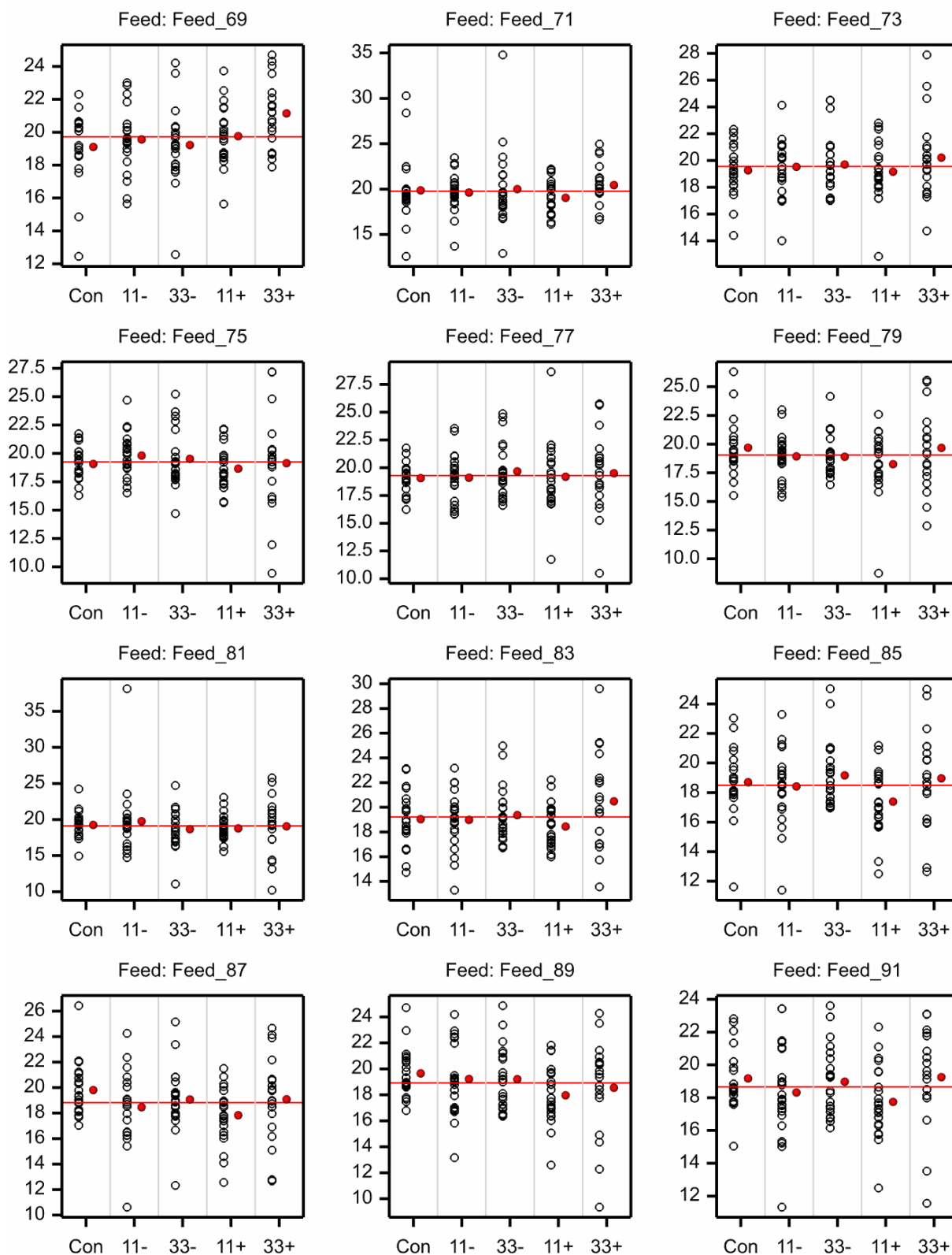
Red symbols denote means for feeding groups while the red line denotes the overall mean.

Study A month 24 - Cage Means Original Scale Male



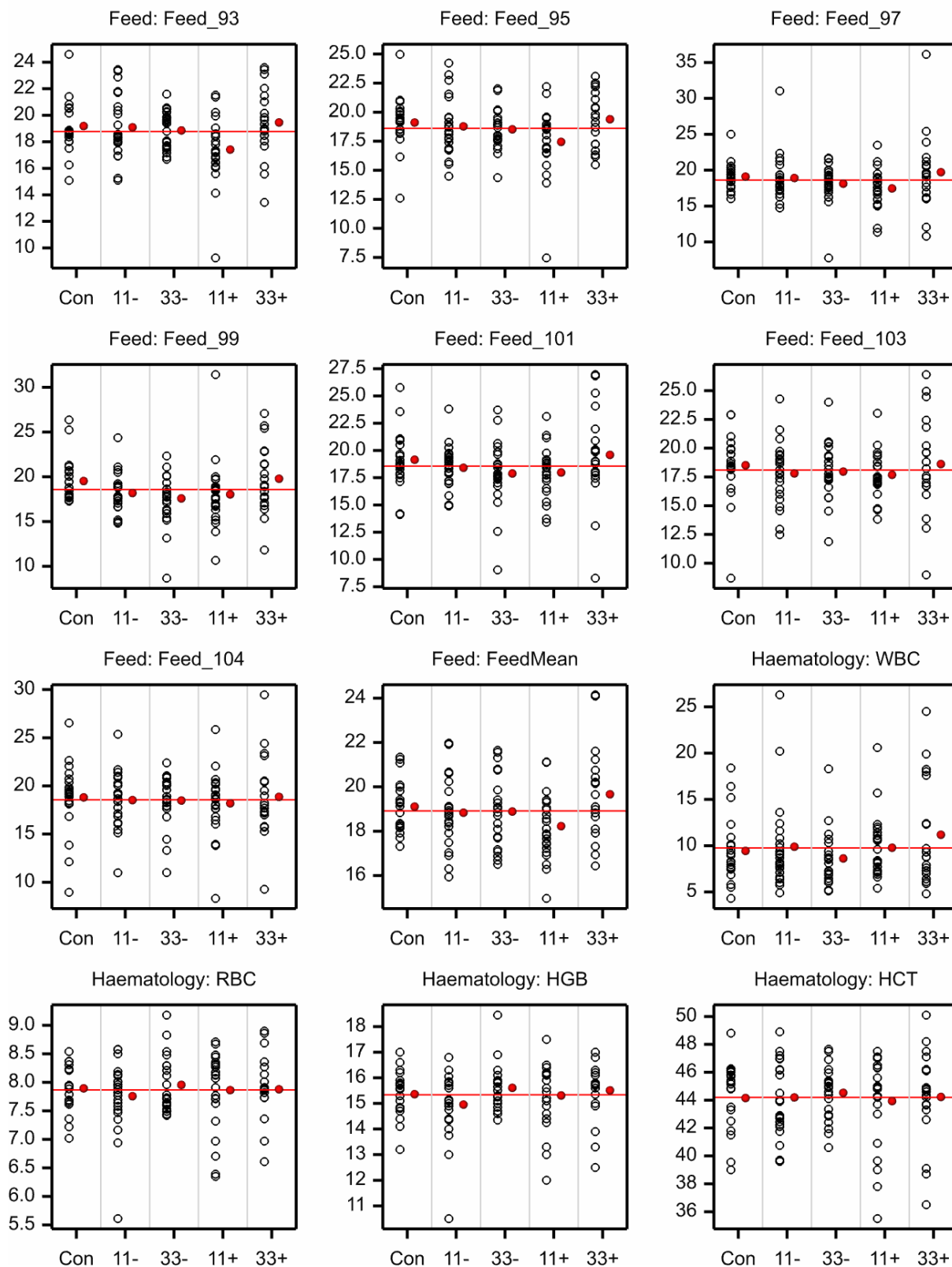
Appendix 3. Graphs of cage means on the original scale (continued)

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

Study A month 24 - Cage Means Original Scale Male

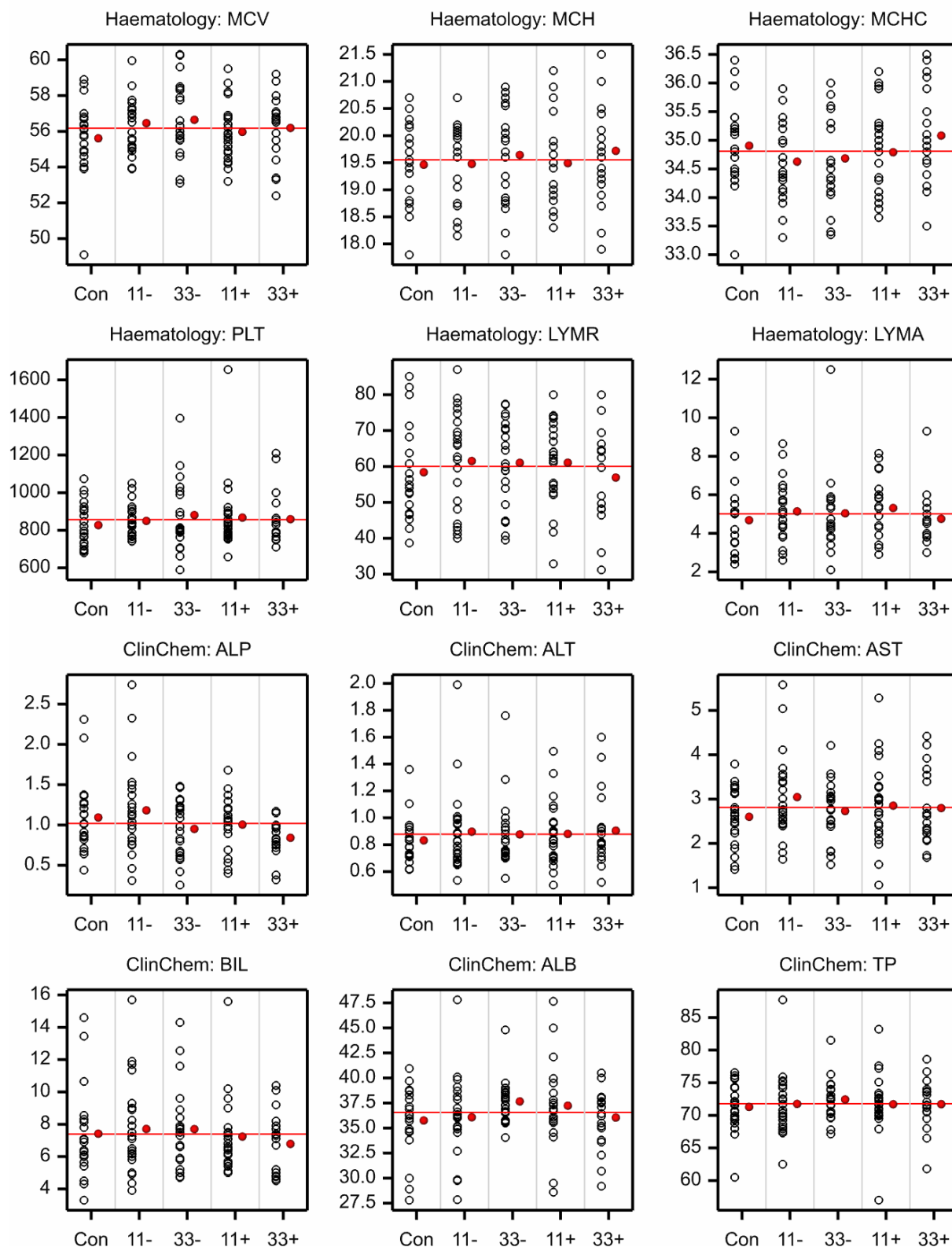
Appendix 3. Graphs of cage means on the original scale (continued)

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

Study A month 24 - Cage Means Original Scale Male

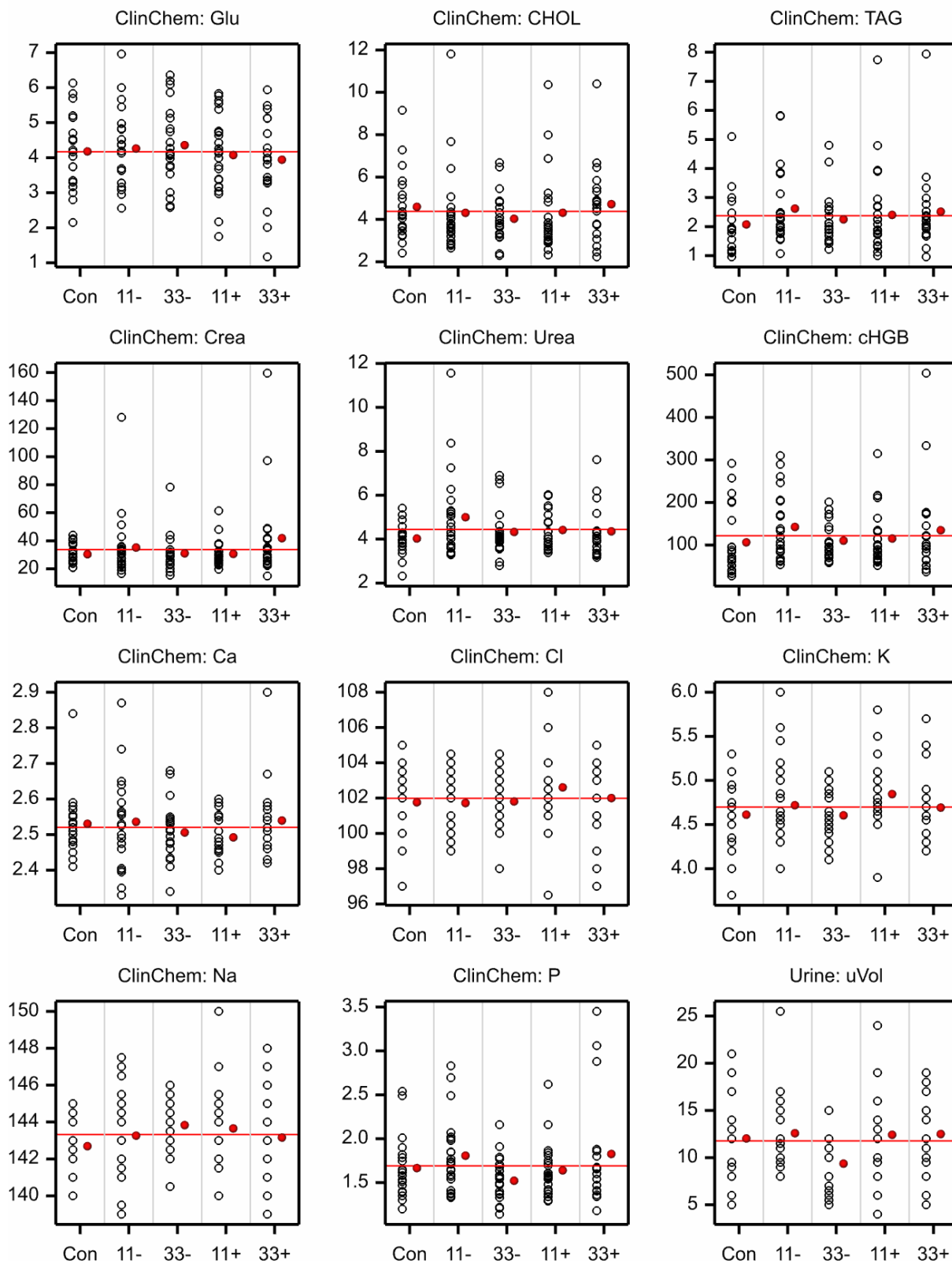
Appendix 3. Graphs of cage means on the original scale (continued)

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

Study A month 24 - Cage Means Original Scale Male

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

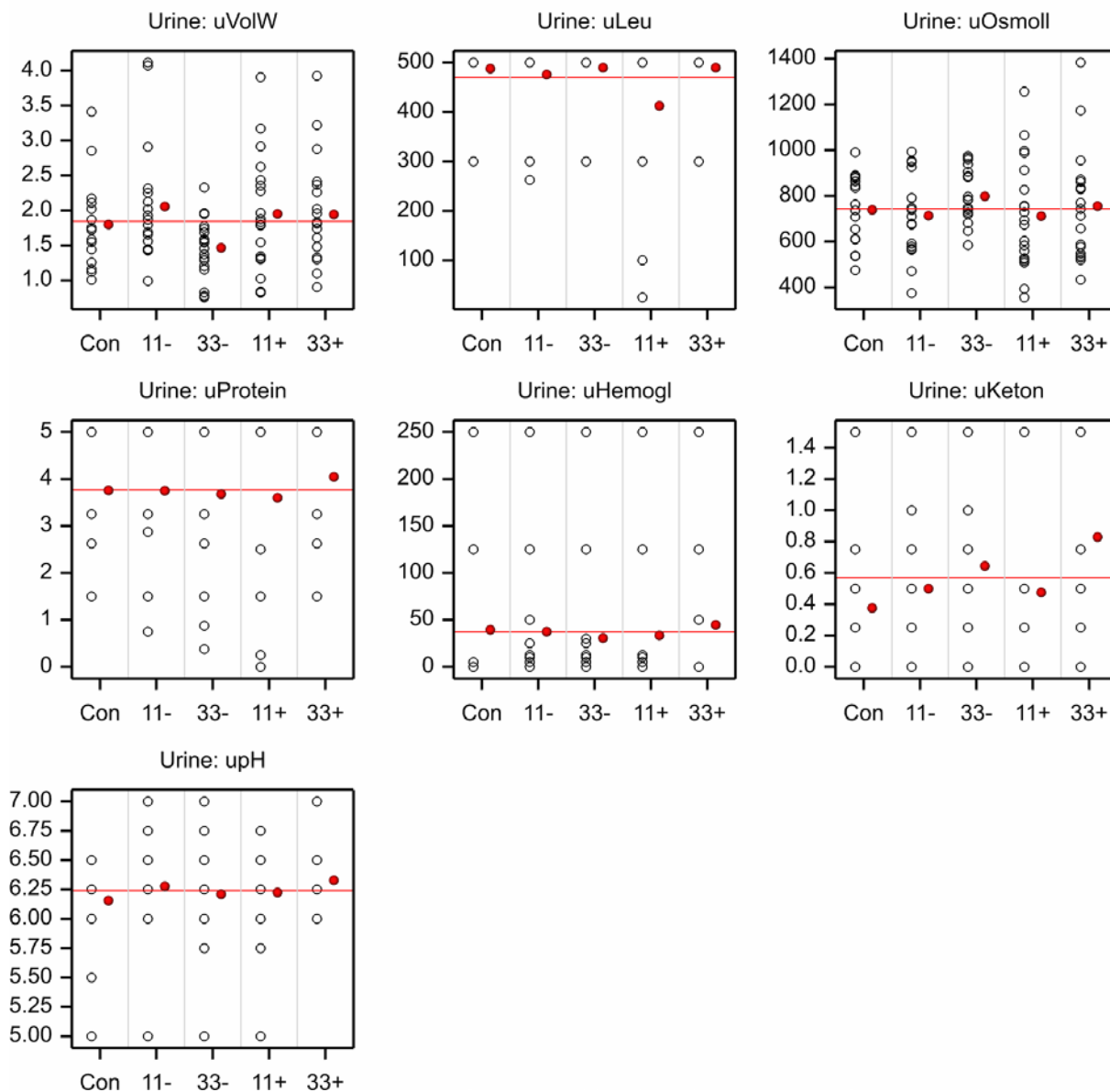
Red symbols denote means for feeding groups while the red line denotes the overall mean.

Study A month 24 - Cage Means Original Scale Male

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

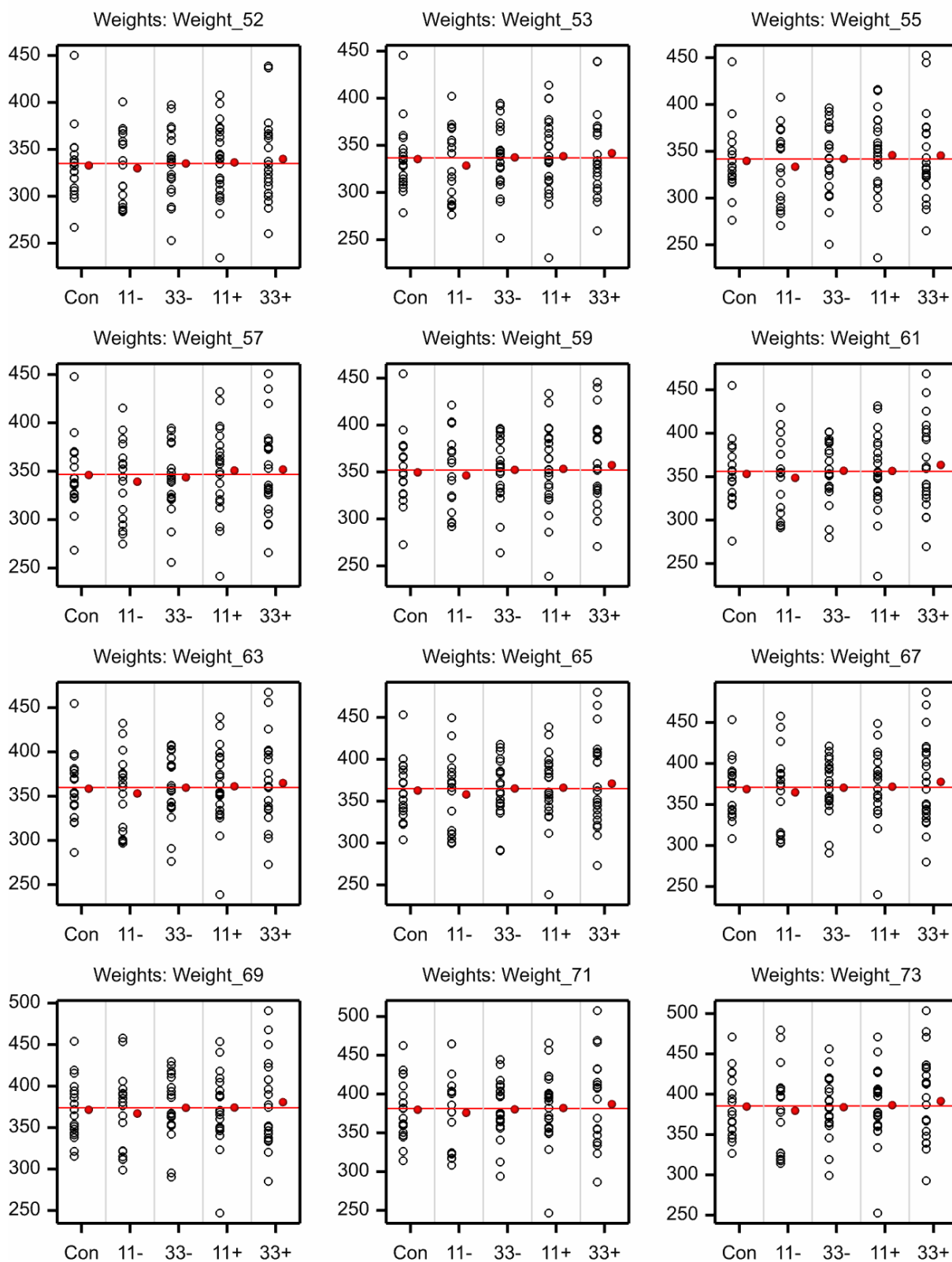
Red symbols denote means for feeding groups while the red line denotes the overall mean.

Study A month 24 - Cage Means Original Scale Male



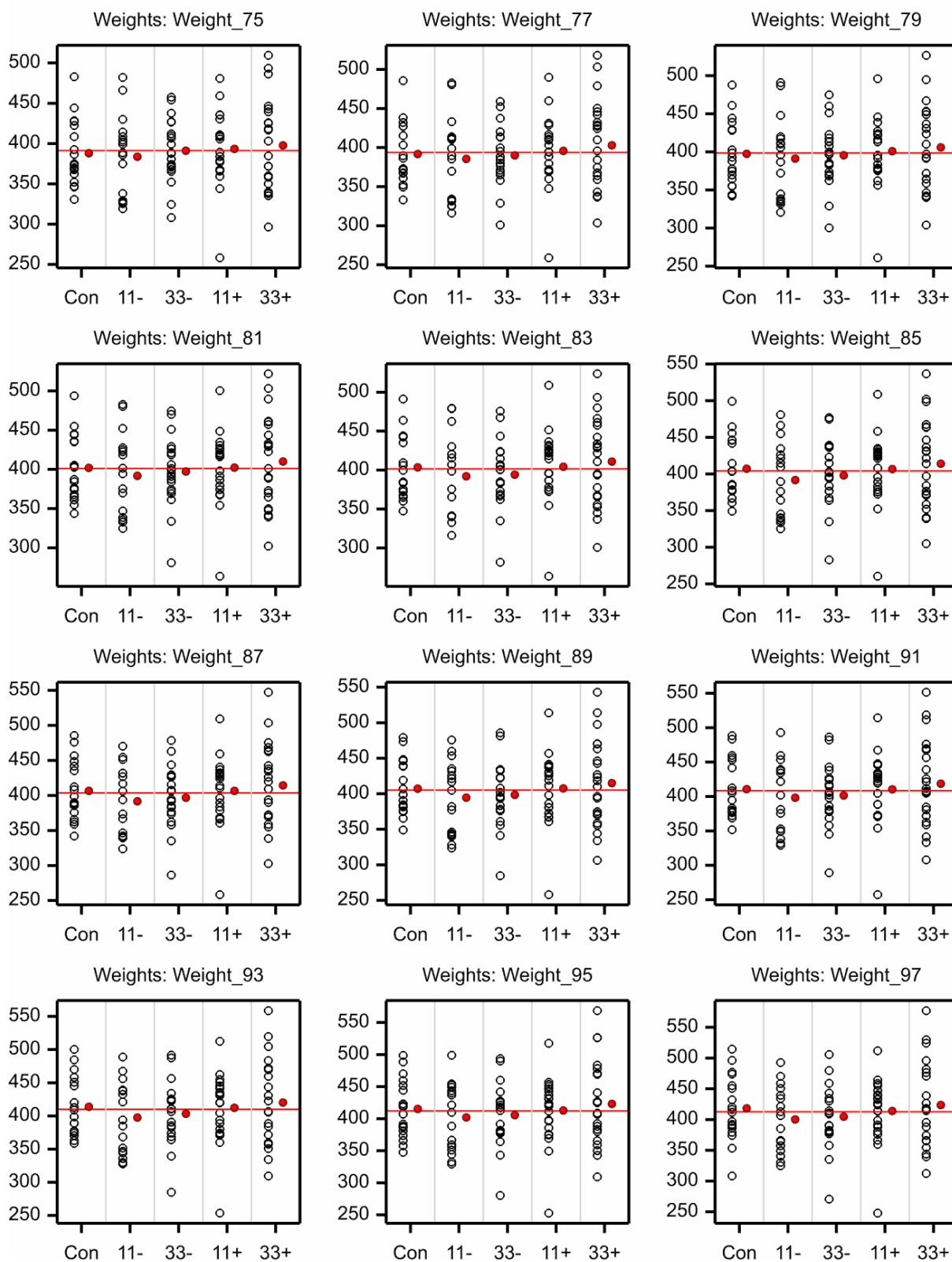
Appendix 3. Graphs of cage means on the original scale (continued)

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

Study A month 24 - Cage Means Original Scale Female

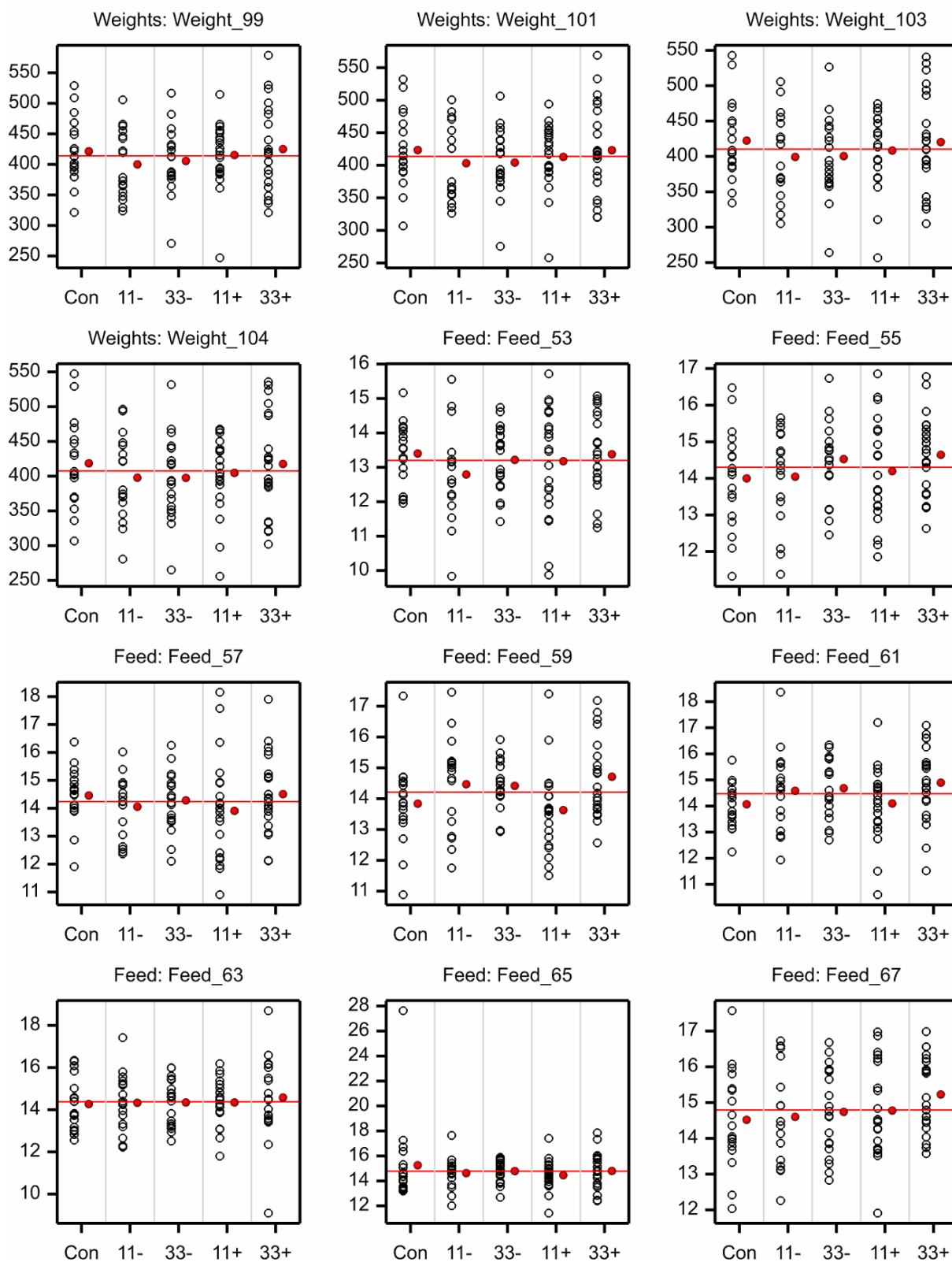
Appendix 3. Graphs of cage means on the original scale (continued)

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

Study A month 24 - Cage Means Original Scale Female

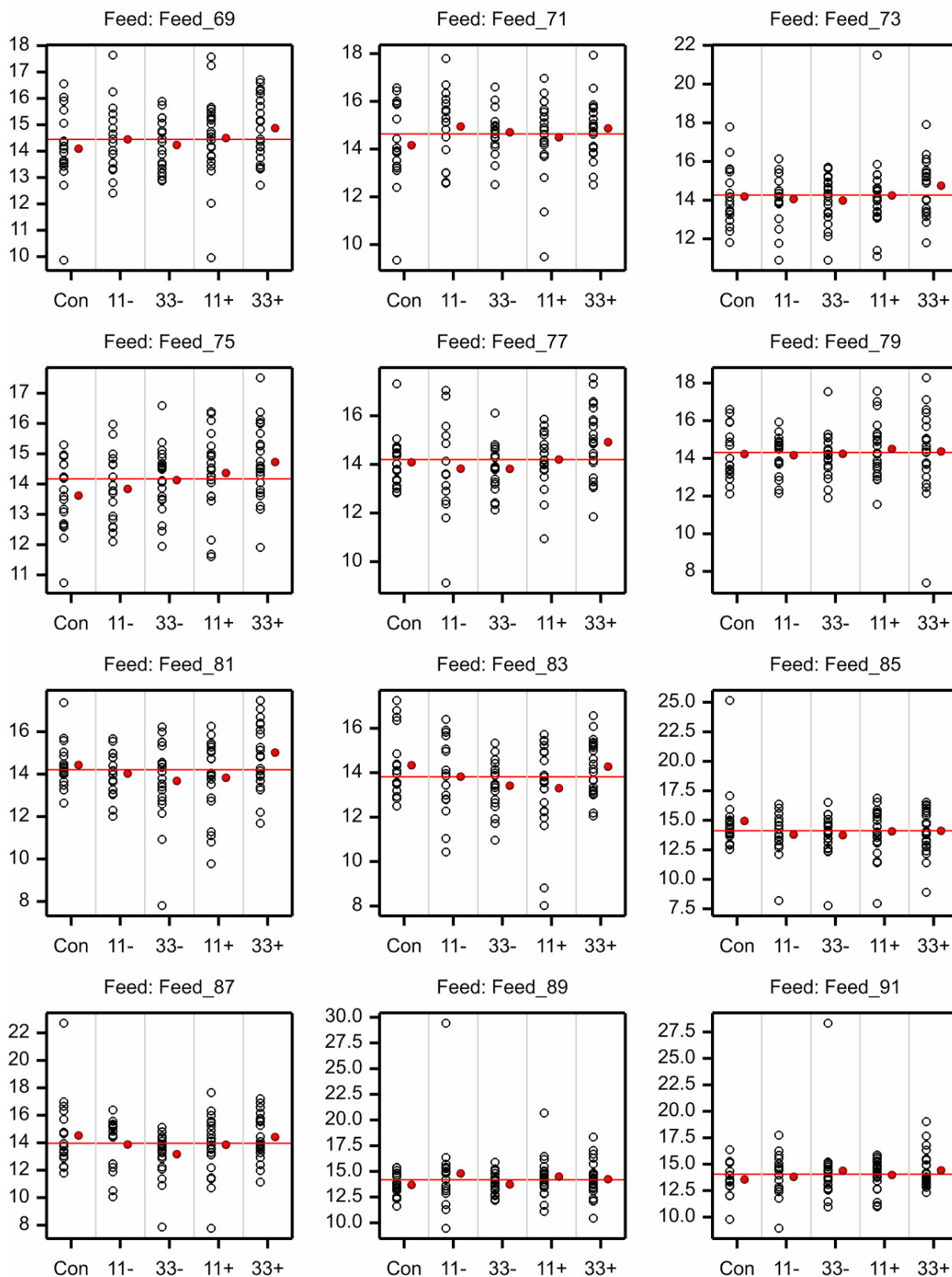
Appendix 3. Graphs of cage means on the original scale (continued)

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

Study A month 24 - Cage Means Original Scale Female

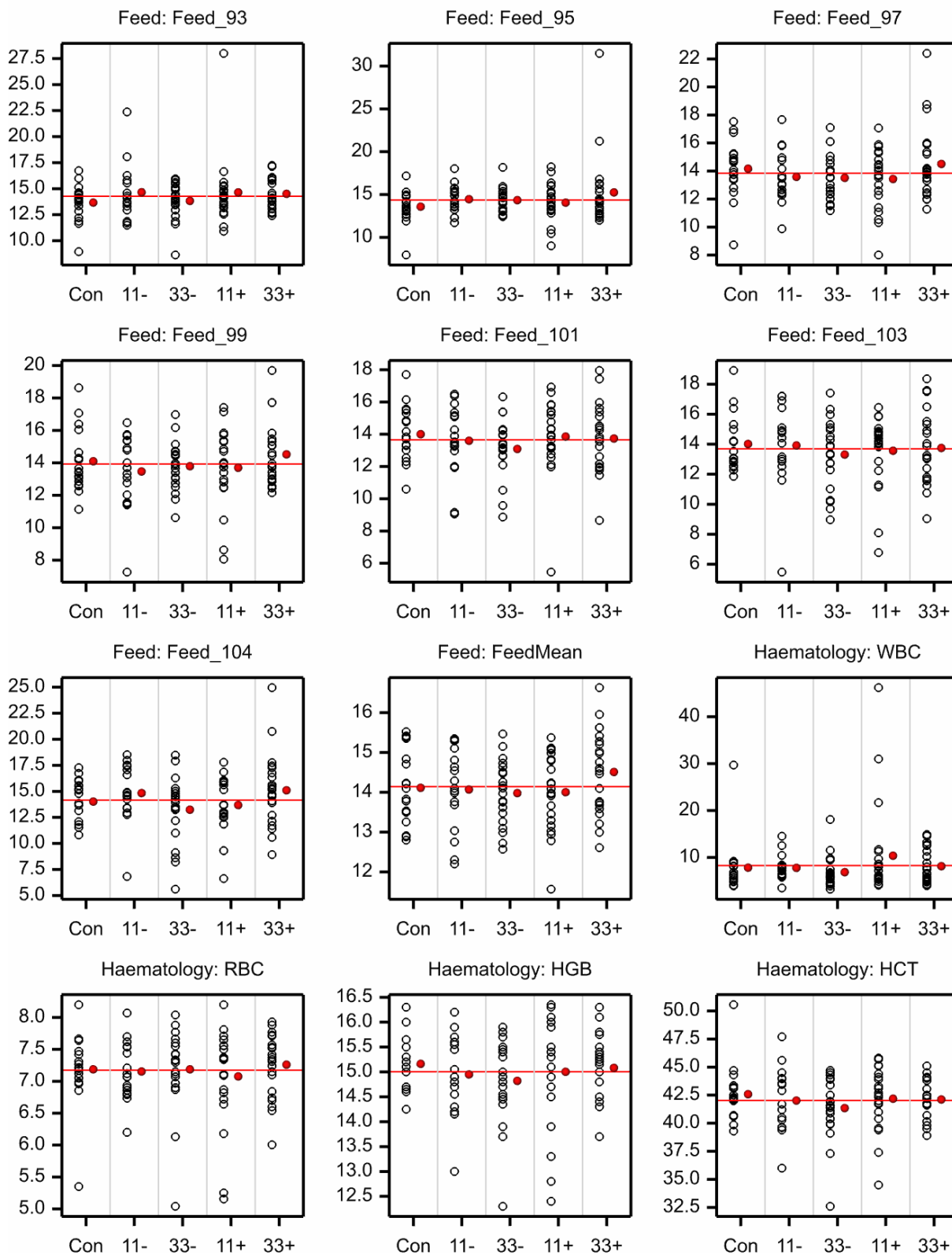
Appendix 3. Graphs of cage means on the original scale (continued)

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

Study A month 24 - Cage Means Original Scale Female

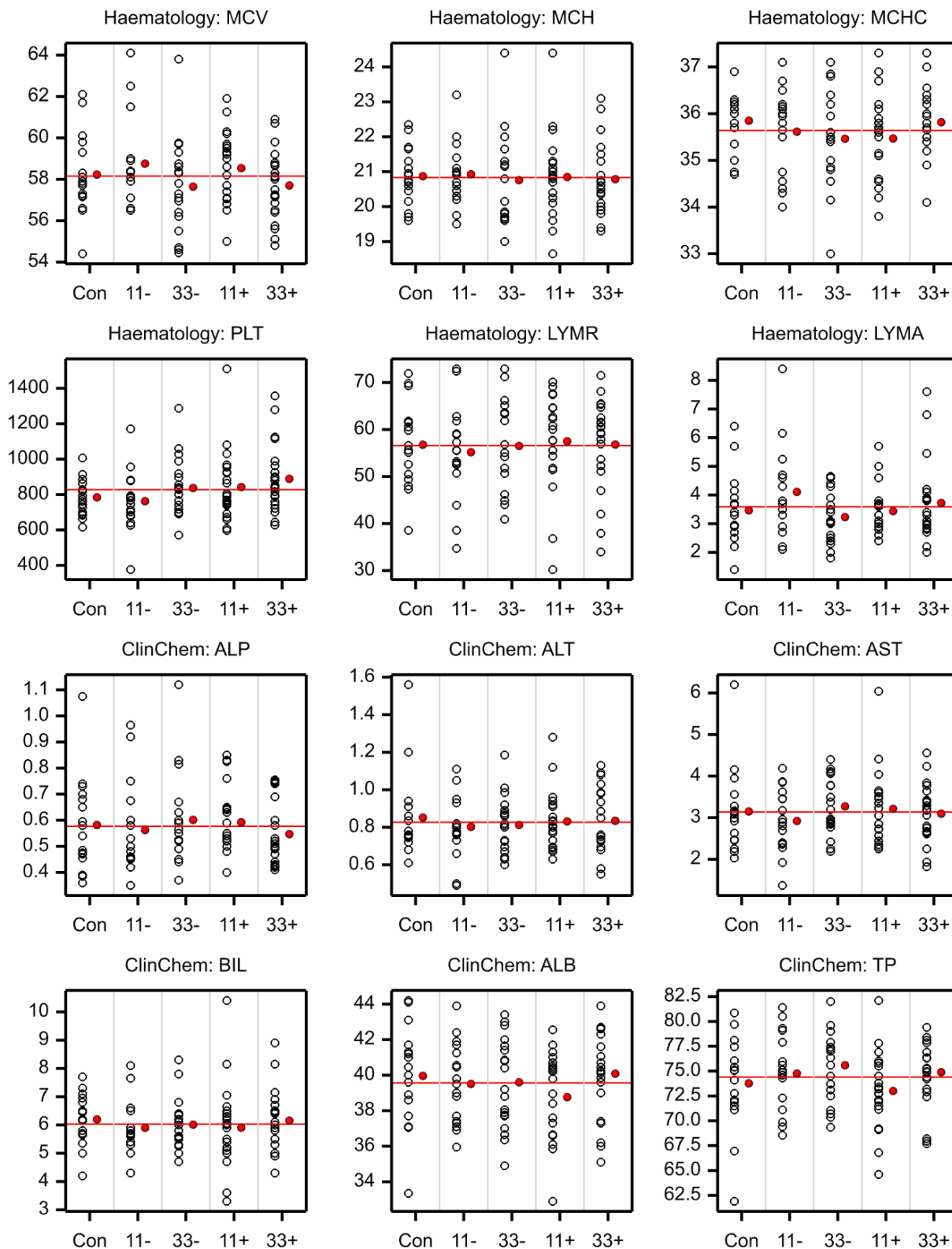
Appendix 3. Graphs of cage means on the original scale (continued)

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

Study A month 24 - Cage Means Original Scale Female

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

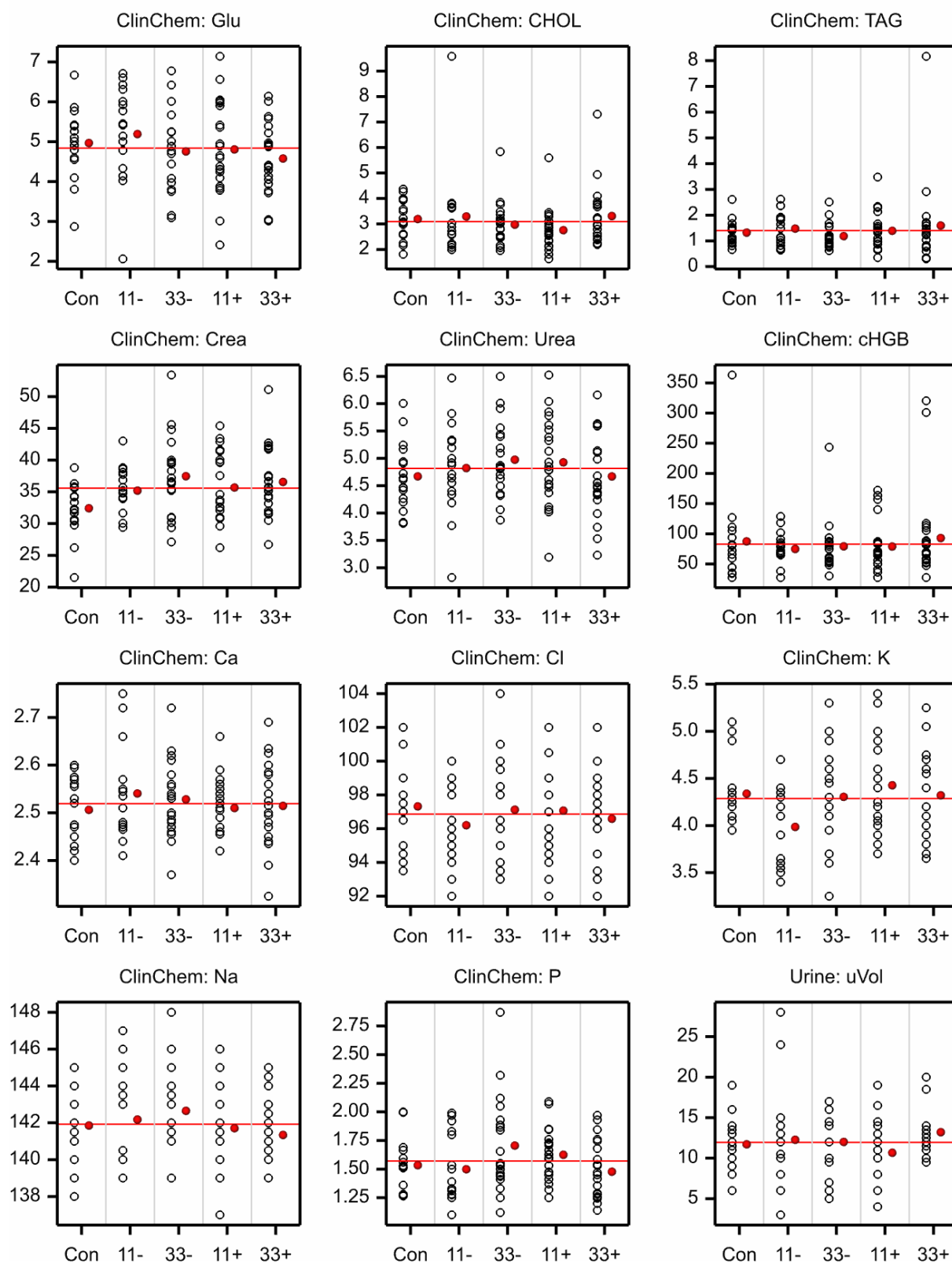
Red symbols denote means for feeding groups while the red line denotes the overall mean.

Study A month 24 - Cage Means Original Scale Female

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.

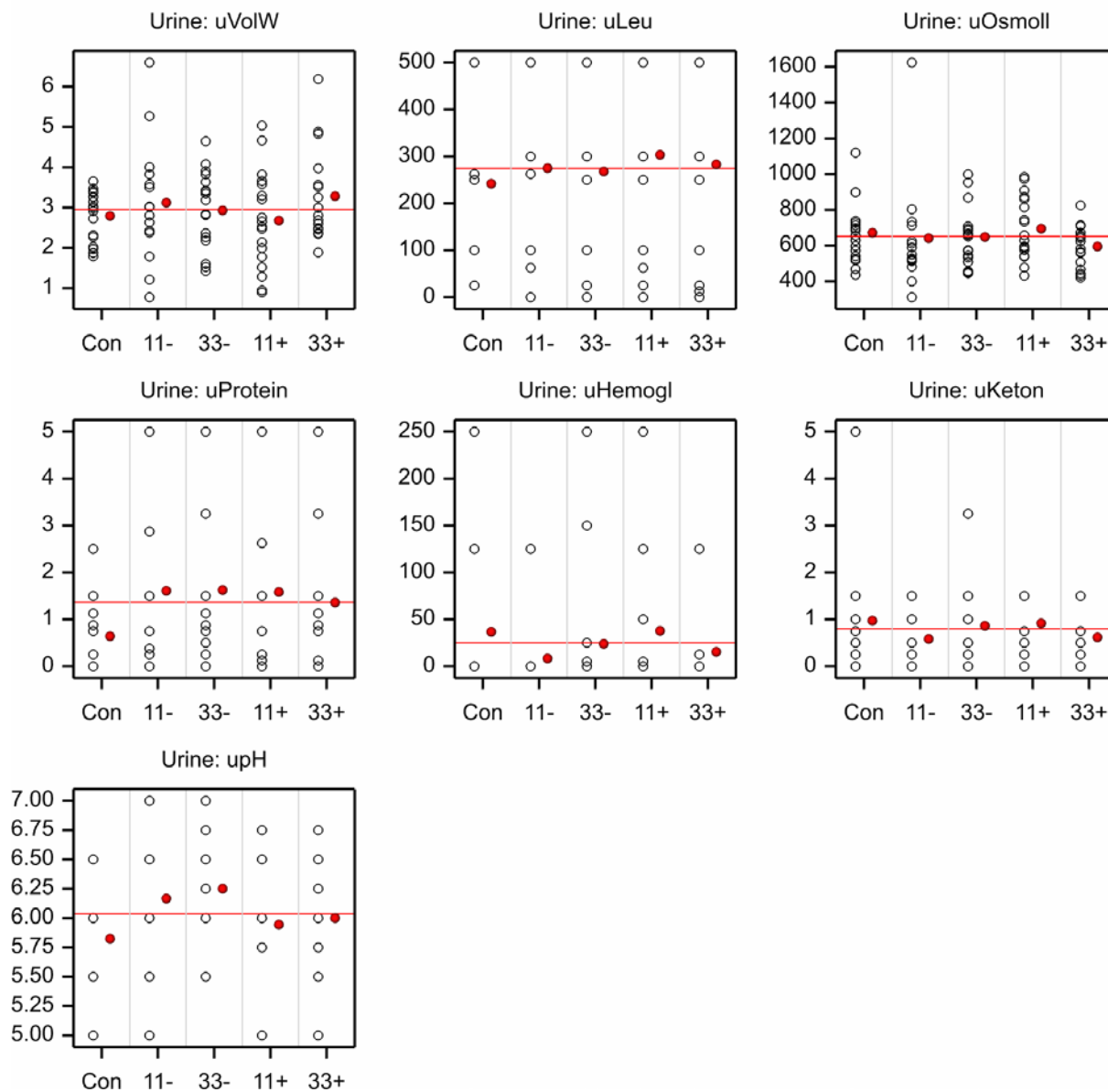
Study A month 24 - Cage Means Original Scale Female



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

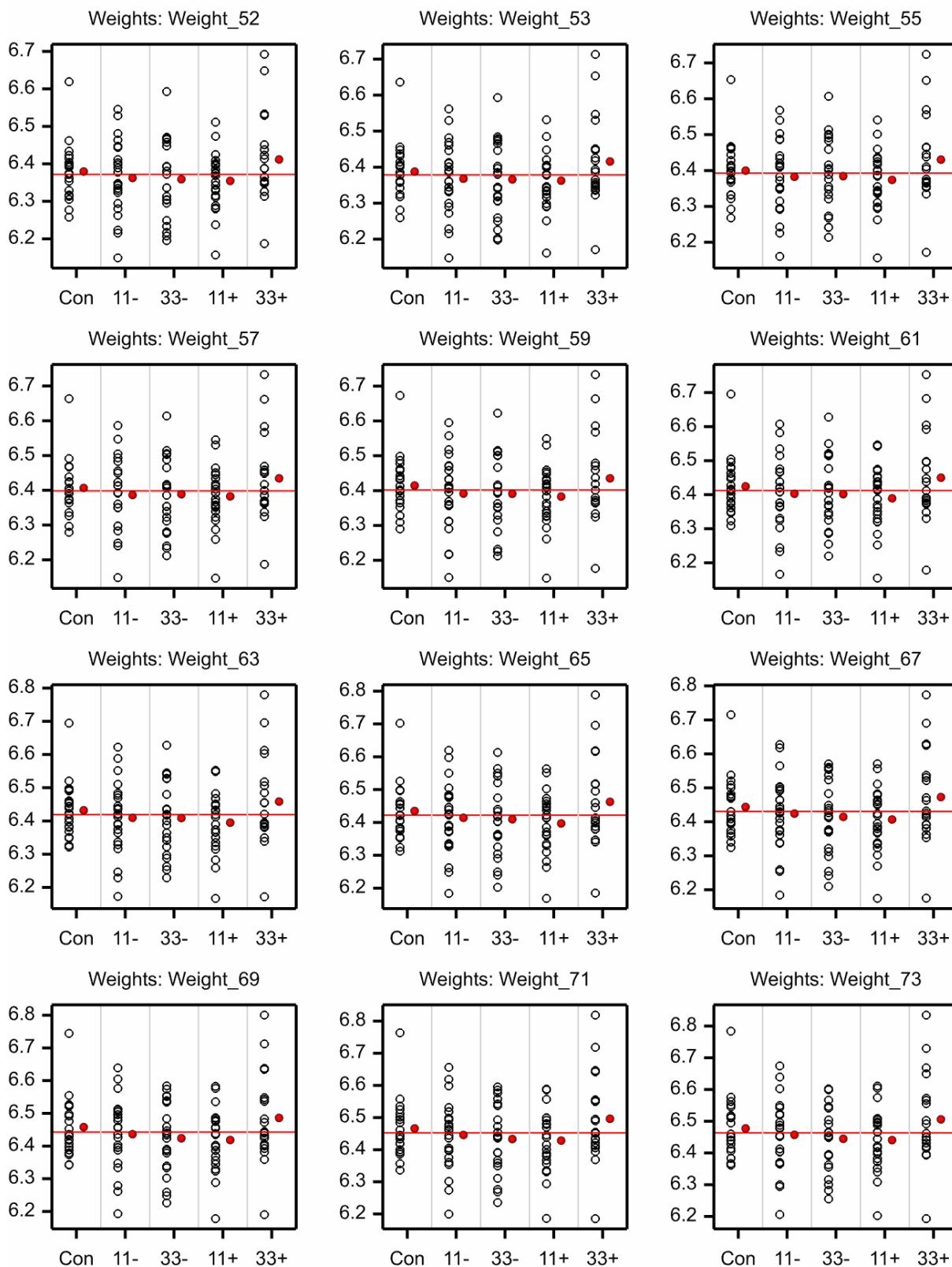
Red symbols denote means for feeding groups while the red line denotes the overall mean.

Study A month 24 - Cage Means Original Scale Female



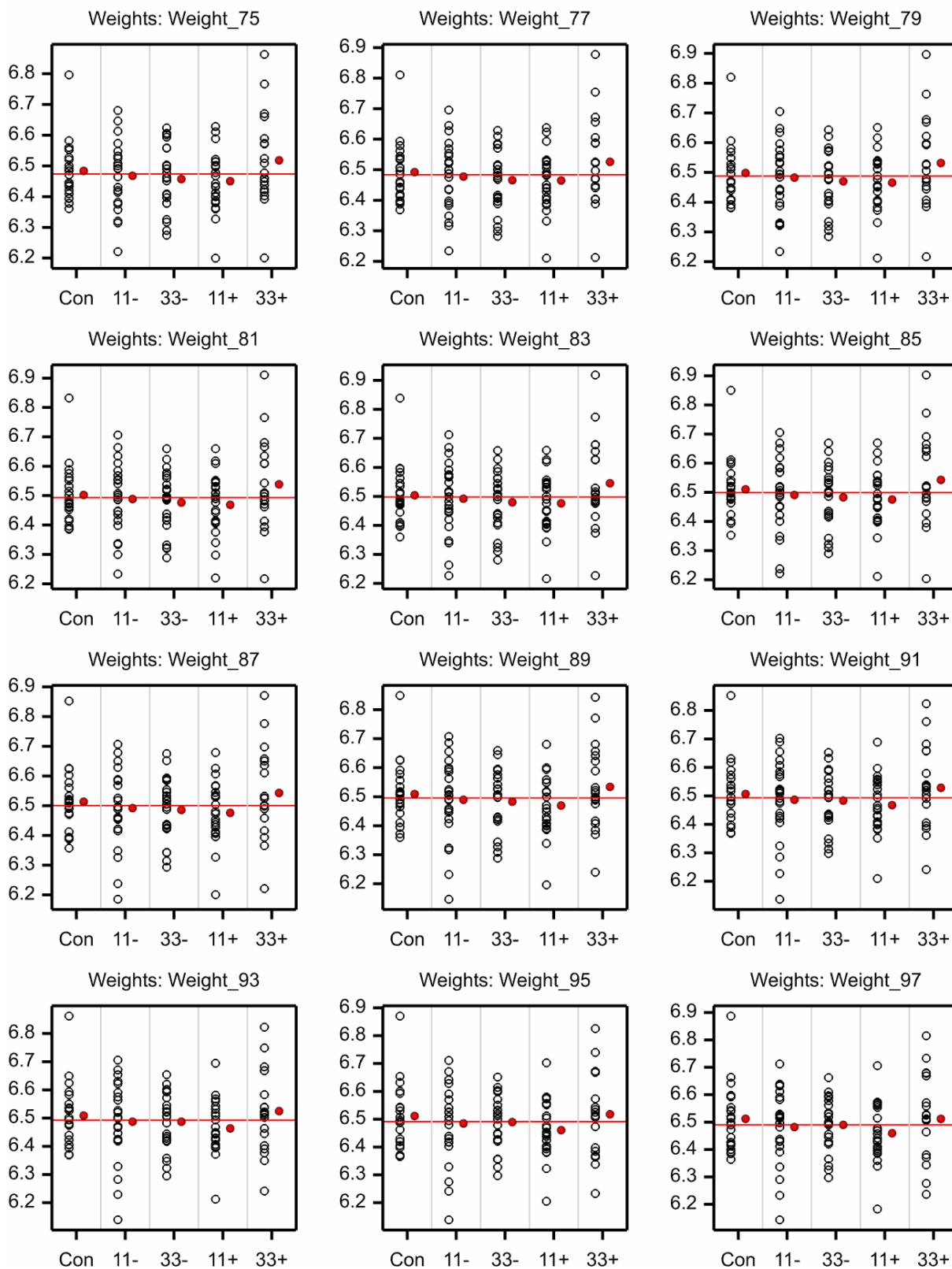
Appendix 4. Graphs of cage means on the log scale

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

Study A month 24 - Cage Means LOG Scale Male

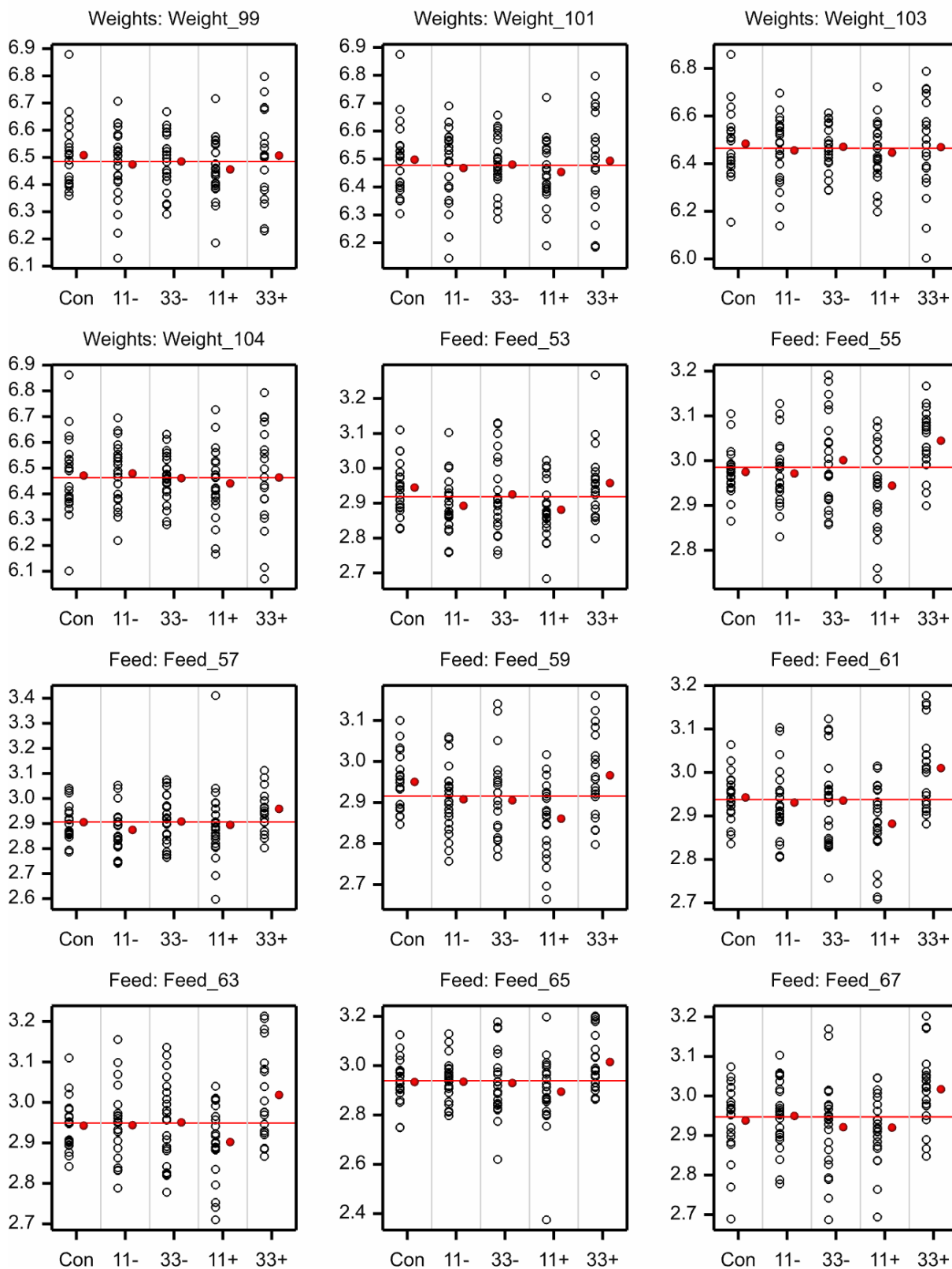
Appendix 4. Graphs of cage means on the log scale (continued)

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

Study A month 24 - Cage Means LOG Scale Male

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

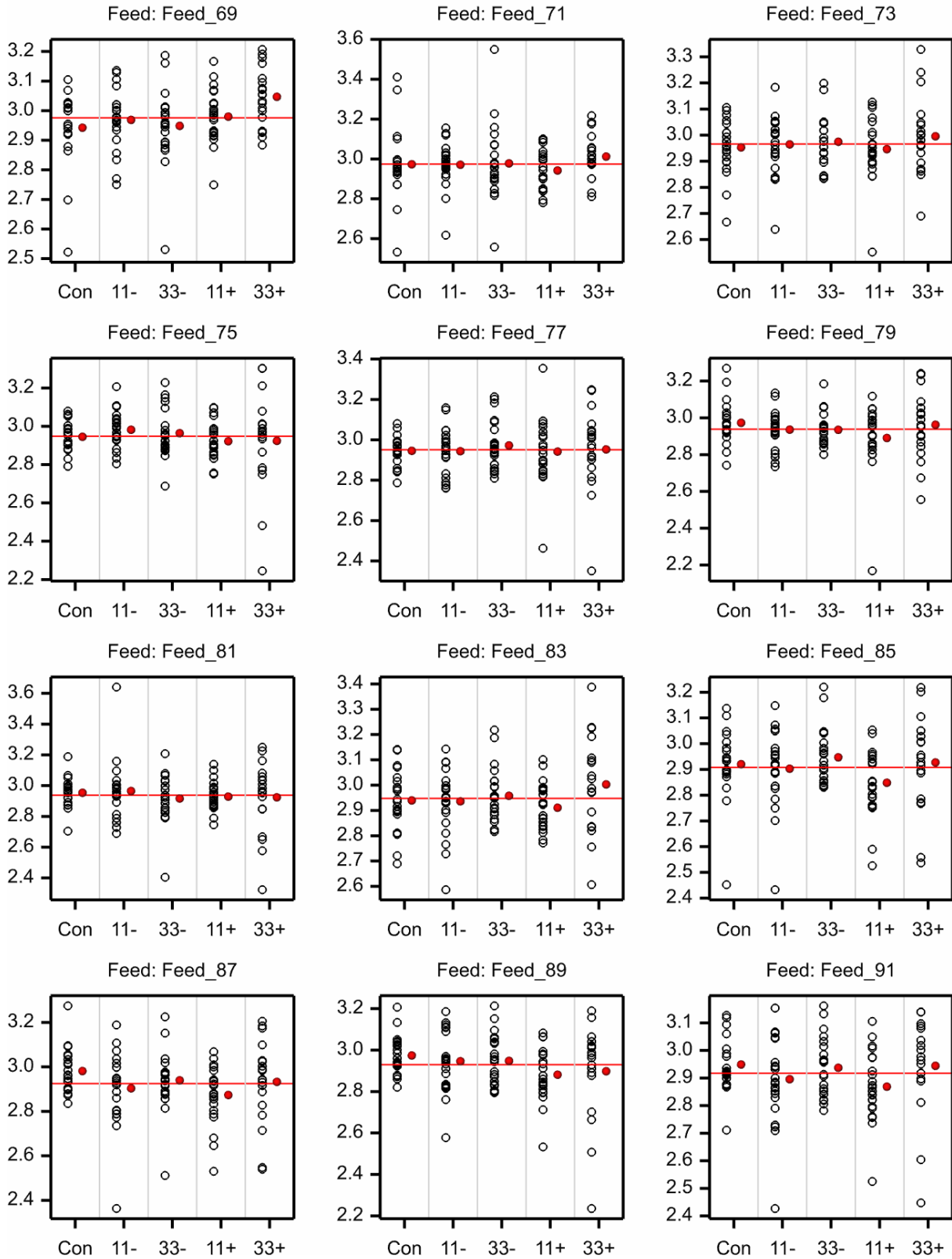
Red symbols denote means for feeding groups while the red line denotes the overall mean.

Study A month 24 - Cage Means LOG Scale Male

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

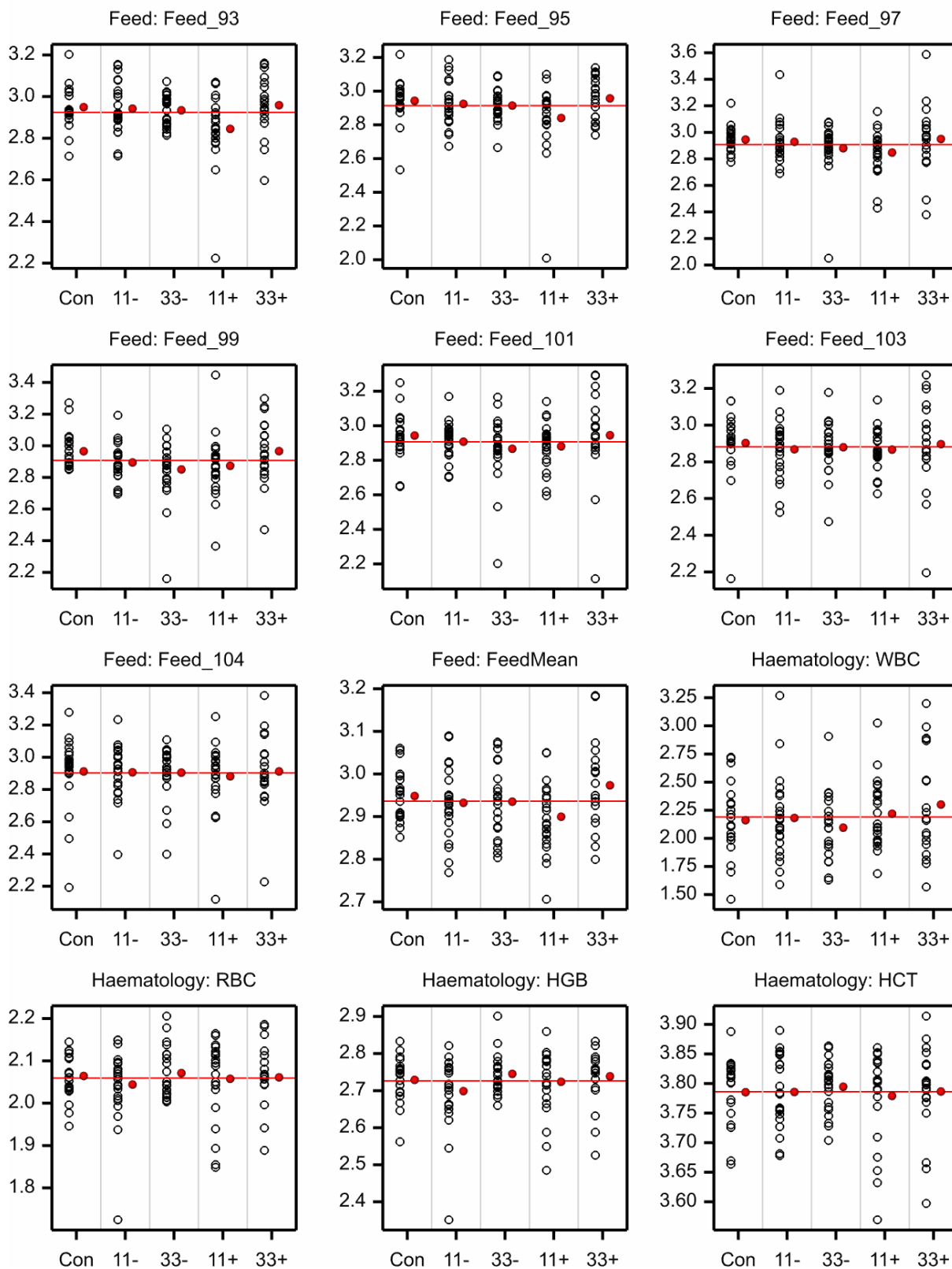
Red symbols denote means for feeding groups while the red line denotes the overall mean.

Study A month 24 - Cage Means LOG Scale Male



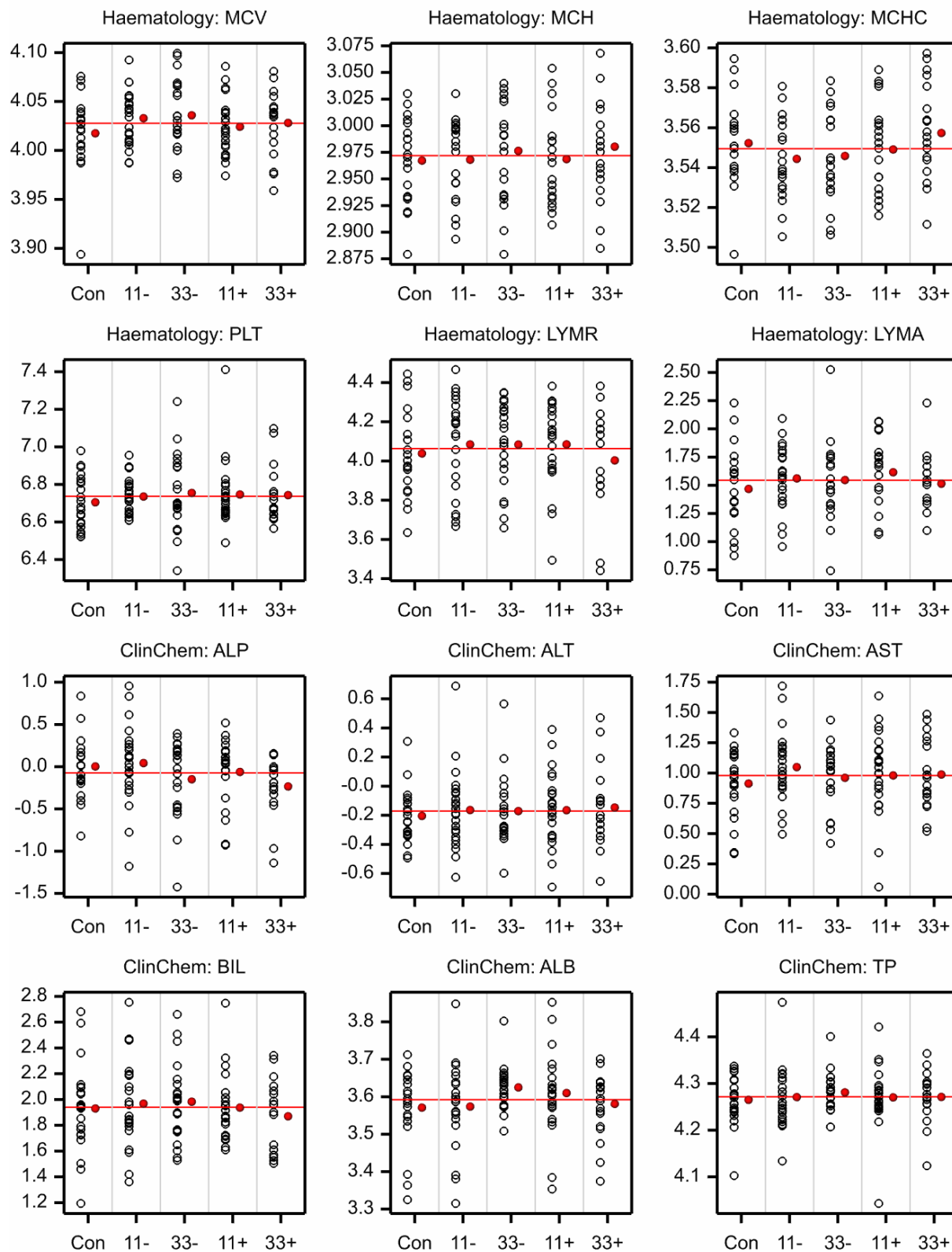
Appendix 4. Graphs of cage means on the log scale (continued)

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

Study A month 24 - Cage Means LOG Scale Male

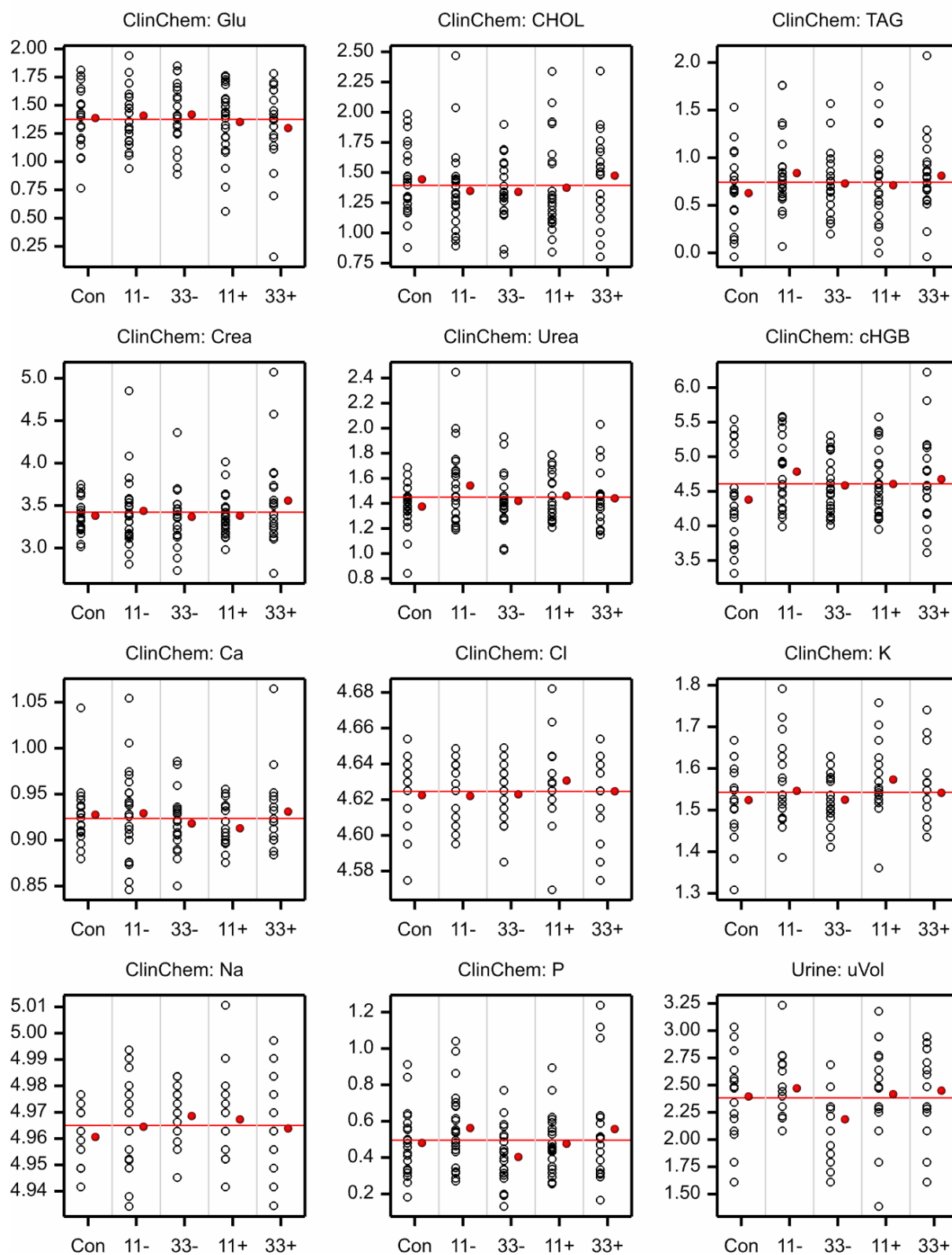
Appendix 4. Graphs of cage means on the log scale (continued)

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

Study A month 24 - Cage Means LOG Scale Male

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

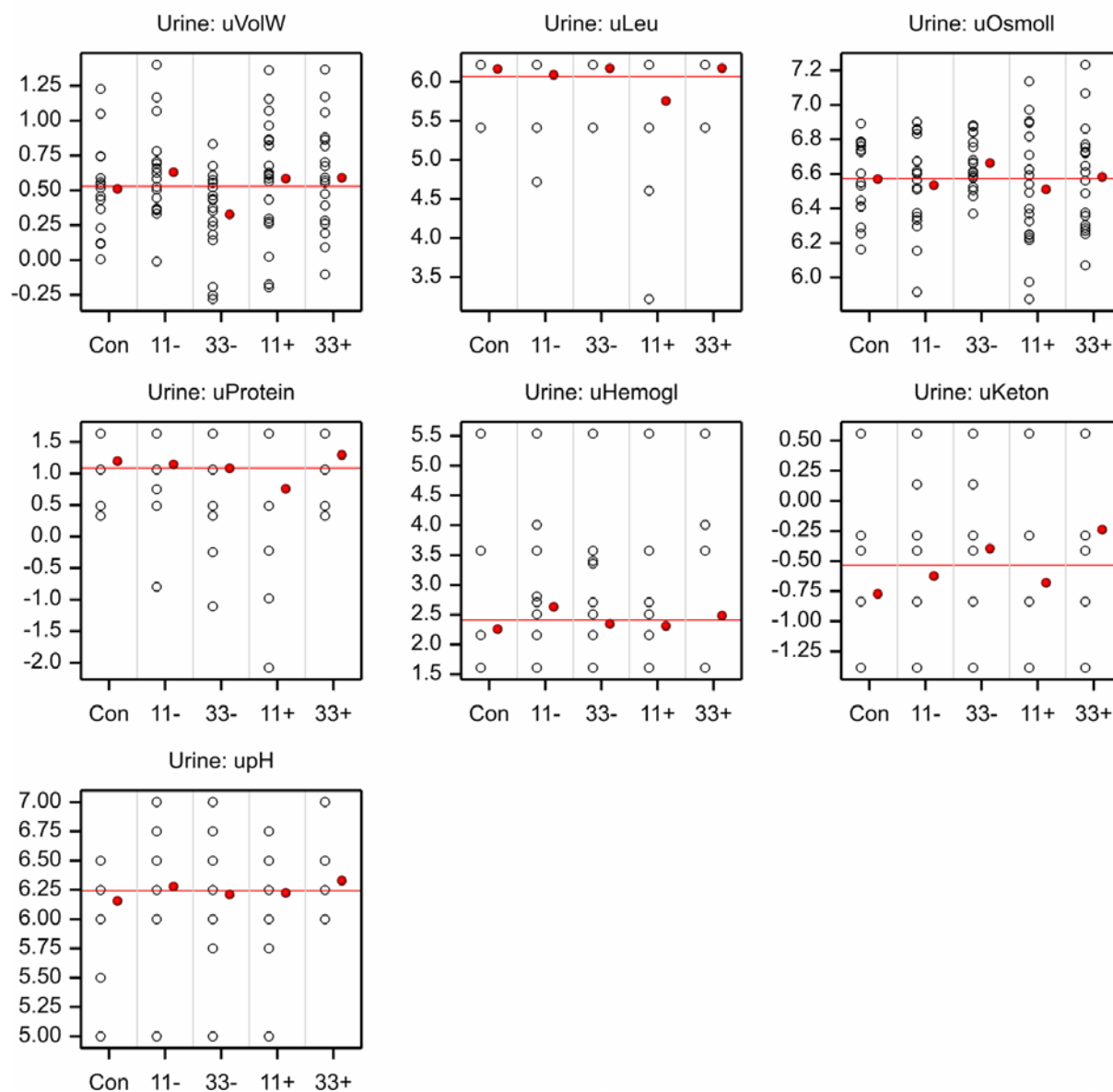
Red symbols denote means for feeding groups while the red line denotes the overall mean.

Study A month 24 - Cage Means LOG Scale Male

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

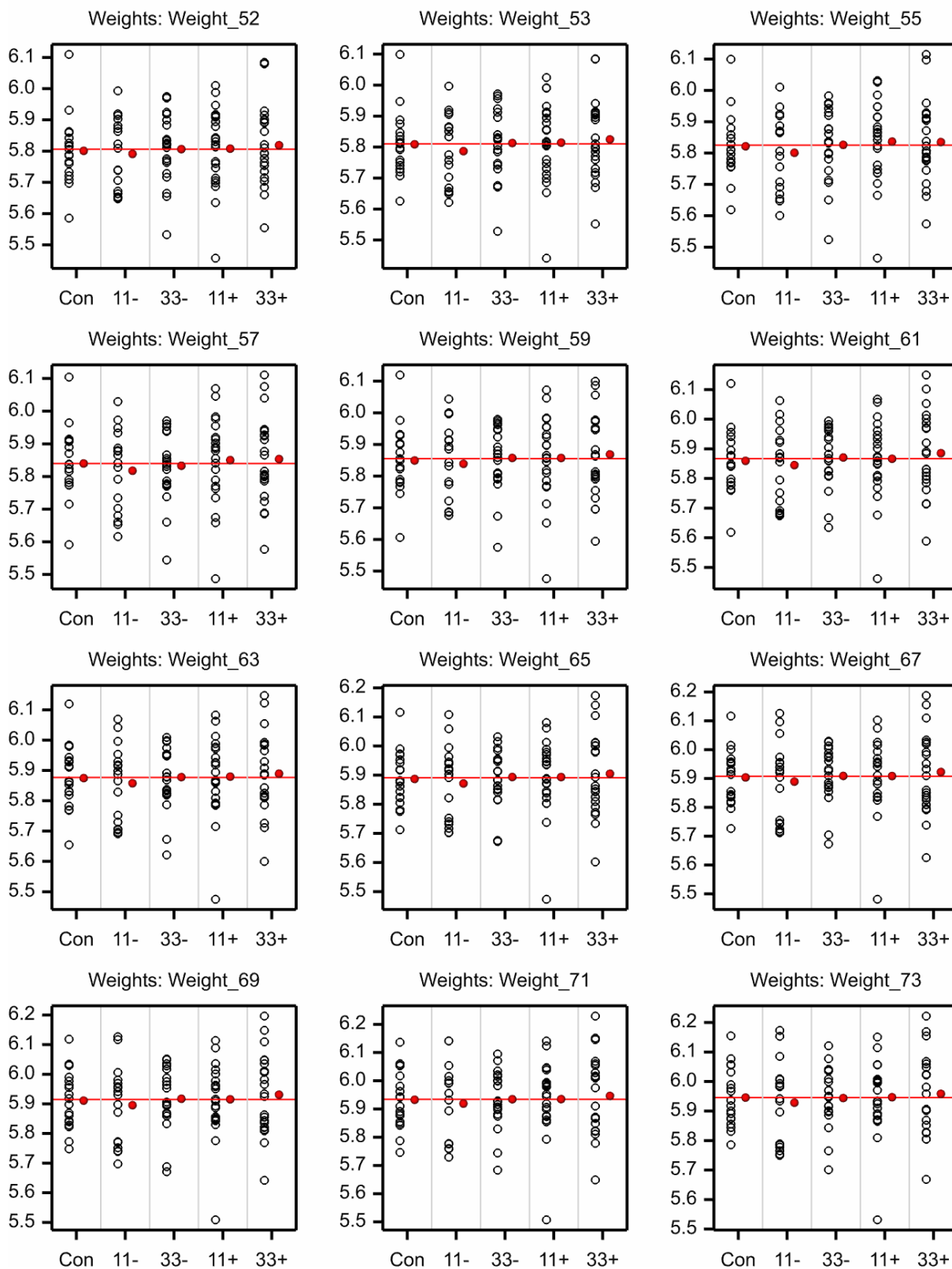
Red symbols denote means for feeding groups while the red line denotes the overall mean.

Study A month 24 - Cage Means LOG Scale Male



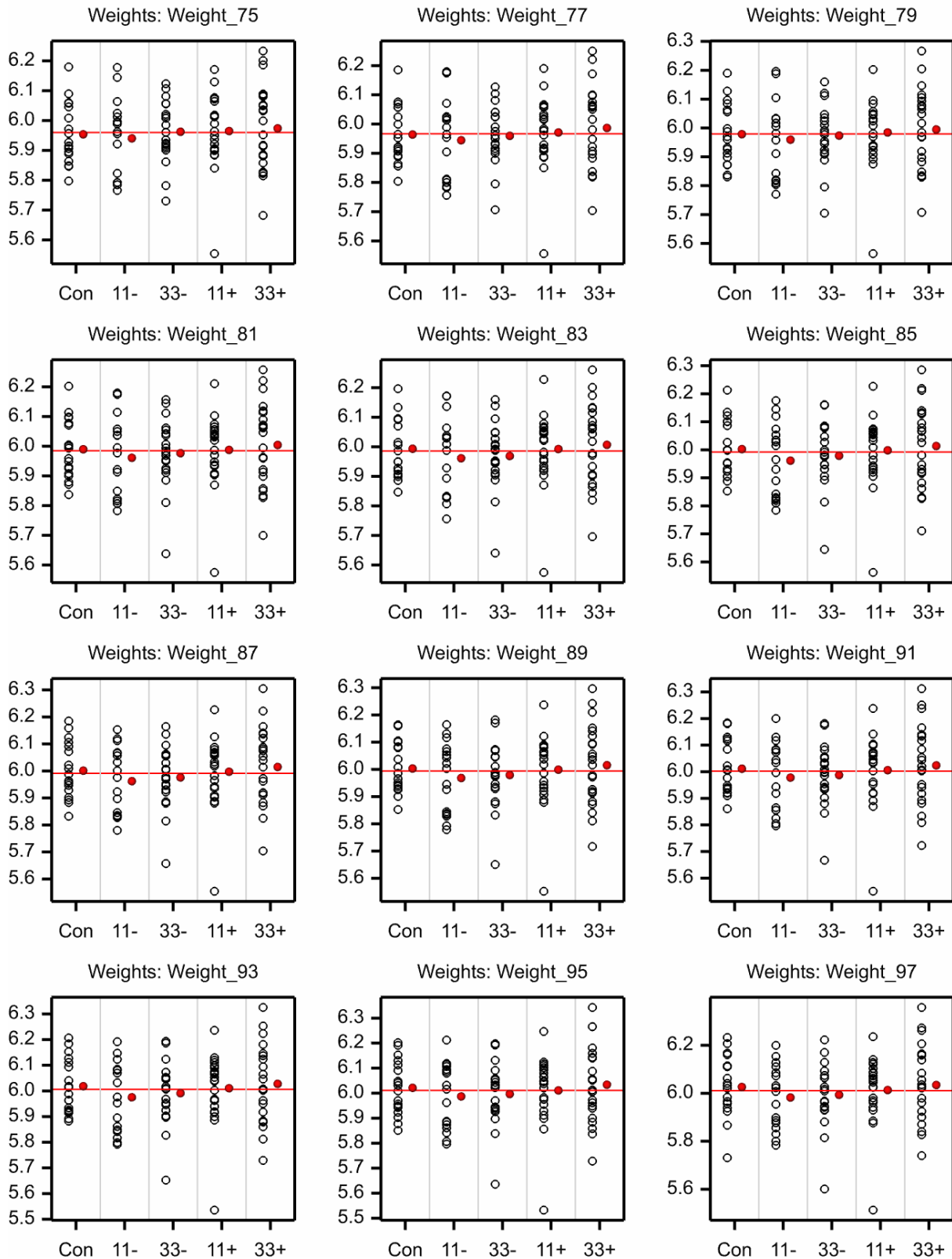
Appendix 4. Graphs of cage means on the log scale (continued)

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

Study A month 24 - Cage Means LOG Scale Female

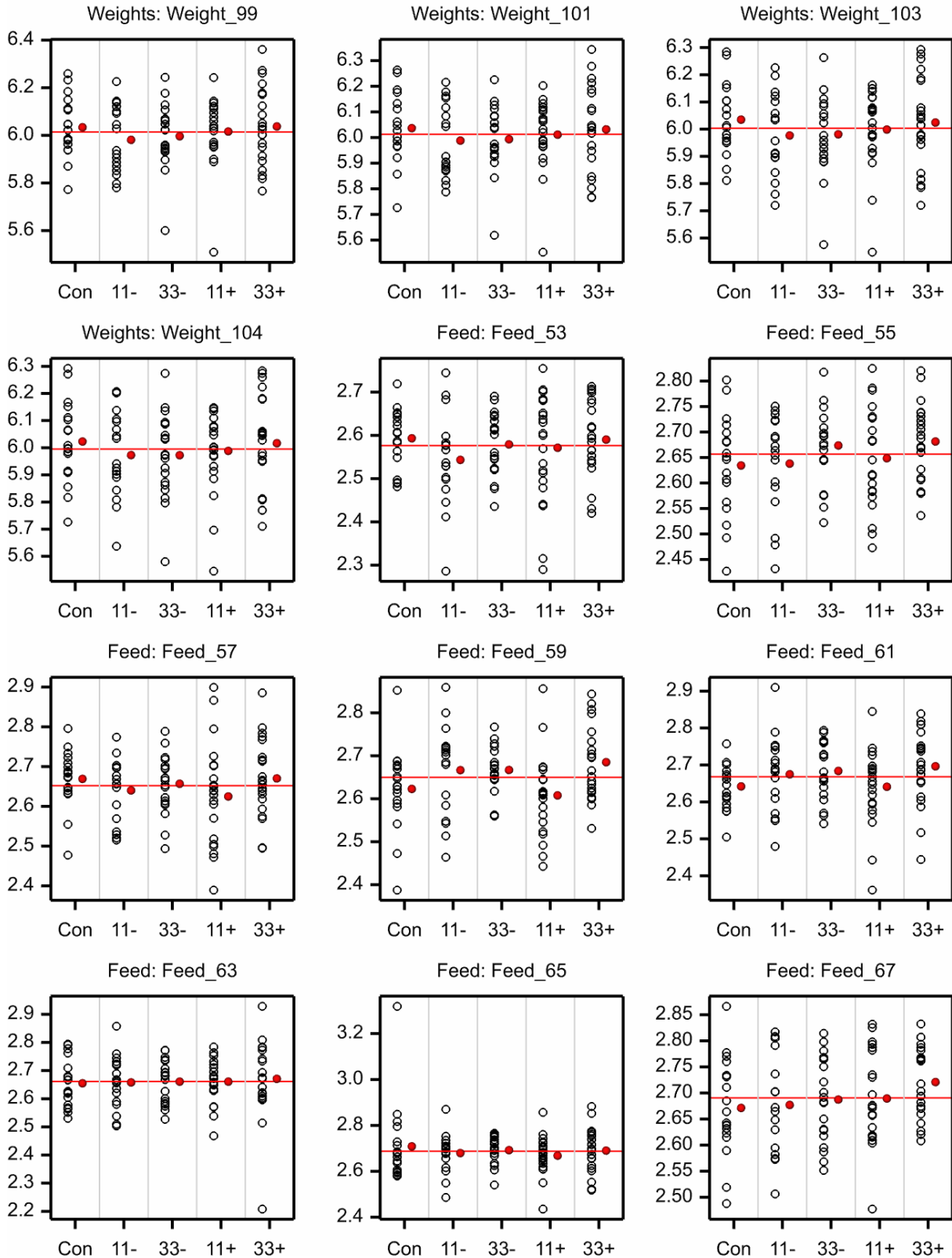
Appendix 4. Graphs of cage means on the log scale (continued)

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

Study A month 24 - Cage Means LOG Scale Female

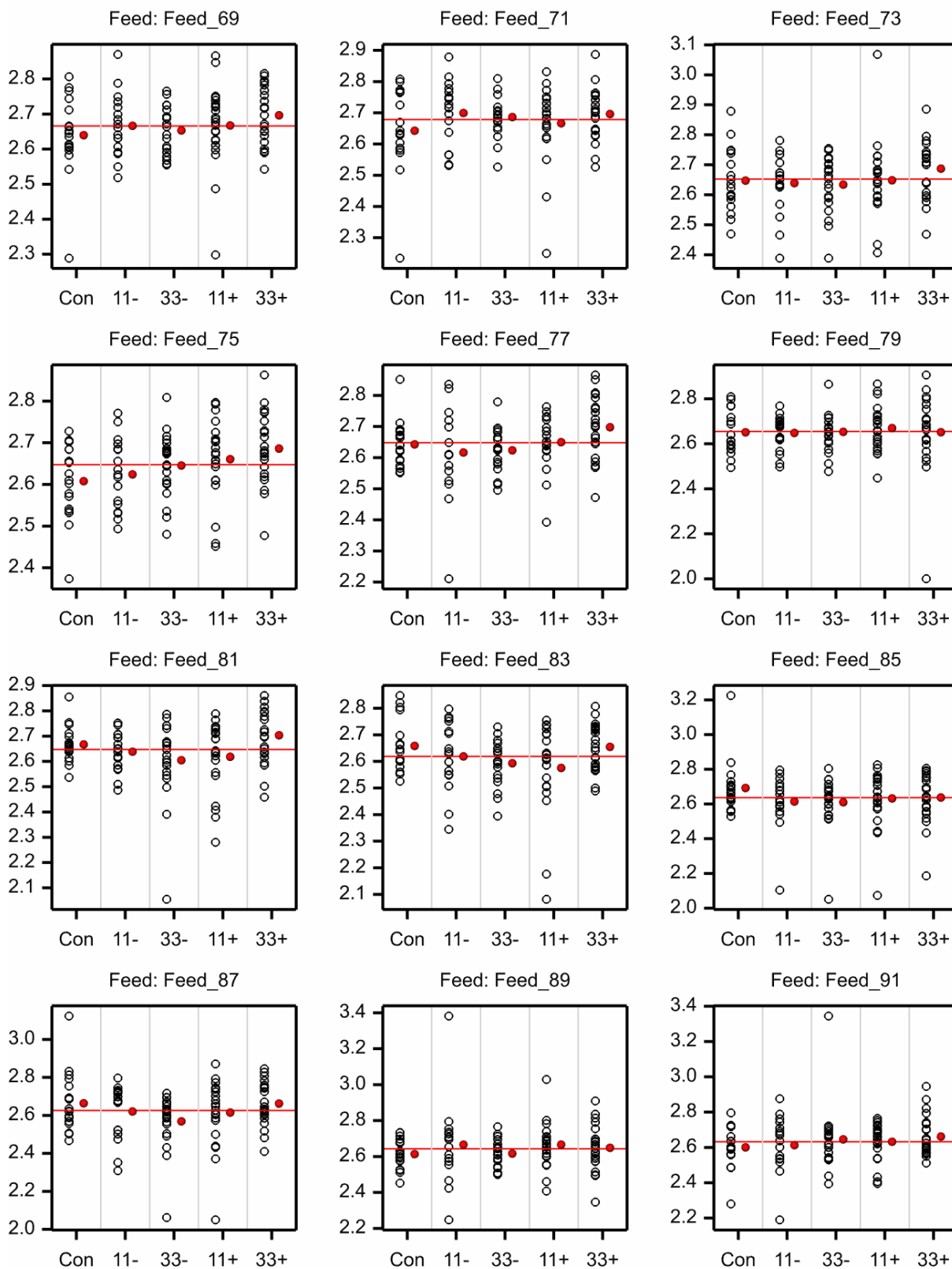
Appendix 4. Graphs of cage means on the log scale (continued)

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

Study A month 24 - Cage Means LOG Scale Female

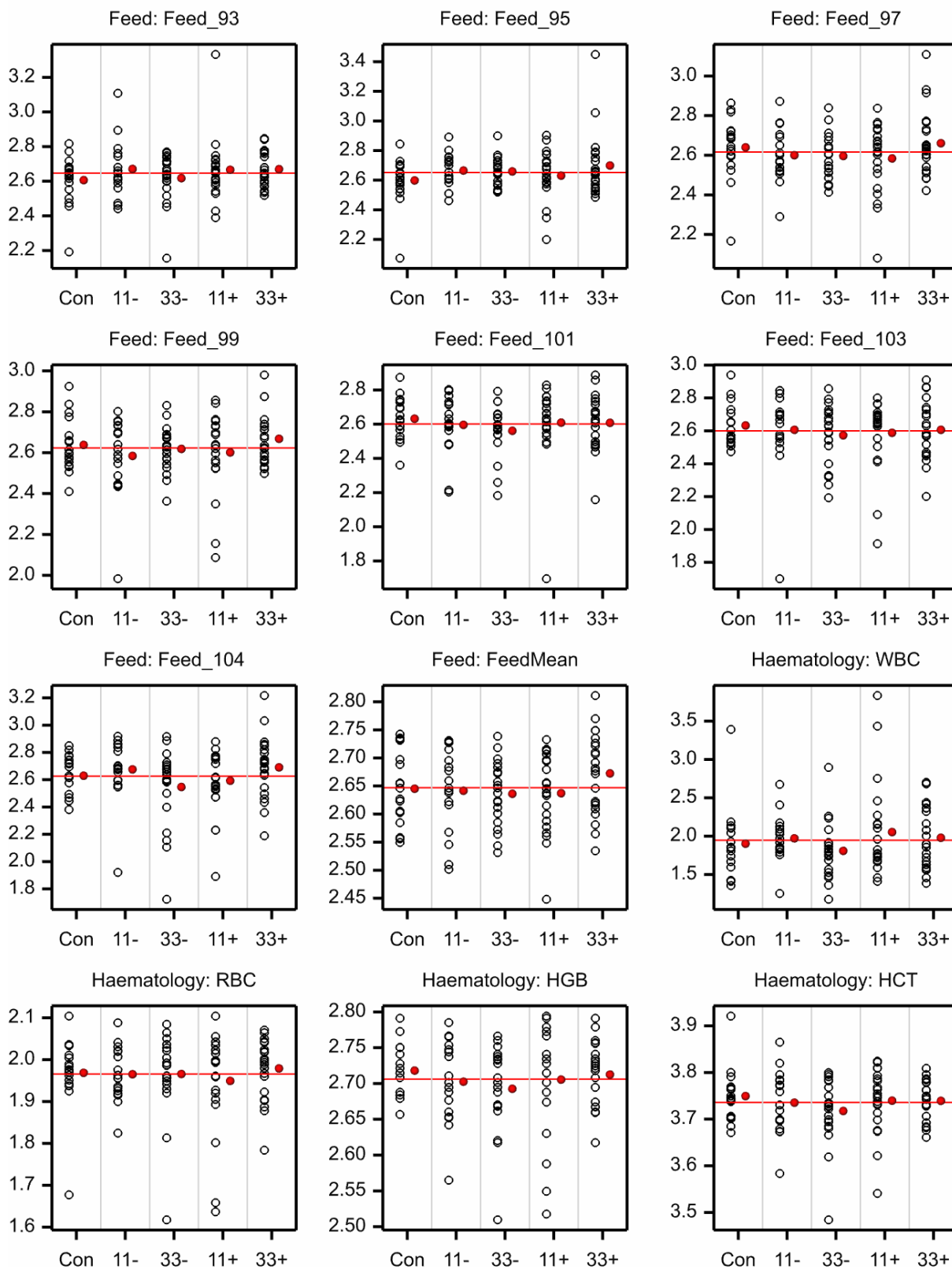
Appendix 4. Graphs of cage means on the log scale (continued)

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

Study A month 24 - Cage Means LOG Scale Female

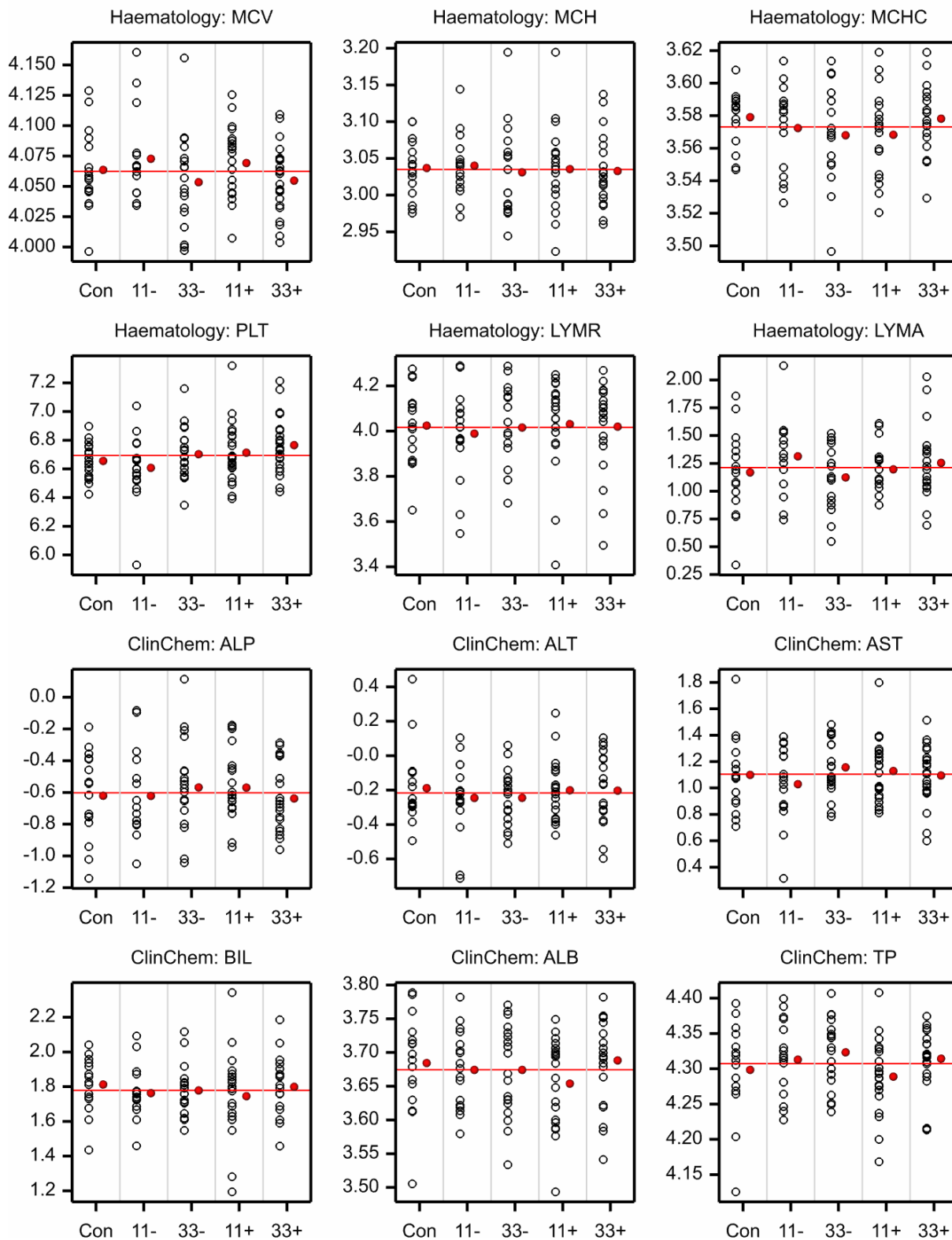
Appendix 4. Graphs of cage means on the log scale (continued)

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

Study A month 24 - Cage Means LOG Scale Female

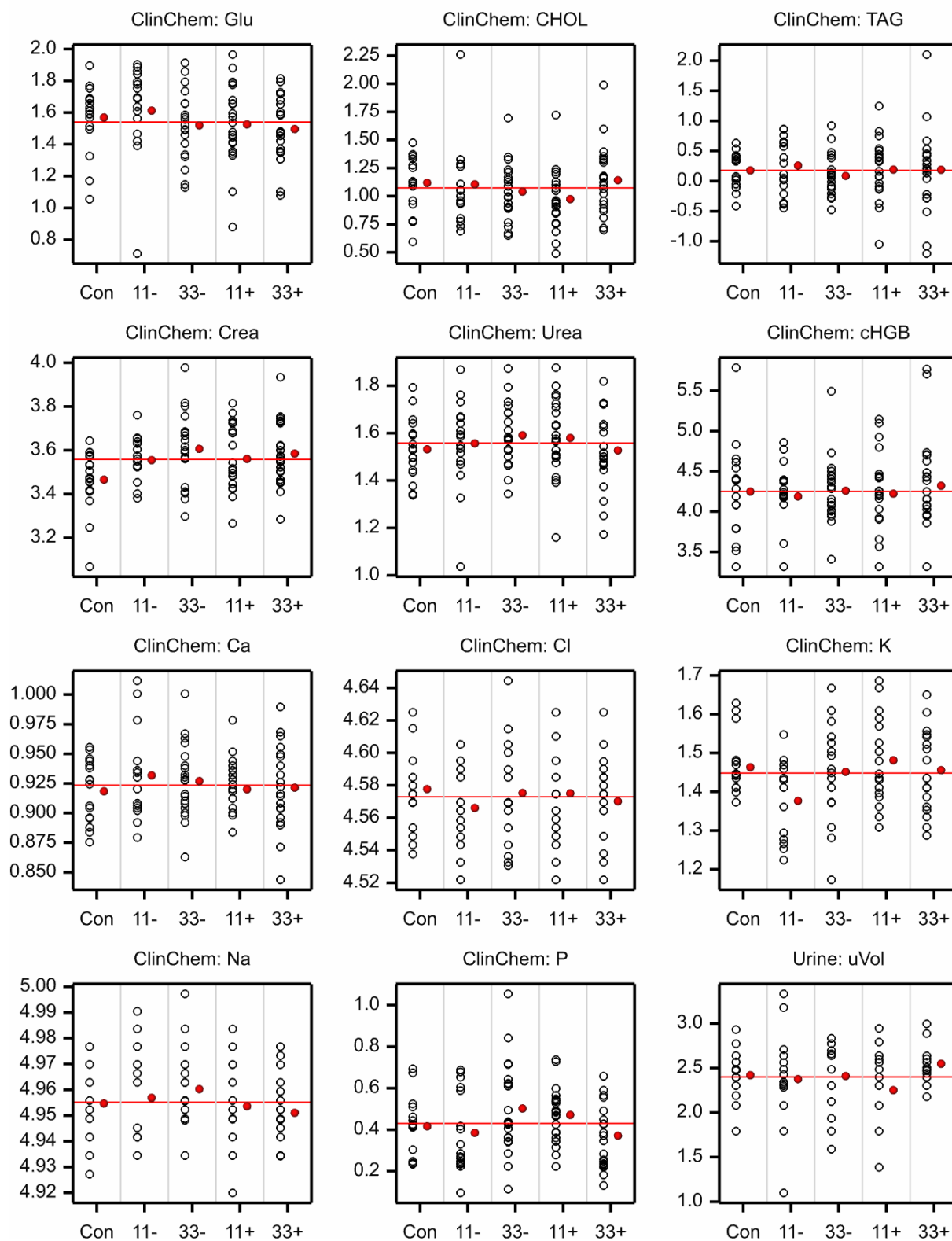
Appendix 4. Graphs of cage means on the log scale (continued)

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

Study A month 24 - Cage Means LOG Scale Female

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

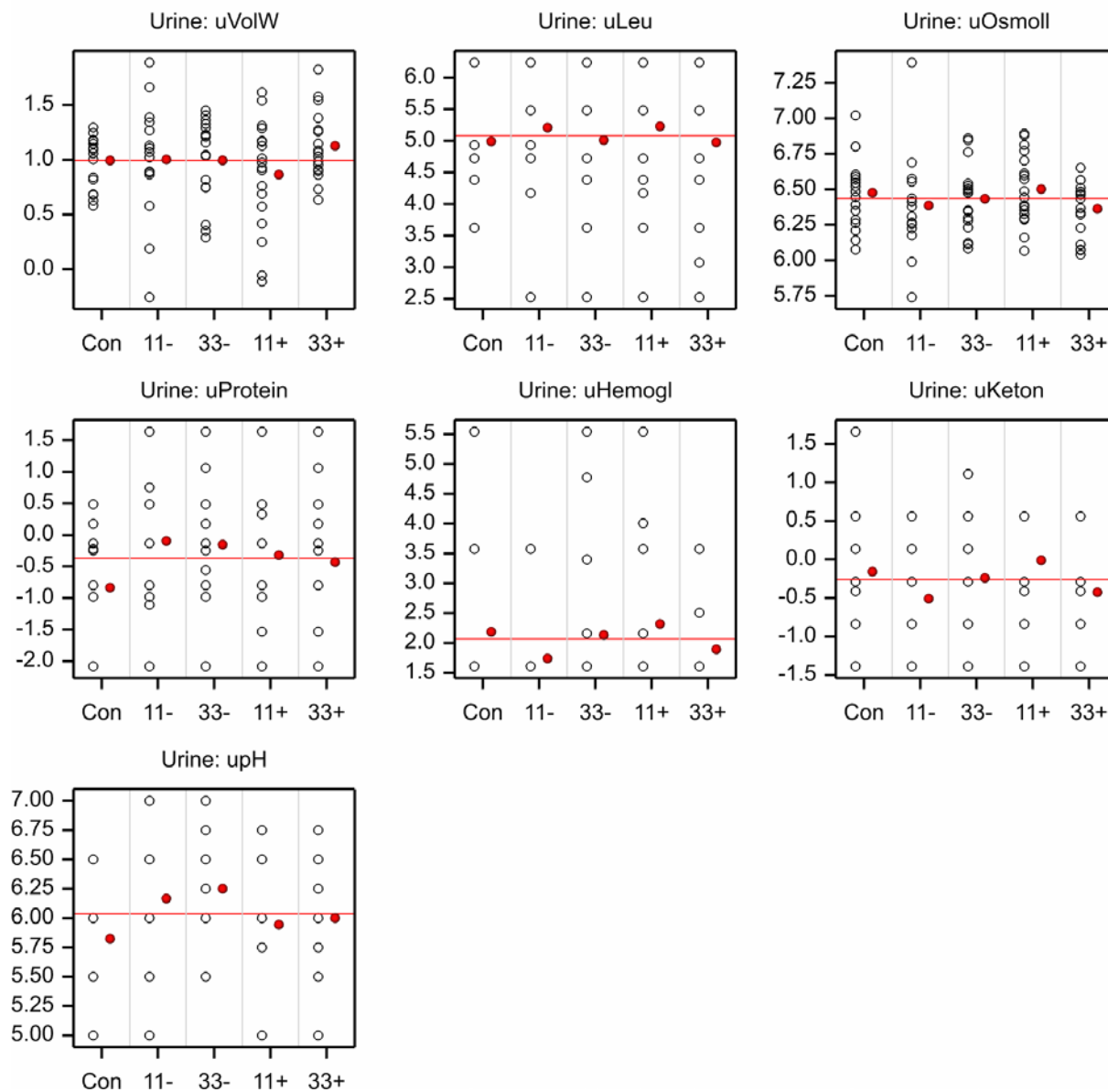
Red symbols denote means for feeding groups while the red line denotes the overall mean.

Study A month 24 - Cage Means LOG Scale Female

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.

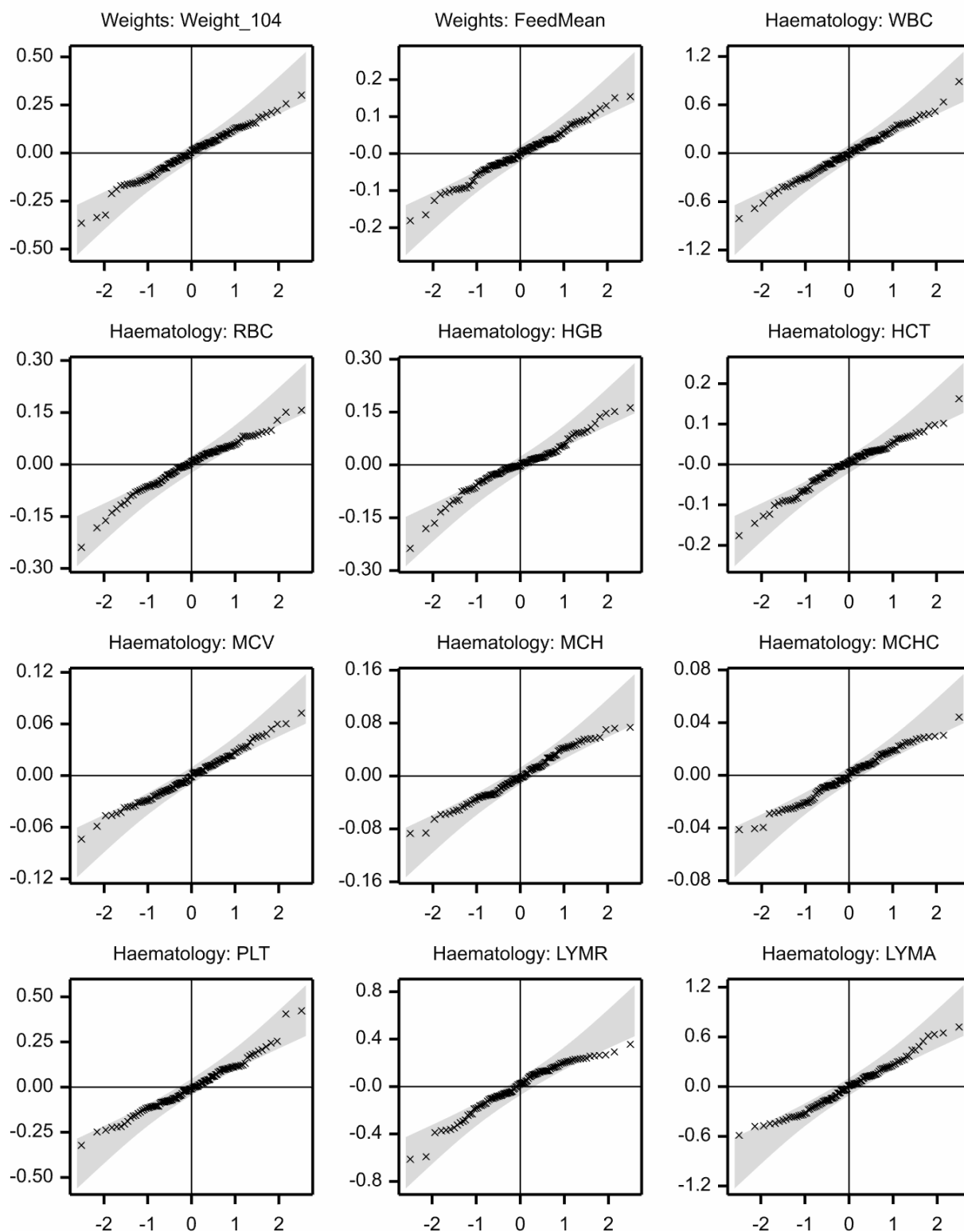
Study A month 24 - Cage Means LOG Scale Female



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.

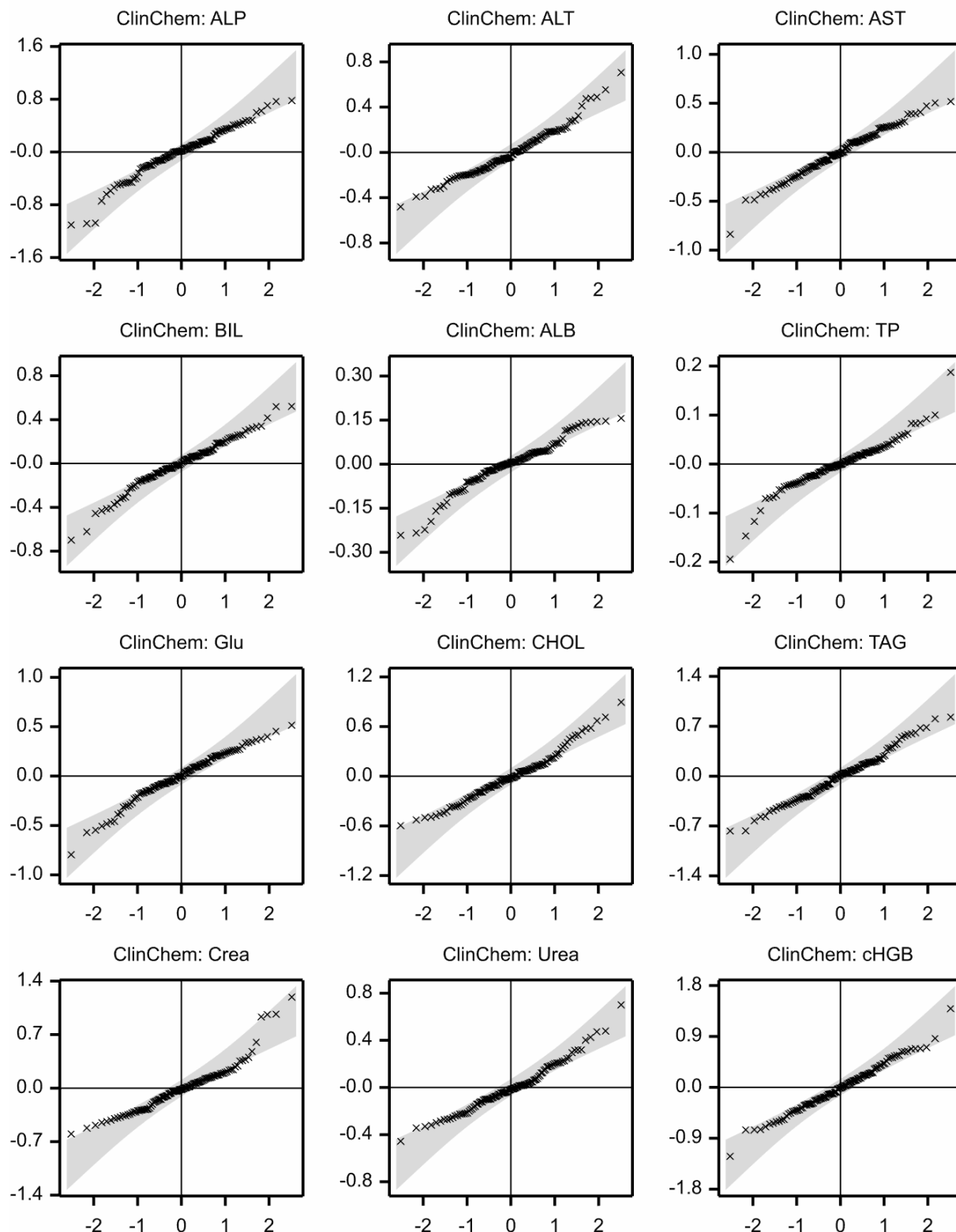
Study A month 24 - Normal Probability Plot Male



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

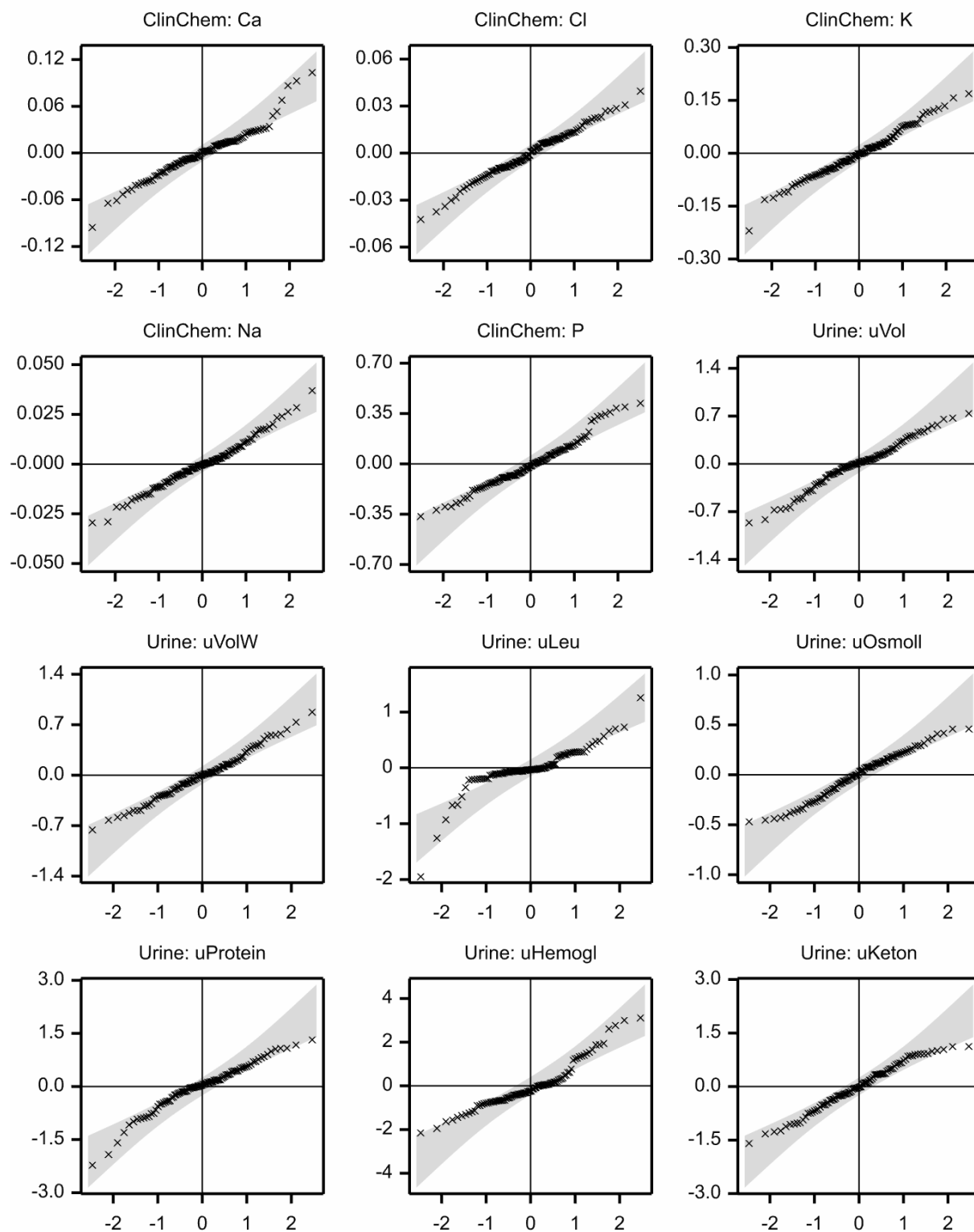
Residuals are obtained from ANOVA of cage means (log scale). A 99% confidence envelop is added.

Study A month 24 - Normal Probability Plot Male



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

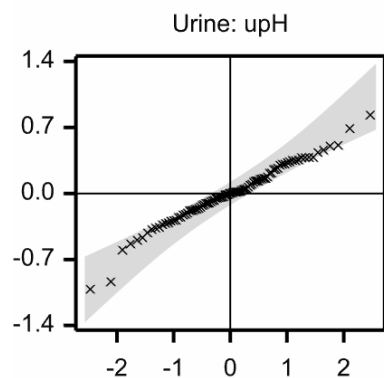
Residuals are obtained from ANOVA of cage means (log scale). A 99% confidence envelop is added.

Study A month 24 - Normal Probability Plot Male

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.

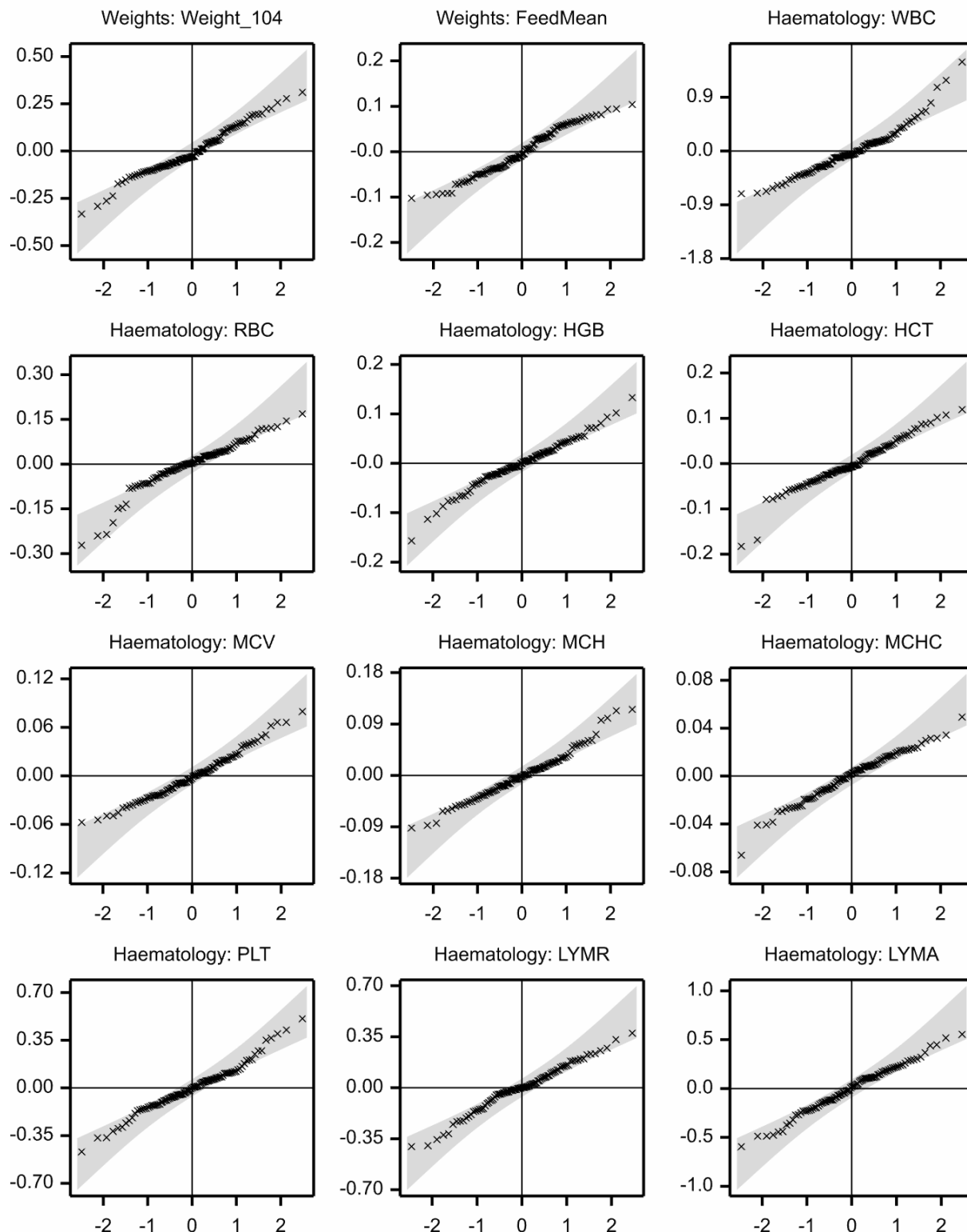
Study A month 24 - Normal Probability Plot Male



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.

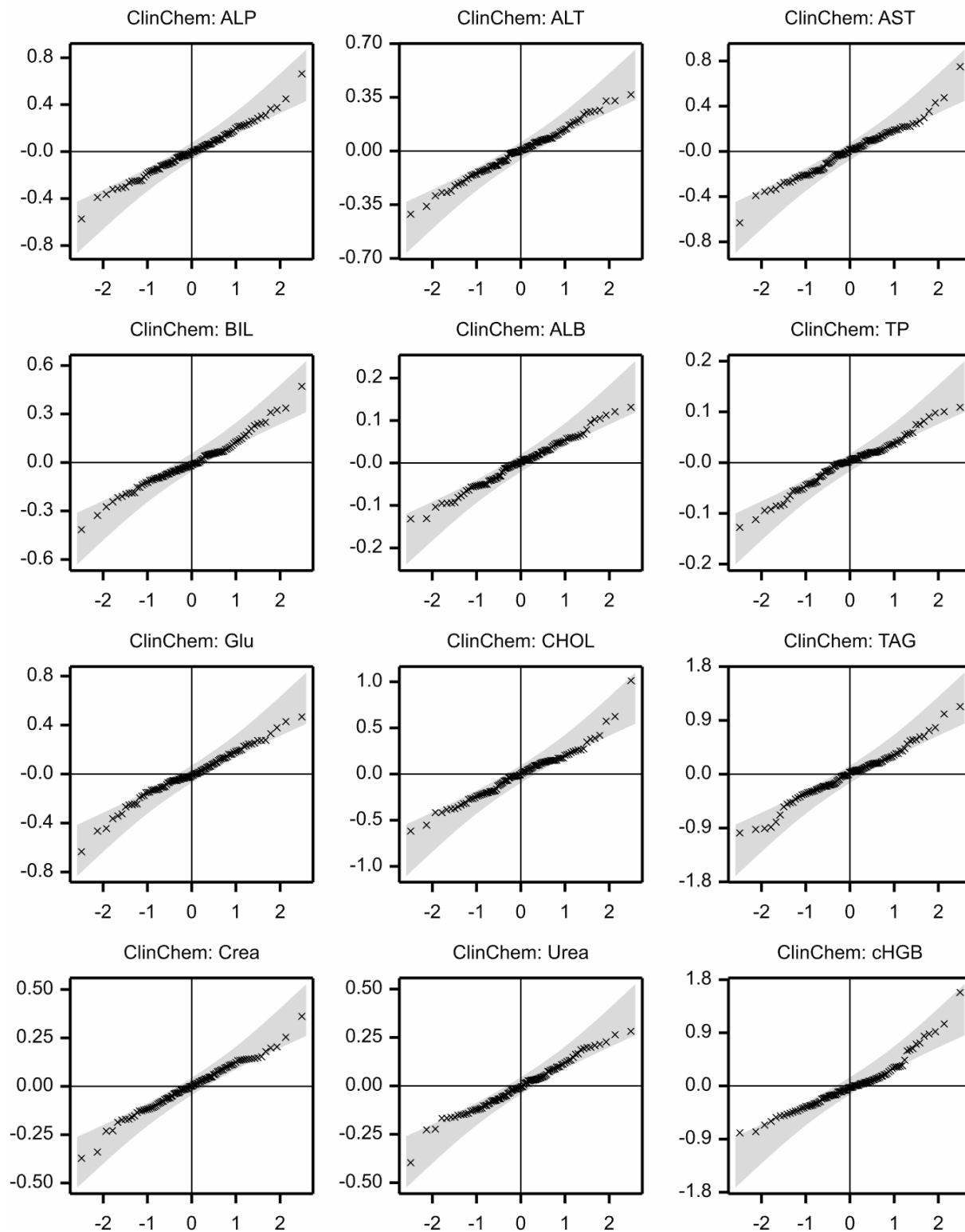
Study A month 24 - Normal Probability Plot Female



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

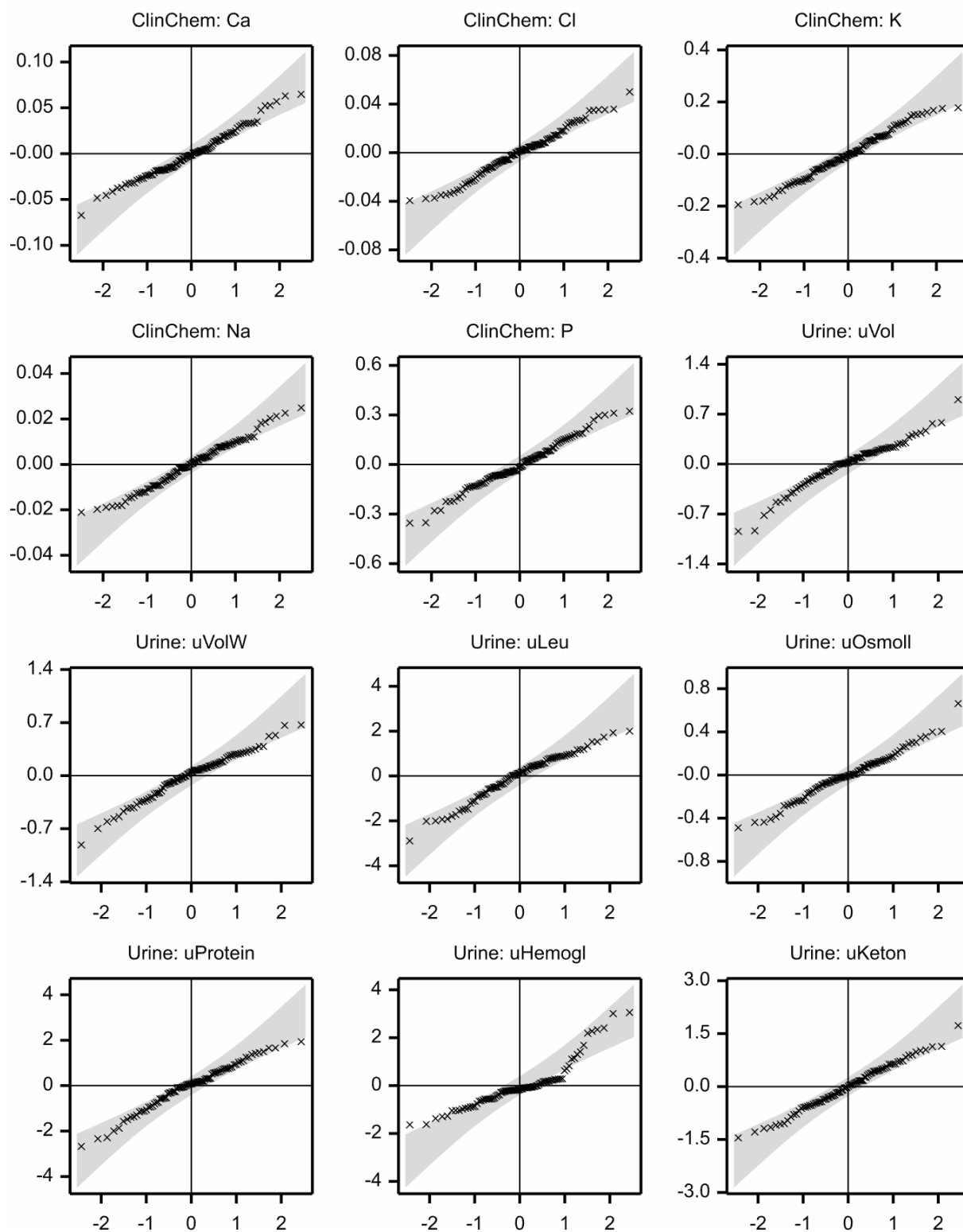
Residuals are obtained from ANOVA of cage means (log scale). A 99% confidence envelop is added.

Study A month 24 - Normal Probability Plot Female



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

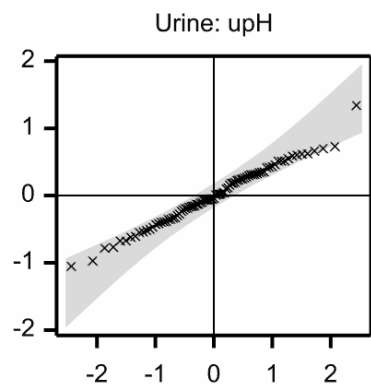
Residuals are obtained from ANOVA of cage means (log scale). A 99% confidence envelop is added.

Study A month 24 - Normal Probability Plot Female

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.

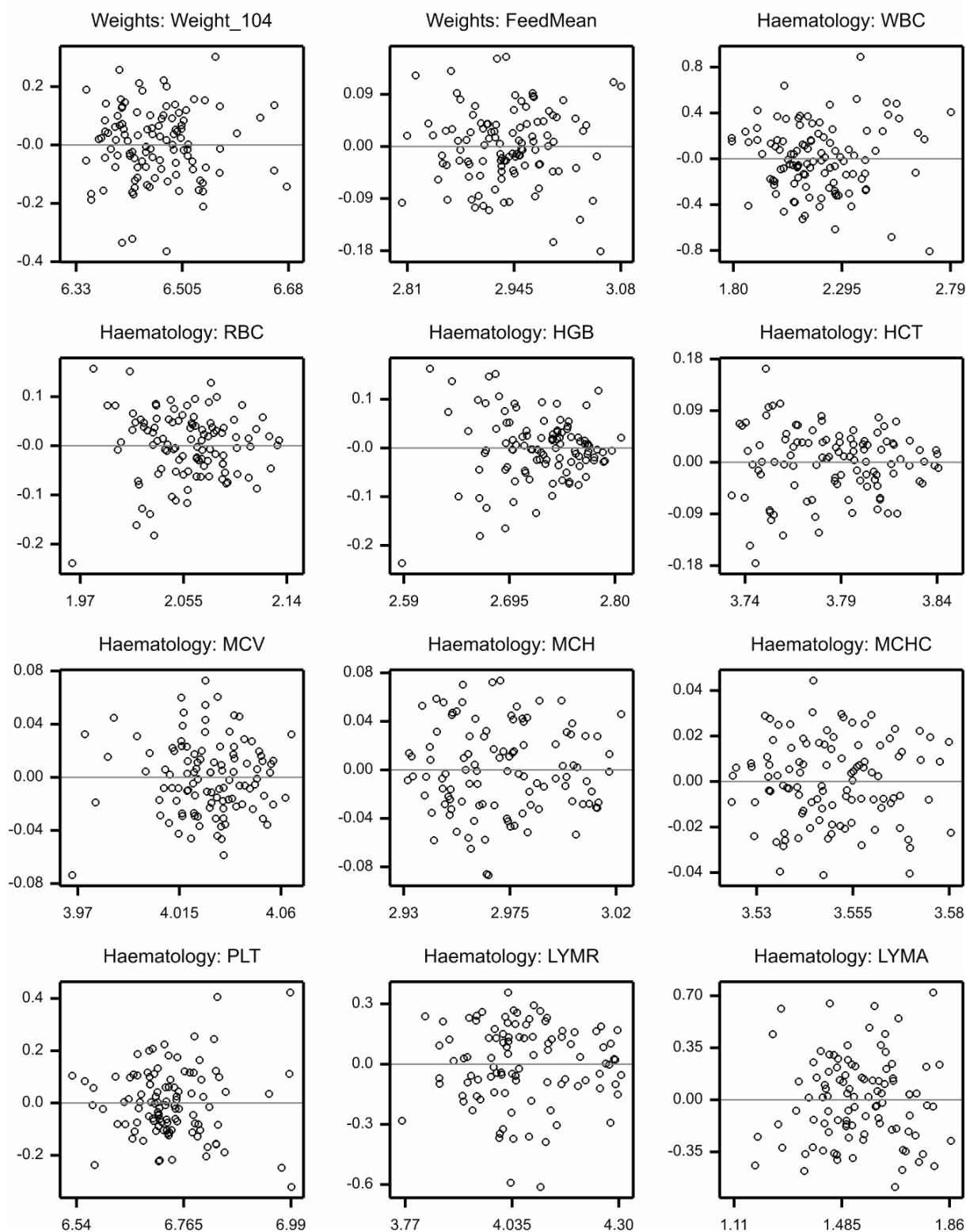
Study A month 24 - Normal Probability Plot Female



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).

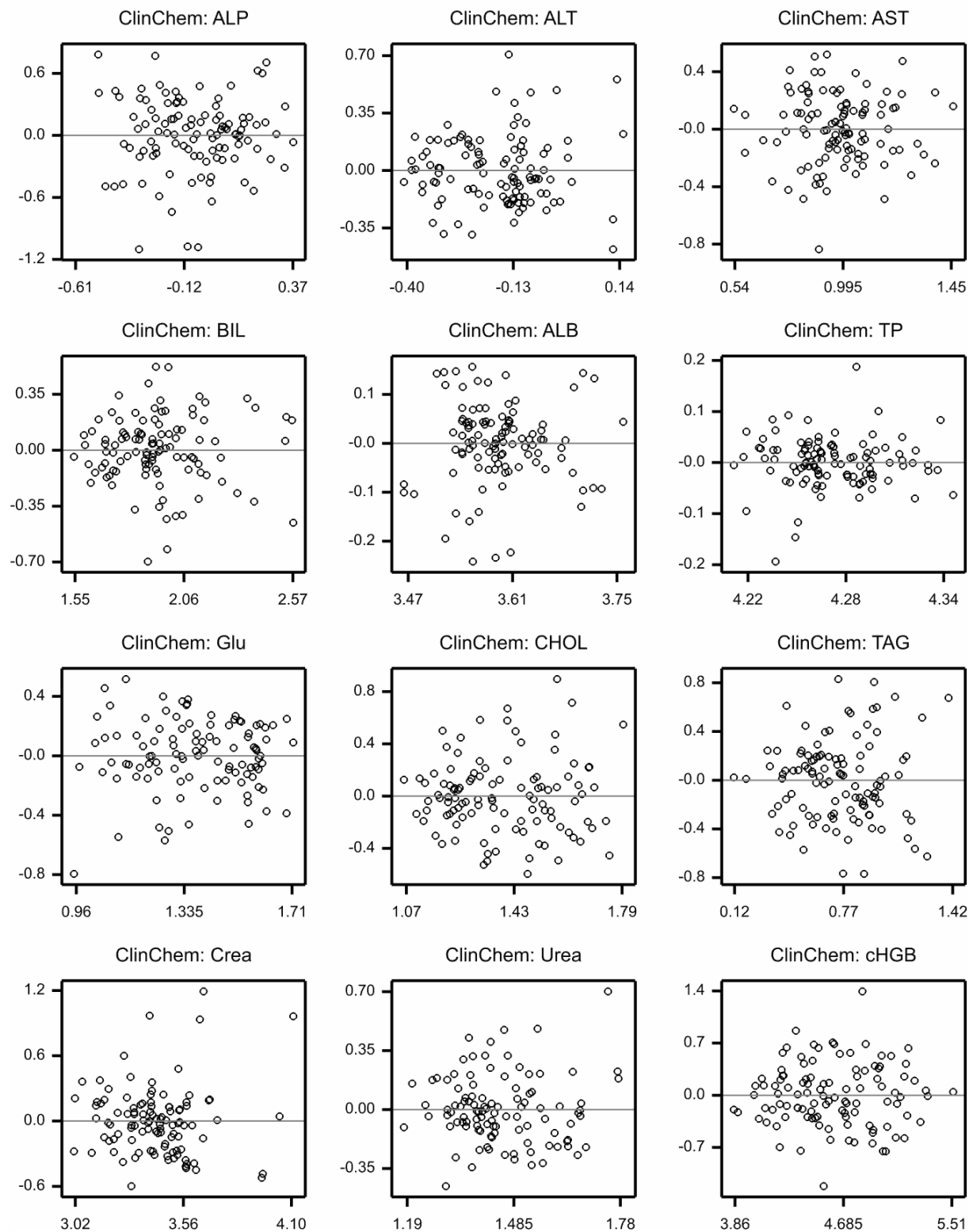
Study A month 24 - Residuals vs Fittedvalues Male



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).

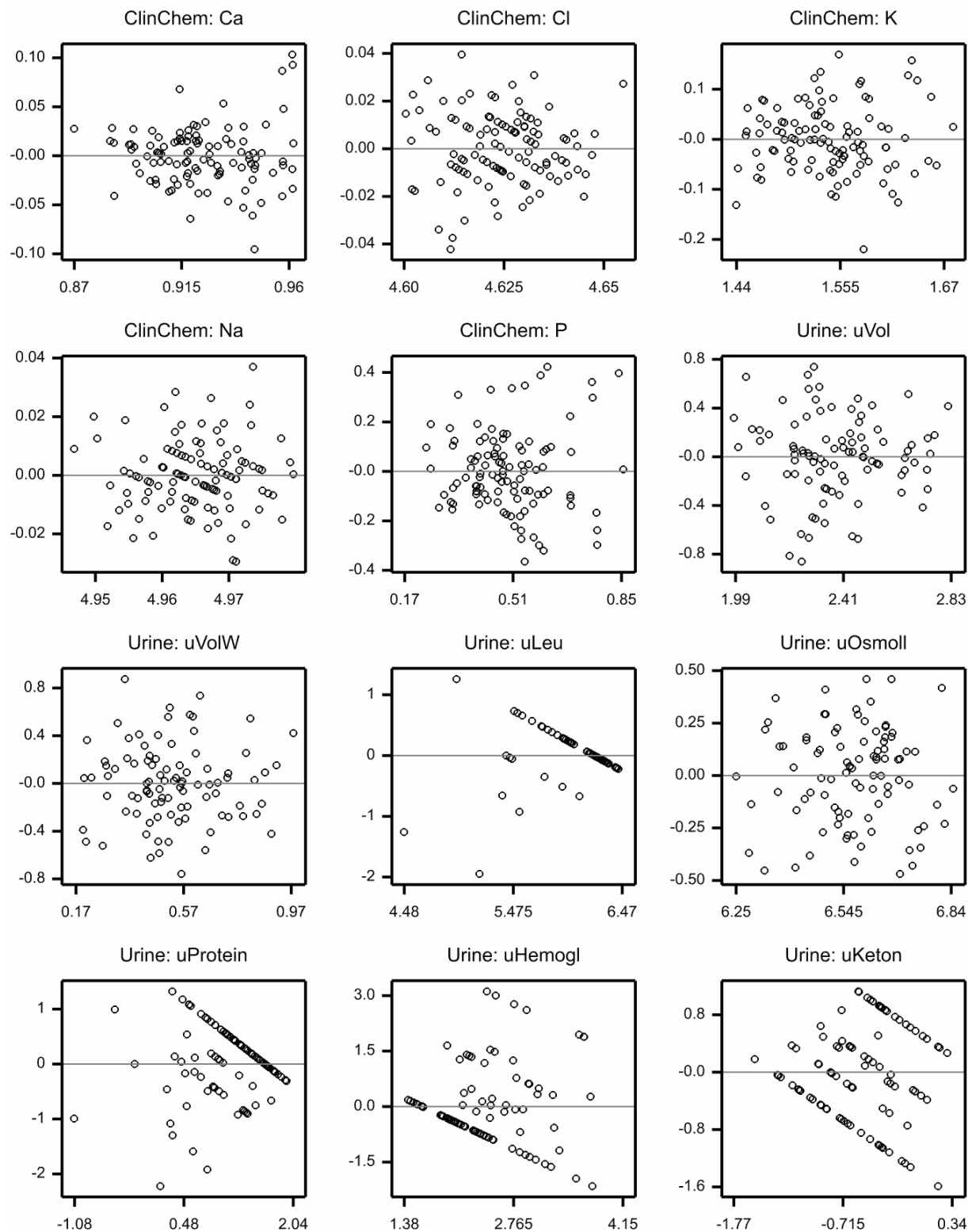
Study A month 24 - Residuals vs Fittedvalues Male



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).

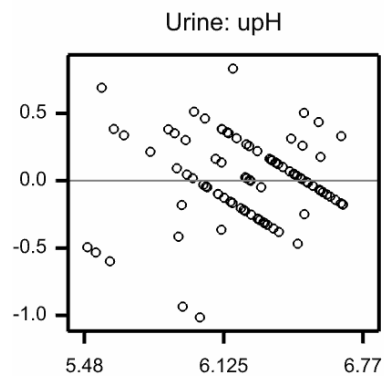
Study A month 24 - Residuals vs Fittedvalues Male



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).

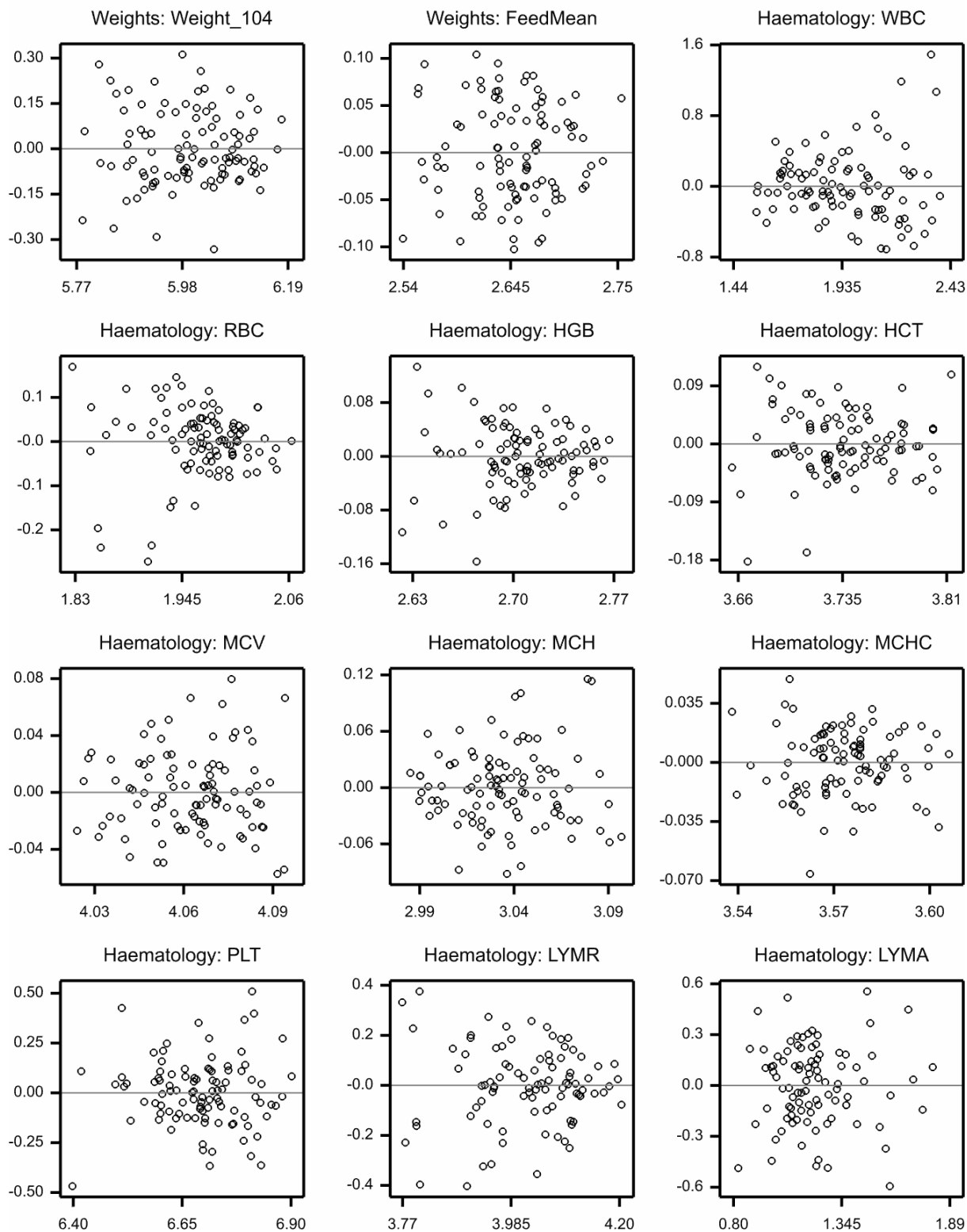
Study A month 24 - Residuals vs Fittedvalues Male



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).

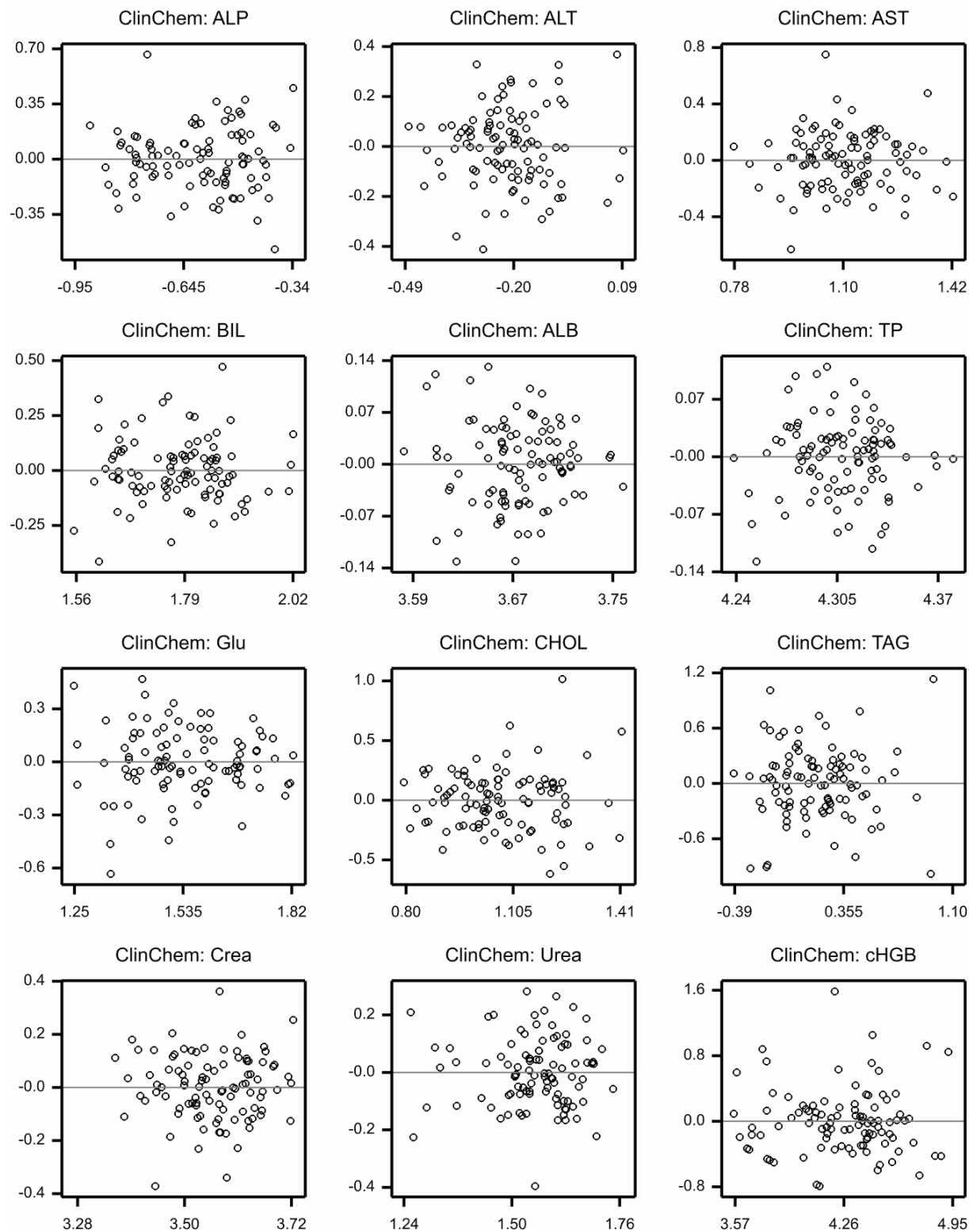
Study A month 24 - Residuals vs Fittedvalues Female



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).

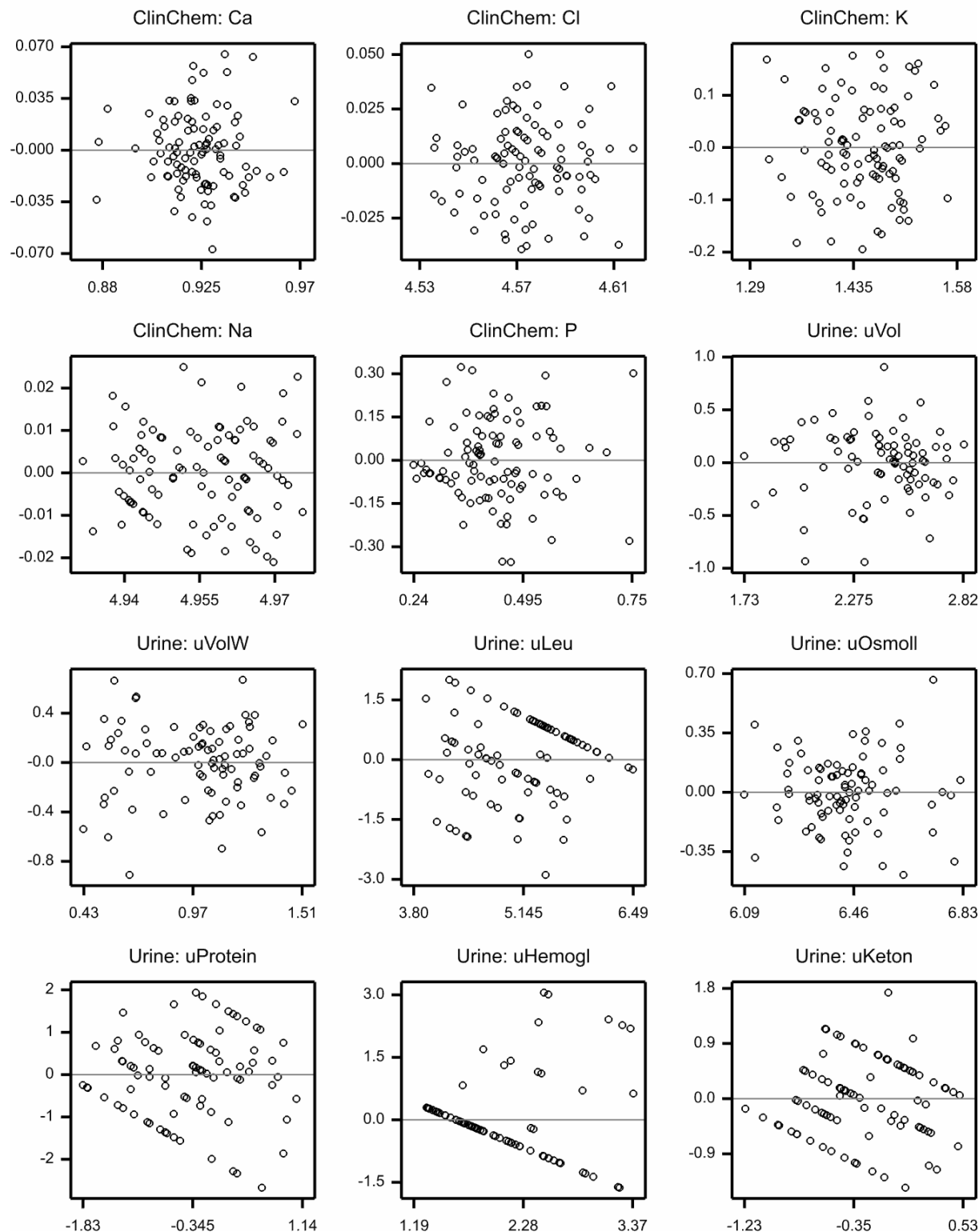
Study A month 24 - Residuals vs Fittedvalues Female



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).

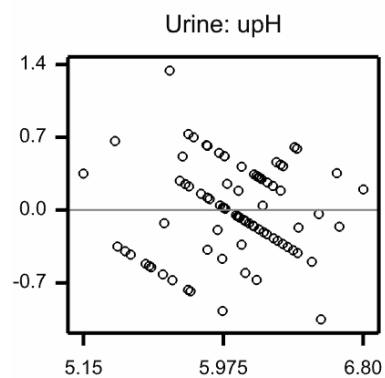
Study A month 24 - Residuals vs Fittedvalues Female



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).

Study A month 24 - Residuals vs Fittedvalues Female



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 is in the interval [75, 79] for males, and in the interval [65, 70] for females. For LYMA the degrees of freedom is somewhat smaller: 70 for males and 62 for females. Differences in degrees of freedom are due to missing values.

Variable	Male rats					Female rats				
	NK11-	NK33-	NK11+	NK33+	SS_F	NK11-	NK33-	NK11+	NK33+	SS_F
Weight_104	0.0077	-0.0208	-0.0436	-0.0205	1.5008	-0.0514	-0.0756	-0.0554	-0.0200	1.5008
FeedMean	-0.0163	-0.0221	-0.0555	0.0261	0.2608	-0.0005	-0.0159	-0.0152	0.0194	0.2608
WBC	0.0401	-0.0756	0.0634	0.1609	14.6114	0.0999	-0.0115	0.2281	0.1069	14.6114
RBC	-0.0188	0.0102	-0.0014	-0.0068	0.5780	-0.0008	0.0104	-0.0202	0.0161	0.5780
HGB	-0.0272	0.0188	0.0005	0.0095	0.2077	-0.0160	-0.0242	-0.0139	-0.0086	0.2077
HCT	-0.0006	0.0065	-0.0074	-0.0020	0.2510	-0.0251	-0.0312	-0.0131	-0.0134	0.2510
MCV	0.0158	0.0184	0.0056	0.0103	0.0759	0.0073	-0.0129	0.0048	-0.0092	0.0759
MCH	0.0030	0.0086	0.0025	0.0136	0.1611	0.0063	-0.0095	-0.0004	-0.0052	0.1611
MCHC	-0.0075	-0.0078	-0.0026	0.0052	0.0358	0.0000	-0.0107	-0.0093	-0.0007	0.0358
PLT	0.0264	0.0470	0.0446	0.0427	2.7851	-0.0218	0.0768	0.0917	0.1132	2.7851
LYMA	0.0854	0.0816	0.1431	0.0714	4.9941	0.1918	-0.0315	0.0475	0.0985	4.9941
ALP	0.0393	-0.1592	-0.0862	-0.2686	3.7554	0.0306	0.0970	0.0889	0.0453	3.7554
ALT	0.0295	0.0195	0.0197	0.0454	2.2590	-0.0382	-0.0253	0.0066	0.0163	2.2590
AST	0.1234	0.0469	0.0476	0.0573	4.1053	-0.0466	0.0749	0.0553	0.0267	4.1053
BIL	0.0320	0.0377	0.0051	-0.0467	1.9976	-0.0066	-0.0042	-0.0473	0.0049	1.9976
ALB	0.0000	0.0539	0.0441	0.0137	0.2907	-0.0007	-0.0009	-0.0262	0.0100	0.2907
TP	0.0059	0.0154	0.0077	0.0077	0.2054	0.0206	0.0302	-0.0096	0.0196	0.2054
Glu	0.0008	0.0234	-0.0262	-0.1068	3.4542	0.0127	-0.0749	-0.0839	-0.0751	3.4542
CHOL	-0.0779	-0.1197	-0.0672	0.0461	6.1569	0.0350	-0.0613	-0.1227	0.0309	6.1569
TAG	0.2282	0.0732	0.0435	0.2007	14.6675	0.0713	-0.1776	-0.0813	-0.0636	14.6675
Crea	0.0476	-0.0414	-0.0362	0.1161	1.4170	0.0956	0.1366	0.1036	0.1323	1.4170
Urea	0.1626	0.0229	0.0595	0.0515	1.3913	0.0231	0.0874	0.0364	0.0165	1.3913
cHGB	0.3716	0.1228	0.1639	0.2947	15.0702	-0.0959	-0.0765	-0.1143	-0.0300	15.0702
Ca	0.0044	-0.0116	-0.0124	0.0042	0.0632	0.0149	0.0113	0.0072	0.0063	0.0632
Cl	-0.0004	0.0016	0.0094	0.0023	0.0358	-0.0177	-0.0091	-0.0060	-0.0082	0.0358
K	0.0258	0.0106	0.0532	0.0289	0.7794	-0.0866	-0.0130	0.0229	-0.0031	0.7794
Na	0.0035	0.0081	0.0068	0.0021	0.0103	0.0019	0.0048	0.0008	-0.0013	0.0103
P	0.0824	-0.0835	0.0005	0.0682	1.9372	0.0019	0.1026	0.0934	-0.0304	1.9372

Appendix 8. Intervals for equivalence tests (continued)

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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
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
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

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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_104	0.999	0.861	0.729	0.972	0.641	0.541	0.718	0.326	0.465	0.977	0.659	0.487
FeedMean	0.883	0.476	0.277	0.740	0.342	0.374	0.059	0.018	0.080	0.650	0.281	0.487
Haematology	NK11-			NK33-			NK11+			NK33+		
Males	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox
WBC	0.986	0.702	0.956	0.892	0.486	0.932	0.933	0.550	0.123	0.400	0.149	0.263
RBC	0.858	0.449	0.794	0.984	0.692	0.927	1.000	0.956	0.766	0.997	0.795	0.782
HGB	0.622	0.266	0.374	0.865	0.457	0.782	1.000	0.982	0.551	0.987	0.712	0.159
HCT	1.000	0.977	0.984	0.995	0.766	0.854	0.990	0.731	0.609	1.000	0.930	0.860
MCV	0.314	0.112	0.114	0.215	0.072	0.580	0.945	0.573	0.738	0.714	0.322	0.098
MCH	0.998	0.818	0.931	0.916	0.524	0.678	0.999	0.852	0.966	0.715	0.326	0.093
MCHC	0.600	0.254	0.113	0.597	0.252	0.190	0.984	0.693	0.799	0.859	0.450	0.379
PLT	0.946	0.573	0.622	0.730	0.332	0.551	0.749	0.346	0.332	0.821	0.407	0.639
LYMR	0.971	0.639	0.468	0.941	0.564	0.244	0.969	0.634	0.747	0.895	0.491	0.685
LYMA	0.838	0.426	0.609	0.869	0.459	0.433	0.481	0.188	0.174	0.934	0.551	0.376
ClinChem	NK11-			NK33-			NK11+			NK33+		
Males	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox
ALP	0.994	0.760	0.409	0.568	0.232	0.442	0.907	0.507	0.441	0.156	0.051	0.051
ALT	0.985	0.694	0.312	0.997	0.802	0.523	0.997	0.795	0.922	0.943	0.567	0.963
AST	0.415	0.156	0.143	0.957	0.600	0.229	0.951	0.586	1.000	0.922	0.531	0.678
BIL	0.982	0.680	0.498	0.971	0.638	0.551	1.000	0.948	0.829	0.947	0.576	0.404
ALB	1.000	1.000	0.984	0.216	0.073	0.196	0.361	0.132	0.293	0.975	0.654	0.579
TP	0.991	0.734	0.701	0.801	0.390	0.766	0.977	0.660	0.293	0.981	0.676	0.890
Glu	1.000	0.992	0.734	0.997	0.799	0.597	0.995	0.771	0.431	0.618	0.267	0.502
CHOL	0.860	0.447	0.177	0.615	0.259	0.108	0.913	0.516	0.623	0.980	0.670	0.747
TAG	0.178	0.058	0.030	0.935	0.553	0.766	0.989	0.718	0.490	0.319	0.114	0.120
Crea	0.980	0.673	0.595	0.989	0.723	0.712	0.993	0.754	1.000	0.722	0.331	0.940

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Urea	0.091	0.028	0.156	0.994	0.761	0.747	0.839	0.427	0.404	0.907	0.509	0.562
cHGB	0.050	0.015	0.021	0.841	0.428	1.000	0.649	0.280	0.258	0.197	0.066	0.329
Ca	0.983	0.686	0.596	0.684	0.302	0.551	0.627	0.266	0.284	0.988	0.712	0.890
Cl	1.000	0.935	0.852	0.996	0.777	0.477	0.254	0.087	0.171	0.984	0.691	0.977
K	0.654	0.283	0.277	0.979	0.667	0.695	0.096	0.030	0.033	0.608	0.255	0.579
Na	0.829	0.416	0.296	0.203	0.068	0.015	0.329	0.118	0.538	0.973	0.647	0.816
P	0.442	0.170	0.568	0.459	0.179	0.378	1.000	0.993	0.854	0.648	0.282	0.744
Urine	NK11-			NK33-			NK11+			NK33+		
Males	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox
uVol	0.894	0.499	0.470	0.461	0.184	0.173	0.999	0.852	0.834	1.000	0.998	0.791
uVolW	0.773	0.377	0.301	0.592	0.254	0.296	0.930	0.554	0.685	0.994	0.761	0.677
uLeu	1.000	0.909	1.000	0.999	0.851	1.000	0.167	0.057	1.000	0.705	0.326	1.000
uOsmoll	0.984	0.700	0.970	0.892	0.496	0.296	0.818	0.416	0.340	0.989	0.725	0.970
uProtein	0.999	0.839	0.734	0.999	0.842	1.000	0.739	0.350	1.000	0.589	0.253	0.490
uHemogl	0.632	0.278	0.058	0.997	0.813	0.813	0.996	0.788	0.684	0.999	0.857	0.278
uKeton	0.912	0.525	0.298	0.737	0.349	0.241	0.866	0.465	0.722	0.138	0.046	0.330
upH	0.963	0.625	0.474	1.000	0.891	0.680	0.994	0.769	0.197	0.511	0.210	0.301

Weights	NK11-			NK33-			NK11+			NK33+		
Females	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox
Weight_104	0.703	0.321	0.340	0.352	0.131	0.502	0.594	0.252	0.375	0.980	0.679	0.782
FeedMean	1.000	0.983	0.497	0.850	0.444	0.715	0.857	0.452	0.159	0.724	0.336	0.252
Haematology	NK11-			NK33-			NK11+			NK33+		
Females	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox
WBC	0.928	0.551	0.110	1.000	0.944	0.970	0.382	0.146	0.389	0.886	0.489	0.562
RBC	1.000	0.981	0.519	0.993	0.752	0.850	0.913	0.525	0.426	0.955	0.603	0.706
HGB	0.839	0.440	0.320	0.551	0.234	0.320	0.870	0.474	1.000	0.972	0.653	0.389
HCT	0.607	0.267	0.465	0.392	0.153	0.204	0.918	0.537	0.502	0.907	0.522	0.359
MCV	0.933	0.555	0.677	0.663	0.295	1.000	0.982	0.686	0.426	0.828	0.422	0.900
MCH	0.987	0.717	1.000	0.939	0.570	0.906	1.000	0.979	0.169	0.992	0.746	0.980
MCHC	1.000	0.997	0.266	0.475	0.190	0.380	0.573	0.243	0.078	1.000	0.926	0.860
PLT	0.994	0.766	0.677	0.636	0.280	0.893	0.456	0.181	0.229	0.269	0.097	0.193

LYMR	0.994	0.763	0.278	1.000	0.884	0.846	0.999	0.840	0.470	1.000	0.920	0.502
LYMA	0.212	0.074	0.147	0.994	0.764	1.000	0.969	0.642	0.424	0.685	0.312	0.252
ClinChem	NK11-			NK33-			NK11+			NK33+		
Females	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox
ALP	0.988	0.724	0.365	0.571	0.246	0.677	0.610	0.269	0.187	0.937	0.572	0.934
ALT	0.933	0.559	0.910	0.981	0.686	0.666	1.000	0.914	0.804	0.996	0.787	0.744
AST	0.951	0.596	1.000	0.772	0.377	0.168	0.895	0.501	0.804	0.991	0.743	0.404
BIL	1.000	0.915	0.689	1.000	0.944	0.588	0.816	0.413	0.121	1.000	0.932	0.980
ALB	1.000	0.976	0.898	1.000	0.969	0.970	0.563	0.242	0.454	0.972	0.655	0.762
TP	0.662	0.297	0.307	0.307	0.113	0.216	0.953	0.601	0.524	0.640	0.284	0.782
Glu	1.000	0.876	1.000	0.736	0.348	0.733	0.619	0.270	0.599	0.695	0.319	0.252
CHOL	0.992	0.745	0.569	0.930	0.554	0.685	0.537	0.224	0.135	0.993	0.756	0.900
TAG	0.977	0.668	0.910	0.615	0.268	0.367	0.953	0.600	0.720	0.980	0.679	0.348
Crea	0.194	0.067	0.077	0.025	0.007	0.094	0.106	0.034	0.188	0.024	0.007	0.034
Urea	0.972	0.651	0.204	0.224	0.079	0.127	0.848	0.446	0.978	0.989	0.727	0.706
cHGB	0.938	0.569	0.970	0.967	0.637	0.946	0.868	0.468	0.900	0.999	0.847	0.348
Ca	0.442	0.175	0.424	0.641	0.284	0.170	0.878	0.480	0.679	0.918	0.535	0.860
Cl	0.105	0.034	0.042	0.589	0.253	0.367	0.833	0.431	0.594	0.637	0.282	0.404
K	0.083	0.026	0.204	0.989	0.725	0.497	0.909	0.521	0.691	1.000	0.929	1.000
Na	0.975	0.661	0.838	0.594	0.256	0.421	0.999	0.854	0.670	0.993	0.756	0.980
P	1.000	0.975	0.380	0.228	0.080	0.168	0.277	0.101	0.330	0.947	0.587	0.464
Urine	NK11-			NK33-			NK11+			NK33+		
Females	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox	Dunnet	t-test	Wilcox
uVol	1.000	0.902	1.000	0.975	0.654	0.765	0.940	0.564	0.903	0.688	0.306	0.024
uVolW	0.983	0.689	0.695	0.907	0.508	0.700	0.988	0.716	0.761	0.678	0.299	0.193
uLeu	0.979	0.668	0.293	1.000	0.945	0.944	0.934	0.552	0.609	0.984	0.694	0.529
uOsmoll	0.872	0.463	0.695	0.850	0.439	0.700	1.000	0.894	0.583	0.617	0.262	0.064
uProtein	0.382	0.142	0.066	0.665	0.291	0.241	0.637	0.273	0.249	0.997	0.801	0.333
uHemogl	0.819	0.408	1.000	1.000	0.918	1.000	0.996	0.789	1.000	0.806	0.396	0.581
uKeton	0.774	0.369	0.767	0.976	0.658	0.766	0.885	0.479	0.452	0.744	0.346	0.128
upH	0.418	0.158	0.226	0.100	0.031	0.104	0.663	0.289	0.303	0.813	0.402	0.394

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_104	0.448	0.978	0.897	0.927	0.871	0.422	0.018	0.037
FeedMean	0.256	0.687	0.338	0.935	0.630	0.754	0.229	0.374
Male Haematology	SW Control	SW NK11-	SW NK33-	SW NK11+	SW NK33+	SW residual	Bartlett	Levene
WBC	0.721	0.085	0.356	0.314	0.225	0.998	0.189	0.095
RBC	0.361	0.000	0.034	0.003	0.321	0.064	0.072	0.448
HGB	0.437	0.001	0.152	0.012	0.003	0.017	0.052	0.398
HCT	0.093	0.304	0.678	0.002	0.105	0.118	0.090	0.343
MCV	0.014	0.741	0.607	0.797	0.586	0.957	0.453	0.708
MCH	0.774	0.130	0.316	0.105	0.993	0.345	0.753	0.807
MCHC	0.418	0.983	0.178	0.220	0.750	0.350	0.799	0.587
PLT	0.275	0.243	0.756	0.000	0.007	0.164	0.015	0.120
LYMR	0.741	0.080	0.096	0.061	0.180	0.002	0.821	0.651
LYMA	0.870	0.936	0.162	0.422	0.352	0.319	0.673	0.677
Male ClinChem	SW Control	SW NK11-	SW NK33-	SW NK11+	SW NK33+	SW residual	Bartlett	Levene
ALP	0.915	0.633	0.025	0.011	0.007	0.009	0.471	0.432
ALT	0.255	0.061	0.019	0.992	0.251	0.026	0.477	0.732
AST	0.144	0.698	0.276	0.638	0.439	0.449	0.662	0.805
BIL	0.656	0.816	0.434	0.017	0.092	0.116	0.686	0.779
ALB	0.018	0.218	0.047	0.153	0.262	0.002	0.045	0.341
TP	0.042	0.035	0.266	0.001	0.234	0.000	0.313	0.816
Glu	0.847	0.975	0.667	0.205	0.034	0.077	0.271	0.644
CHOL	0.768	0.006	0.777	0.025	0.917	0.075	0.391	0.558
TAG	0.822	0.036	0.442	0.445	0.105	0.517	0.671	0.697
Crea	0.590	0.007	0.093	0.154	0.019	0.000	0.000	0.089
Urea	0.212	0.020	0.104	0.035	0.068	0.040	0.181	0.317
chGB	0.179	0.247	0.157	0.083	0.606	0.729	0.110	0.160
Ca	0.001	0.612	0.583	0.277	0.003	0.002	0.011	0.151
Cl	0.402	0.212	0.642	0.016	0.055	0.880	0.220	0.394

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K	0.604	0.175	0.743	0.015	0.078	0.566	0.262	0.598
Na	0.102	0.797	0.393	0.066	0.471	0.512	0.130	0.520
P	0.431	0.212	0.921	0.179	0.008	0.048	0.049	0.277
Male Urine	SW Control	SW NK11-	SW NK33-	SW NK11+	SW NK33+	SW residual	Bartlett	Levene
uVol	0.913	0.241	0.047	0.168	0.097	0.278	0.143	0.205
uVolW	0.526	0.456	0.172	0.839	0.999	0.868	0.683	0.690
uLeu	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
uOsmoll	0.280	0.434	0.591	0.945	0.678	0.210	0.015	0.024
uProtein	0.001	0.000	0.000	0.000	0.000	0.010	0.000	0.000
uHemogl	0.000	0.008	0.000	0.000	0.000	0.000	0.841	0.568
uKeton	0.005	0.014	0.029	0.000	0.000	0.151	0.829	0.279
upH	0.002	0.005	0.040	0.001	0.001	0.179	0.143	0.656

Female Weights	SW Control	SW NK11-	SW NK33-	SW NK11+	SW NK33+	SW residual	Bartlett	Levene
Weight_104	0.982	0.772	0.827	0.006	0.269	0.140	0.972	0.866
FeedMean	0.211	0.150	0.953	0.165	0.925	0.038	0.842	0.858
Female Haematology	SW Control	SW NK11-	SW NK33-	SW NK11+	SW NK33+	SW residual	Bartlett	Levene
WBC	0.002	0.149	0.161	0.000	0.217	0.001	0.043	0.195
RBC	0.000	0.884	0.001	0.001	0.060	0.000	0.055	0.369
HGB	0.809	0.429	0.022	0.007	0.690	0.384	0.032	0.199
HCT	0.026	0.833	0.005	0.042	0.531	0.012	0.139	0.461
MCV	0.453	0.008	0.307	0.932	0.914	0.268	0.686	0.852
MCH	0.651	0.434	0.091	0.309	0.260	0.133	0.305	0.508
MCHC	0.037	0.244	0.635	0.651	0.947	0.331	0.170	0.200
PLT	0.999	0.034	0.658	0.212	0.587	0.159	0.211	0.694
LYMR	0.707	0.202	0.779	0.002	0.009	0.334	0.843	0.990
LYMA	0.982	0.335	0.615	0.209	0.134	0.779	0.203	0.544
Female ClinChem	SW Control	SW NK11-	SW NK33-	SW NK11+	SW NK33+	SW residual	Bartlett	Levene
ALP	0.786	0.106	0.542	0.074	0.141	0.816	0.469	0.570
ALT	0.007	0.095	0.803	0.174	0.438	0.952	0.513	0.808
AST	0.226	0.212	0.251	0.094	0.688	0.130	0.701	0.916
BIL	0.539	0.653	0.241	0.229	0.949	0.176	0.105	0.325

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ALB	0.499	0.847	0.451	0.093	0.113	0.804	0.920	0.856
TP	0.142	0.576	0.356	0.850	0.012	0.184	0.735	0.891
Glu	0.054	0.003	0.915	0.566	0.569	0.264	0.573	0.853
CHOL	0.387	0.003	0.611	0.254	0.199	0.016	0.450	0.848
TAG	0.377	0.144	0.433	0.780	0.059	0.162	0.005	0.246
Crea	0.024	0.432	0.813	0.242	0.673	0.487	0.473	0.403
Urea	0.871	0.199	0.992	0.807	0.569	0.472	0.489	0.796
cHGB	0.351	0.038	0.055	0.427	0.041	0.000	0.398	0.544
Ca	0.324	0.089	0.950	0.545	0.997	0.447	0.203	0.368
Cl	0.799	0.359	0.575	0.733	0.901	0.485	0.895	0.784
K	0.004	0.219	0.877	0.257	0.517	0.383	0.489	0.354
Na	0.667	0.032	0.192	0.621	0.193	0.499	0.554	0.104
P	0.083	0.039	0.578	0.777	0.100	0.551	0.098	0.029
Female Urine	SW Control	SW NK11-	SW NK33-	SW NK11+	SW NK33+	SW residual	Bartlett	Levene
uVol	0.566	0.400	0.026	0.027	0.032	0.026	0.004	0.017
uVolW	0.032	0.472	0.061	0.469	0.654	0.311	0.013	0.110
uLeu	0.005	0.008	0.014	0.002	0.003	0.104	0.741	0.345
uOsmoll	0.888	0.070	0.283	0.684	0.115	0.525	0.149	0.765
uProtein	0.015	0.218	0.185	0.034	0.045	0.252	0.615	0.416
uHemogl	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.013
uKeton	0.402	0.010	0.013	0.002	0.043	0.945	0.558	0.344
upH	0.015	0.175	0.037	0.002	0.050	0.790	0.300	0.126

Appendix 11. Statistical analysis for data including outliers

For male animals, that survived for 24 months, there are outlying values for Weight_104 (2×), RBC (3×), HCT (5×), MCV (1×), MCHC (3×), ALP (1×), ALT (3×), BIL (4×), TP (5×), Glu (5×), Crea (6×), Urea (6×), Ca (4×), Na (1×) and P (3×). For female animals, that survived for 24 months, there are outlying values for WBC (3×), HGB (9×), HCT (7×), MCV (5×), MCH (1×), MCHC (5×), PLT (4×), ALT (2×), BIL (4×), ALB (3×), TP (2×), Glu (4×), Ca (1×) and uVol (1×).

Equivalence tests, using the historical GRACE data, were not considered to be useful for the 24 months data and were therefore not repeated. Results of the classical analysis without and with outliers are given in the tables below. Note that the top parts of the tables are identical to the values in Table 17 and Table 18.

Conclusion: for males the significant difference at 5% for Urea (NK11-, t-test) disappears when outliers are included. For females a significant difference at 5% for MCHC (NK11+, Wilcoxon) is introduced when outliers are included. These are the only differences.

Without Outliers	Control		NK11-			NK33-			NK11+			NK33+		
Males	Mean	CV	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig
Weight_104	655.8	15.9	658.7	11.5		644.0	9.2		634.0	13.4		653.5	19.3	
RBC	7.894	5.3	7.758	8.1		7.956	6.2		7.864	8.7		7.879	7.8	
HCT	44.15	5.7	44.20	6.1		44.52	4.4		43.93	7.4		44.23	7.5	
MCV	55.61	3.8	56.46	2.8		56.65	3.7		55.97	2.8		56.19	3.3	
MCHC	34.91	2.2	34.63	1.9		34.68	2.5		34.79	2.2		35.08	2.4	
ALP	1.093	40.6	1.181	47.3		0.951	37.1		1.005	31.5		0.841	27.0	
ALT	0.832	20.3	0.897	33.6		0.876	29.2		0.880	26.8		0.904	30.3	
BIL	7.417	37.0	7.711	36.5		7.700	33.4		7.235	31.5		6.781	28.6	
TP	71.29	5.2	71.75	6.7		72.43	4.3		71.70	6.4		71.71	5.2	
Glu	4.179	26.2	4.263	25.4		4.359	26.4		4.075	27.6		3.942	32.0	
Crea	30.44	22.6	35.19	64.1		31.05	41.5		30.67	30.1		41.88	79.8	
Urea	4.028	17.8	4.997	38.4	t	4.324	25.9		4.415	20.5		4.354	27.0	
Ca	2.530	3.4	2.536	4.9		2.506	3.2		2.492	2.2		2.539	4.3	
Na	142.7	1.0	143.3	1.6		143.8	1.0	w	143.7	1.5		143.2	1.6	
P	1.666	21.5	1.807	22.7		1.522	16.9		1.640	18.5		1.826	33.8	
With Outliers	Control		NK11-			NK33-			NK11+			NK33+		
Males	Mean	CV	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig
Weight_104	655.8	15.9	641.7	12.9		644.0	9.2		634.0	13.4		653.5	19.3	
RBC	7.747	10.2	7.688	8.6		7.956	6.2		7.806	9.5		7.879	7.8	
HCT	43.17	11.9	43.22	9.1		45.06	6.9		43.61	8.2		44.23	7.5	
MCV	55.61	3.8	56.27	3.1		56.65	3.7		55.97	2.8		56.19	3.3	
MCHC	34.44	5.4	34.63	1.9		34.68	2.5		35.23	7.2		35.08	2.4	
ALP	1.093	40.6	1.167	49.1		0.951	37.1		1.005	31.5		0.841	27.0	
ALT	0.832	20.3	0.990	60.1		0.982	71.6		0.880	26.8		0.904	30.3	
BIL	7.42	37.0	10.15	88.5		7.70	33.4		8.55	96.3		7.88	65.2	
TP	71.29	5.2	70.81	7.8		72.43	4.3		72.11	7.6		71.71	5.2	
Glu	3.842	38.7	4.180	27.4		4.359	26.4		3.996	29.5		3.771	38.0	
Crea	54.75	144.5	38.31	67.0		35.30	57.1		56.39	154.1		41.88	79.8	
Urea	5.649	102.7	5.358	44.2		4.324	25.9		6.458	105.0		4.915	54.9	
Ca	2.540	4.1	2.522	5.1		2.506	3.2		2.548	8.2		2.539	4.3	
Na	142.7	1.0	143.5	1.7		143.8	1.0	w	143.7	1.5		143.2	1.6	
P	1.826	44.6	1.807	22.7		1.522	16.9		1.838	37.6		1.826	33.8	

Without Outliers	Control		NK11-			NK33-			NK11+			NK33+		
Females	Mean	CV	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig
WBC	7.84	75.0	7.80	33.7		6.87	50.1		10.38	97.8		8.15	44.0	
HGB	15.16	3.7	14.95	5.6		14.82	5.9		15.00	7.3		15.08	4.4	
HCT	42.58	6.1	42.02	6.7		41.35	6.9		42.18	6.7		42.11	4.2	
MCV	58.23	3.3	58.76	3.6		57.64	4.0		58.54	3.0		57.70	2.9	
MCH	20.87	3.9	20.93	4.2		20.76	6.0		20.85	5.7		20.79	4.8	
MCHC	35.85	1.6	35.61	2.5		35.46	2.9		35.47	2.6		35.82	2.0	
PLT	784.1	13.0	762.6	21.7		836.8	20.0		842.2	23.6		888.8	21.3	
ALT	0.852	26.5	0.802	20.6		0.812	18.2		0.831	18.2		0.835	19.6	
BIL	6.197	14.5	5.900	16.2		6.011	14.7		5.905	25.0		6.152	17.1	
ALB	39.96	7.1	39.51	5.7		39.60	6.3		38.76	6.3		40.08	6.0	
TP	73.77	6.2	74.76	5.3		75.59	4.7		73.00	5.1		74.89	4.6	
Glu	4.965	17.4	5.190	23.1		4.754	21.3		4.805	24.1		4.577	19.0	
Ca	2.506	2.6	2.541	3.7		2.528	3.1		2.510	2.2		2.515	3.4	
uVol	11.71	26.4	12.27	52.2		12.00	32.4		10.67	42.3		13.21	24.4	w
With Outliers	Control		NK11-			NK33-			NK11+			NK33+		
Females	Mean	CV	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig	Mean	CV	Sig
WBC	7.84	75.0	7.80	33.7		11.14	173.9		10.38	97.8		11.72	94.6	
HGB	15.01	9.7	14.95	5.6		14.54	10.3		14.26	16.1		14.73	9.2	
HCT	41.86	9.3	42.02	6.7		41.35	6.9		40.44	13.0		41.47	7.2	
MCV	58.23	3.3	58.76	3.6		59.31	9.4		59.65	6.7		58.40	7.3	
MCH	20.87	3.9	20.93	4.2		20.76	6.0		20.85	5.7		20.60	4.7	
MCHC	35.85	1.6	35.61	2.5		35.12	5.3		35.02	5.5	w	35.38	4.0	
PLT	770.8	17.5	762.6	21.7		802.8	27.8		827.7	26.6		866.9	19.5	
ALT	0.985	56.1	0.802	20.6		0.812	18.2		0.822	20.4		0.835	19.6	
BIL	7.241	64.5	5.900	16.2		8.367	102.5		7.257	82.5		6.152	17.1	
ALB	39.11	11.4	39.51	5.7		40.04	8.6		38.76	6.3		39.77	7.3	
TP	73.77	6.2	74.76	5.3		75.64	7.0		73.00	5.1		74.89	4.6	
Glu	4.965	17.4	5.012	24.0		4.580	27.4		4.723	26.6		4.500	21.4	
Ca	2.506	2.6	2.541	3.7		2.528	3.1		2.518	2.6		2.515	3.4	
uVol	11.71	26.4	12.27	52.2		11.78	34.9		10.67	42.3		13.21	24.4	w

Appendix 12. Classical statistical analysis on the animal level

The classical statistical analysis in section 3.5 employs cage means, for those animals that survived for 24 months, which enables t-tests, Dunnett tests and Wilcoxon tests. Moreover cage means were also employed in the classical statistical analysis for data obtained after 3, 6 and 12 months. However since the number of cages with one animal and with two animals at 24 months is unbalanced over the five feeding groups, see Table 1, an analysis on cage means might be sub-optimal. Therefore an alternative statistical analysis on the animal level, rather than the cage level, was performed for all variables to check whether such an analysis gives different conclusions. Due to the unbalance the analysis on the animal level, again only for those animals that survived for 24 months, was performed by means of linear mixed modelling via residual maximum likelihood (REML) in GenStat (VSN International, 2015), with random model Block/Cage/Animal and fixed effects given by the five feeding groups. The REML estimates of the fixed effects and the corresponding variance-covariance matrix were used for two-sided pairwise testing of the feeding groups; this testing employs the normal distribution. The estimated ratios between the GM feeding groups and the non-GM control group are given in the two tables below, where colouring is used for significant difference at the 5% and the 1% level. For comparison the ratios and the significance according to pairwise t-tests obtained from the analysis at the cage level, as in Table 14 and Table 15, are added. Note that Dunnett's test can also be performed after a REML analysis in R employing the `lmer()` and `glht()` functions, while there is no analogue for the non-parametric Wilcoxon test at the animal level.

For most variables and comparisons there is neither a significant difference at the animal level nor at the cage level. For four variables in males (LYMA, uVol, uLeu and uKeton) and for one variable in females (Cl) there is a difference in significance although the estimated ratios are quite similar.

It was concluded that there are only minor differences between the two analyses, and that therefore an analysis on the cage level is sufficient.

Table. Estimated ratios for males between the four GM feeding groups and the non-GM control group for an analysis on the animal level and for an analysis on the cage level. A ratio which is significantly different from the value one at the 5% / 1% level is given in yellow / gold.

Weights	NK11- vs Control		NK33- vs Control		NK11+ vs Control		NK33+ vs Control	
Males	Animal	Cage	Animal	Cage	Animal	Cage	Animal	Cage
Weight_104	1.00	1.01	0.97	0.98	0.98	0.96	1.00	0.98
FeedMean		0.98		0.98		0.95		1.03
Haematology	NK11- vs Control		NK33- vs Control		NK11+ vs Control		NK33+ vs Control	
Males	Animal	Cage	Animal	Cage	Animal	Cage	Animal	Cage
WBC	1.02	1.04	0.93	0.93	1.09	1.07	1.16	1.17
RBC	0.99	0.98	1.01	1.01	0.99	1.00	1.00	0.99
HGB	0.98	0.97	1.02	1.02	1.00	1.00	1.01	1.01
HCT	1.00	1.00	1.01	1.01	0.99	0.99	1.00	1.00
MCV	1.02	1.02	1.02	1.02	1.00	1.01	1.01	1.01
MCH	1.00	1.00	1.01	1.01	1.00	1.00	1.01	1.01
MCHC	0.99	0.99	0.99	0.99	1.00	1.00	1.01	1.01
PLT	1.04	1.03	1.04	1.05	1.04	1.05	1.04	1.04
LYMR	1.07	1.04	1.05	1.05	1.06	1.04	0.95	0.94
LYMA	1.15	1.09	1.08	1.08	1.21	1.15	1.07	1.07
ClinChem	NK11- vs Control		NK33- vs Control		NK11+ vs Control		NK33+ vs Control	
Males	Animal	Cage	Animal	Cage	Animal	Cage	Animal	Cage
ALP	1.05	1.04	0.85	0.85	0.93	0.92	0.78	0.76
ALT	1.03	1.03	1.02	1.02	1.04	1.02	1.07	1.05
AST	1.15	1.13	1.03	1.05	1.07	1.05	1.10	1.06
BIL	1.03	1.03	1.00	1.04	0.97	1.01	0.93	0.95
ALB	0.99	1.00	1.04	1.06	1.04	1.05	1.00	1.01
TP	0.99	1.01	1.00	1.02	1.00	1.01	1.00	1.01
Glu	0.98	1.00	1.03	1.02	0.97	0.97	0.90	0.90
CHOL	0.86	0.93	0.86	0.89	0.94	0.93	1.01	1.05
TAG	1.17	1.26	1.03	1.08	1.10	1.04	1.18	1.22
Crea	1.04	1.05	0.99	0.96	1.01	0.96	1.15	1.12
Urea	1.15	1.18	1.03	1.02	1.08	1.06	1.02	1.05
cHGB	1.39	1.45	1.12	1.13	1.19	1.18	1.31	1.34
Ca	1.00	1.00	0.99	0.99	0.99	0.99	1.00	1.00
Cl	1.00	1.00	1.00	1.00	1.01	1.01	1.00	1.00
K	1.02	1.03	1.00	1.01	1.05	1.05	1.02	1.03
Na	1.00	1.00	1.01	1.01	1.01	1.01	1.00	1.00
P	1.09	1.09	0.93	0.92	1.02	1.00	1.06	1.07
Urine	NK11- vs Control		NK33- vs Control		NK11+ vs Control		NK33+ vs Control	
Males	Animal	Cage	Animal	Cage	Animal	Cage	Animal	Cage
uVol	1.10	1.10	0.79	0.83	1.02	1.03	1.03	1.00
uVolW	1.16	1.13	0.82	0.86	1.07	1.08	1.05	1.04
uLeu	0.90	0.98	1.00	1.03	0.72	0.73	1.02	1.18
uOsmoll	0.94	0.96	1.11	1.07	0.94	0.92	1.02	1.04
uProtein	0.88	1.06	0.83	0.95	0.72	0.77	1.11	1.38
uHemogl	1.42	1.64	1.14	1.11	1.02	1.13	1.28	1.08
uKeton	1.25	1.20	1.36	1.29	1.01	1.22	1.56	1.76
upH	1.08	1.07	1.04	0.98	1.07	1.04	1.18	1.18

Table. Estimated ratios for males between the four GM feeding groups and the non-GM control group for an analysis on the animal level and for an analysis on the cage level. A ratio which is significantly different from the value one at the 5% / 1% level is given in yellow / gold.

Weights	NK11- vs Control		NK33- vs Control		NK11+ vs Control		NK33+ vs Control	
Females	Animal	Cage	Animal	Cage	Animal	Cage	Animal	Cage
Weight_104	0.96	0.95	0.95	0.93	0.97	0.95	0.99	0.98
FeedMean		1.00		0.98		0.98		1.02
Haematology	NK11- vs Control		NK33- vs Control		NK11+ vs Control		NK33+ vs Control	
Females	Animal	Cage	Animal	Cage	Animal	Cage	Animal	Cage
WBC	1.16	1.11	0.95	0.99	1.17	1.26	1.16	1.11
RBC	0.99	1.00	1.00	1.01	0.97	0.98	1.01	1.02
HGB	0.99	0.98	0.98	0.98	0.99	0.99	1.00	0.99
HCT	0.99	0.98	0.97	0.97	0.99	0.99	0.99	0.99
MCV	1.01	1.01	0.99	0.99	1.01	1.00	0.99	0.99
MCH	1.00	1.01	0.99	0.99	0.99	1.00	0.99	0.99
MCHC	0.99	1.00	0.99	0.99	0.99	0.99	1.00	1.00
PLT	0.97	0.98	1.02	1.08	1.03	1.10	1.10	1.12
LYMR	0.97	0.98	0.99	0.99	1.03	1.01	1.01	1.01
LYMA	1.17	1.21	0.97	0.97	1.07	1.05	1.12	1.10
ClinChem	NK11- vs Control		NK33- vs Control		NK11+ vs Control		NK33+ vs Control	
Females	Animal	Cage	Animal	Cage	Animal	Cage	Animal	Cage
ALP	1.03	1.03	1.05	1.10	1.06	1.09	1.00	1.05
ALT	0.96	0.96	0.95	0.98	0.99	1.01	1.00	1.02
AST	0.96	0.95	1.06	1.08	1.06	1.06	1.04	1.03
BIL	0.95	0.99	0.97	1.00	0.94	0.95	0.99	1.00
ALB	0.99	1.00	0.98	1.00	0.97	0.97	1.01	1.01
TP	1.01	1.02	1.01	1.03	0.99	0.99	1.01	1.02
Glu	1.00	1.01	0.97	0.93	0.98	0.92	0.92	0.93
CHOL	1.00	1.04	0.92	0.94	0.88	0.88	1.00	1.03
TAG	1.02	1.07	0.88	0.84	1.02	0.92	0.99	0.94
Crea	1.09	1.10	1.13	1.15	1.10	1.11	1.12	1.14
Urea	1.03	1.02	1.06	1.09	1.05	1.04	0.99	1.02
cHGB	0.87	0.91	0.93	0.93	0.90	0.89	1.00	0.97
Ca	1.01	1.01	1.01	1.01	1.00	1.01	1.00	1.01
Cl	0.99	0.98	1.00	0.99	1.00	0.99	1.00	0.99
K	0.92	0.92	0.99	0.99	1.02	1.02	1.01	1.00
Na	1.00	1.00	1.01	1.00	1.00	1.00	1.00	1.00
P	0.97	1.00	1.09	1.11	1.06	1.10	0.96	0.97
Urine	NK11- vs Control		NK33- vs Control		NK11+ vs Control		NK33+ vs Control	
Females	Animal	Cage	Animal	Cage	Animal	Cage	Animal	Cage
uVol	0.95	1.02	0.95	1.07	0.88	0.92	1.11	1.16
uVolW	1.01	1.06	0.95	1.09	0.93	0.95	1.11	1.15
uLeu	1.07	1.22	0.94	0.97	1.09	1.30	0.92	0.83
uOsmoll	0.96	0.93	1.01	0.93	1.03	0.99	0.93	0.90
uProtein	1.82	1.99	1.89	1.61	1.62	1.61	1.43	1.12
uHemogl	0.72	0.69	1.00	0.96	1.19	1.12	0.86	0.69
uKeton	0.71	0.76	0.98	0.88	1.16	1.22	0.77	0.76
upH	1.39	1.34	1.51	1.54	1.21	1.22	1.17	1.18