G-TWYST
GM PLANTS TWO YEAR SAFETY TESTING

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Power analysis for 2-year and 90-days rat feeding studies with 33%-50% maize

Paul W. Goedhart & Hilko van der Voet

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Biometris, Wageningen University & Research
P.O. Box 16
6700 AA Wageningen, The Netherlands

Visiting address:
Buildingnumber 107
Droevendaalsesteeg 1, 6708 PD Wageningen, The Netherlands

Phone: +31 317 480798 or +31 317 486001
E-mail: biometris@wur.nl

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1 Power analysis for the 2-year carcinogenicity study

The main interest in the 2-year carcinogenicity study was whether the GM feeds resulted in a higher proportion of cancers as compared to the Control food, and whether there was an effect on survival.

It is assumed that the rats develop cancers independently from each other, implying that there is no cage effect. Define π_C as the probability that a Control rat develops a cancer and define π_T as the probability that a rat fed with a GM feed develops a cancer. With N Control rats, the number of rats that develop a cancer in the Control group follows a binomial distribution with binomial denominator N and probability π_C, and similarly for the GM group. It is of interest to know the power of a statistical test of the one-sided null hypotheses H_0: $\pi_T \leq \pi_C$ when N rats are allotted to each group and when the true differences equals $\Delta = \pi_T - \pi_C$. Or, alternatively, given π_C what value of π_T can be found significantly different with a given power when testing with confidence level α. Here we will employ a power of 0.80, a confidence level α = 0.05, and Fisher's exact test which is the usual test when testing equality of binomial probabilities. Note that, due to the discrete nature of the data, the true confidence level of Fisher's exact test will be smaller than α. Table 1 lists the values of π_T, for given values of π_C, that can be found significantly different with power 0.80 employing a one-sided Fisher's exact test with confidence level α = 0.05, for group size N = 16, 50 and 100. These value of N are chosen because 16 is the amount of rats in the G-TwYST 90 days studies, 50 is the amount of rats used in the G-TwYST 2-year study, and N=100 was chose to see what happens when the number of rats is doubled. The values in Table 1 were obtained by means of the GenStat (VSN International, 2015) simulation program in Appendix 1.

Table 1 For given values of π_C the minimal value of π_T is given which can be found significantly different with power 0.80 when employing a one-sided Fisher exact test with α=0.05 for group sizes N equal to 16, 50 and 100.

π_C	π_T		
	N = 16	N = 50	N = 100
0.001	0.39	0.13	0.07
0.01	0.40	0.16	0.09
0.05	0.46	0.23	0.16
0.10	0.55	0.32	0.24
0.20	0.67	0.45	0.37
0.30	0.77	0.57	0.48
0.40	0.86	0.67	0.58
0.50	0.93	0.76	0.68
0.60	0.99	0.84	0.77
0.70	-	0.91	0.86
0.80	-	0.97	0.93
0.90	-	-	0.99

Table 1 reveals that with N=50 animals per group, or even with N=100 animals per group, only relatively large differences in probabilities will be found as significant with sufficient power.

Differences in survival rates between feeding groups in G-TwYST study A were assessed by means of Cox proportional hazard model. Sample size calculations for the comparison of survival curves between two groups under this model can be performed by means of the function ssizeCT.default() in the R package powerSurvEpi (Qiu *et al*, 2018). This function requires specification of the probabilities of death in both groups over the time period of the study, as well as the postulated hazard ratio. The observed probabilities of death at the end of the 2-year G-TwYST study A were between 0.5 and 0.7 for the different feeding groups. These observed probabilities were employed to obtain the hazard ratio which can be found significant with power 0.80 and significance level 0.05 for group sizes of N = 16, 50 and 100. The R program to calculate these is given in Appendix 2, and the resulting hazard ratios are given in Table 2. Note that this involves two-sided testing. The last column in Table 2 gives the minimum across the different probabilities, and is thus on the optimistic side.

Table 2 Hazard ratio between a GM group and the Control group which can be found significant by two-sided testing with power 0.80 when employing a Cox proportional hazard model with α=0.05 for group sizes N equal to 16, 50 and 100, and different values probabilities of death at the end of the study for Control (π_C) and the GM group (π_T). The last column gives the minimum hazard ratio for each row.

π_C	0.5	0.6	0.7	0.5	0.6	0.7	0.5	0.6	0.7	-
π_T	0.5	0.5	0.5	0.6	0.6	0.6	0.7	0.7	0.7	-
N	Hazard Ratio which can be found significant									Minimum
16	7.21	6.19	5.48	6.10	5.41	4.91	5.36	4.87	4.49	4.49
50	2.43	2.32	2.23	2.31	2.23	2.15	2.22	2.15	2.08	2.08
100	1.83	1.77	1.73	1.77	1.73	1.69	1.72	1.69	1.65	1.65

Cox proportional hazard model does not fully specify a distribution for the time of death, but rather specifies a baseline hazard for the Control group and proportional hazards, or hazard ratios, for the GM groups. Alternatively a full distribution for the death times can be specified and it is customary to use the Weibull distribution for this, see e.g. https://en.wikipedia.org/wiki/Weibull_distribution. This distribution has two parameters: a scale parameter λ and a shape parameter k. Suppose that the death times of both the Control and the GM group follows a Weibull distribution with scale parameter λ_C and λ_T respectively and common shape parameter k. The ratio of the mean death times equals $\Delta = \lambda_T/\lambda_C$ and we would like to know which value of Δ can be found significant with power 0.80 under a one-sided difference test of H_0: $\lambda_T \leq \lambda_C$ with significance level α=0.05. This requires known values of λ_C and k, and also a known value for the group size N. Here we took values λ_C=2.141 and k=5.38 such that the median death time is 2 years and 90% of the control rats died before 2.5 years. The effect size Δ, which is significant with power 0.80, was found by a GenStat (VSN International, 2015) simulation program which is given in Appendix 3. Note that the RSURVIVAL directive in GenStat employs the alternative parameterization given in Wikipedia. This implies that the null hypothesis is rejected for large, rather than small, values of the treatment effect. The resulting effect sizes with power 0.80 are given in Table 3

Table 3 The ratio Δ of mean death times which can be found significant by one-sided testing with power 0.80 when employing a Weibull survival model with α=0.05 for group sizes N equal to 16, 50 and 100. The Weibull distribution for the Control feeding group is such that the median death time equals 2 years and 90% of the control rats dies before 2.5 years.

N	Δ
16	0.82
50	0.89
100	0.92

2 Power analysis for the 90-days studies

In G-TwYST studies A, B and C various endpoints were measured after 90 days. Based on the mean residual variance on the cage level across these three studies, for each endpoint the effect size is calculated which has power 0.80 when a two-sided test is employed with α=0.05. The design employed to calculate this effect size is a randomized block design with 5 feeds and 8 cages (or blocks) per feed, like in G-TwYST study B. This implies that the residual degrees of freedom equals 28. The mean residual standard errors for all endpoints are given in Appendix 4 for males and in Appendix 5 for females. The last column in these appendices, which is the squared root of the unweighted mean of the squared standard errors for the three studies, is used for the power analysis. The effect sizes are given in Table 4; they are calculated by means of the TPOWER procedure (Goedhart, 2016) in GenStat (VSN International, 2015).

Table 4 Effect sizes as percentages plus and minus which can be found significant by two-sided testing with power 0.80 and confidence level α=0.05 for all continuous endpoints for males and females.

Group	Endpoint	%minus Males	%plus Males	%minus Females	%plus Females
Weights	BodyWeight	-7	7	-6	7
Weights	growthRate	-3	3	-5	5
Weights	FeedMean	-7	7	-8	9
Group	Endpoint	%minus Males	%plus Males	%minus Females	%plus Females
Haematology	WBC	-22	28	-24	32
Haematology	RBC	-5	5	-6	6
Haematology	HGB	-3	4	-4	4
Haematology	HCT	-4	4	-5	5
Haematology	MCV	-3	3	-3	3
Haematology	MCH	-4	4	-4	4
Haematology	MCHC	-2	2	-3	3
Haematology	PLT	-18	21	-14	16
Haematology	LYMR	-8	9	-9	9
Haematology	LYMA	-23	29	-26	36

Group	Endpoint	%minus Males	%plus Males	%minus Females	%plus Females
diffWBC	Lymphocytes	-10	11	-11	12
diffWBC	Neutrophils	-21	27	-25	34
diffWBC	Monocytes	-35	55	-42	72
diffWBC	Eosinophils	-46	84	-66	198
Group	Endpoint	%minus Males	%plus Males	%minus Females	%plus Females
ClinChem	ALP	-19	24	-22	28
ClinChem	ALT	-16	19	-23	30
ClinChem	AST	-21	27	-22	29
ClinChem	BIL	-24	32	-26	36
ClinChem	ALB	-5	5	-8	9
ClinChem	TP	-4	4	-6	6
ClinChem	Glu	-15	17	-18	22
ClinChem	CHOL	-13	15	-21	26
ClinChem	TAG	-24	32	-24	32
ClinChem	Crea	-14	16	-13	15
ClinChem	Urea	-13	15	-14	16
ClinChem	cHGB	-40	66	-37	60
ClinChem	Ca	-2	2	-3	3
ClinChem	Cl	-2	2	-2	2
ClinChem	K	-9	10	-10	12
ClinChem	Na	-1	1	-2	2
ClinChem	P	-13	15	-20	25
Group	Endpoint	%minus Males	%plus Males	%minus Females	%plus Females
Urine	uVol	-34	51	-34	52
Urine	uVolW	-34	52	-35	54
Urine	uLeu	-49	96	-45	82
Urine	uOsmoll	-31	45	-33	50
Urine	uKeton	-67	203	-37	58
Urine	upH	-35	54	-34	52
Group	Endpoint	%minus Males	%plus Males	%minus Females	%plus Females
Organs	Kidney	-9	10	-10	11
Organs	Spleen	-12	14	-13	14
Organs	Liver	-6	6	-9	9
Organs	AdrenGl	-14	16	-12	14
Organs	Heart	-7	8	-9	10
Organs	Thymus	-17	20	-19	23
Organs	Testis/Uterus	-9	10	-28	38
Organs	Epididymis/Ovary	-11	12	-14	16
Organs	Brain	-7	8	-7	8

Group	Endpoint	%minus Males	%plus Males	%minus Females	%plus Females
Immunology	Monocytes	-10	11	-14	16
Immunology	Granulocytes	-6	6	-7	7
Immunology	RespirBurst	-12	13	-15	18
Immunology	Con	-55	122	-56	125
Immunology	PHA	-50	102	-56	125
Immunology	PWM	-48	91	-49	97
Immunology	Medium	-51	105	-43	75
Immunology	IprConA	-37	60	-38	61
Immunology	IprPHA	-38	60	-49	97
Immunology	IprPWM	-33	48	-34	51
Immunology	G4c1	-62	161	-44	79
Immunology	G4c2	-68	211	-45	82
Immunology	G4c3	-65	186	-44	79
Immunology	NG2c1	-63	168	-43	76
Immunology	NG2c2	-69	220	-48	91
Immunology	NG2c3	-66	196	-45	83
Immunology	A6c1	-66	193	-41	70
Immunology	A6c2	-69	222	-45	82
Immunology	A6c3	-66	194	-46	86
Immunology	Med6d	-72	261	-47	88
Immunology	IprG4c1	-41	69	-39	64
Immunology	IprG4c2	-31	44	-35	55
Immunology	IprG4c3	-40	67	-25	33
Immunology	IprNG2c1	-36	56	-34	51
Immunology	IprNG2c2	-33	49	-31	44
Immunology	IprNG2c3	-34	52	-27	36
Immunology	IprA6c1	-35	54	-24	32
Immunology	IprA6c2	-36	57	-25	34
Immunology	IprA6c3	-36	56	-30	43
Group	Endpoint	%minus Males	%plus Males	%minus Females	%plus Females
Cytokines	IL2	-19	24	-18	23
Cytokines	IL4	-34	52	-48	93
Cytokines	IL10	-65	189	-71	240
Cytokines	IL17A	-57	134	-33	50
Cytokines	TNFa	-31	45	-26	34
Cytokines	IFNg	-31	44	-43	74
Group	Endpoint	%minus Males	%plus Males	%minus Females	%plus Females
CellPhenotype	sp3	-20	26	-15	18
CellPhenotype	sp3_4	-24	32	-18	22
CellPhenotype	sp3_8	-29	40	-17	20
CellPhenotype	sp3_45	-14	17	-11	12

CellPhenotype	sp3_161	-16	20	-11	13
CellPhenotype	ln3	-18	22	-11	13
CellPhenotype	ln3_4	-19	24	-12	13
CellPhenotype	ln3_8	-19	23	-15	18
CellPhenotype	ln3_45	-24	32	-28	38
CellPhenotype	ty3	-18	22	-13	15
CellPhenotype	ty3_4	-17	20	-13	15
CellPhenotype	ty3_8	-20	25	-15	17
CellPhenotype	bm3	-43	77	-38	61
CellPhenotype	bm3_45	-10	11	-12	14
Group	Endpoint	%minus Males	%plus Males	%minus Females	%plus Females
Hormone	Testosteron/betaEstr	-43	77	-43	75
Hormone	T3	-12	14	-23	29
Hormone	T4	-11	12	-40	68

A graphical display of the effect sizes for the main groups of endpoints, i.e. Weights, Haematology, diffWBC, CllinChem and Organs, are given in Figure 1 and Figure 2. Graphs for Urine and Immunology endpoints are given in Figure 3 and Figure 4, while graphs for Cytokines, CellPhenotype and Hormone endpoints are given in Figure 5 and Figure 6. Note that the x-scales in the various figures can be different.

References

Goedhart, P.W. (2016). Procedure TPOWER. In: Biometris GenStat Procedure Library Manual 18th Edition (Editors: Goedhart, P.W. and Thissen, J.T.N.M). Biometris report 27.01.16, Biometris, Wageningen, The Netherlands. Web page: www.wur.nl/en/show/GenStat-Procedures.htm.

Qiu, W., Chavarro, J., Lazarus, R., Rosner, B. & Ma, J. (2018). powerSurvEpi: Power and Sample Size Calculation for Survival Analysis of Epidemiological Studies. R package version 0.1.0. Web page: https://CRAN.R-project.org/package=powerSurvEpi.

VSN International (2015). GenStat for Windows 18th Edition. VSN International, Hemel Hempstead, United Kingdom. Web page: www.Genstat.co.uk.

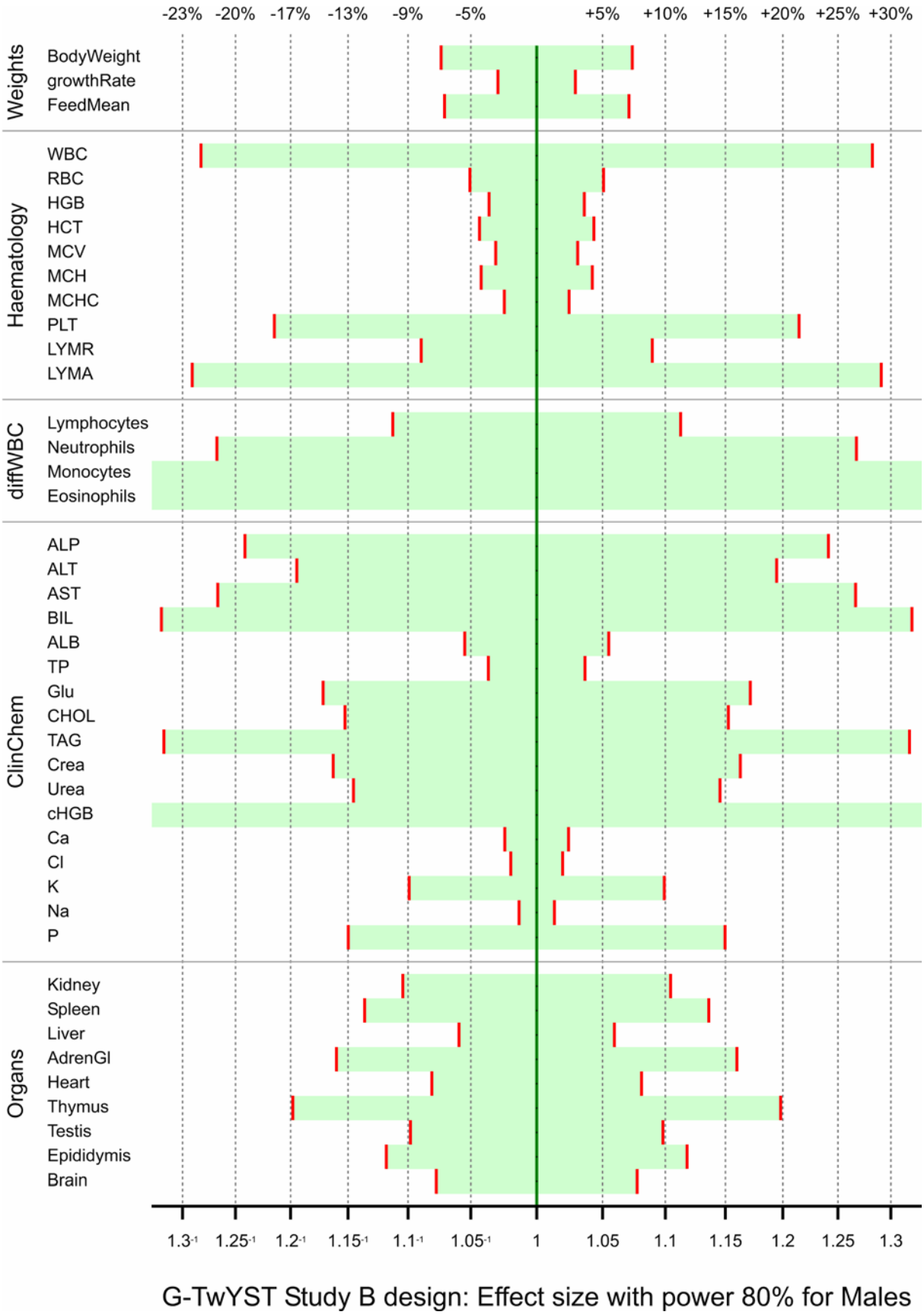

Figure 1 **Effect sizes which can be found significant by two-sided testing with power 0.80 and confidence level α=0.05 for the main endpoints in males in a 90-days study.**

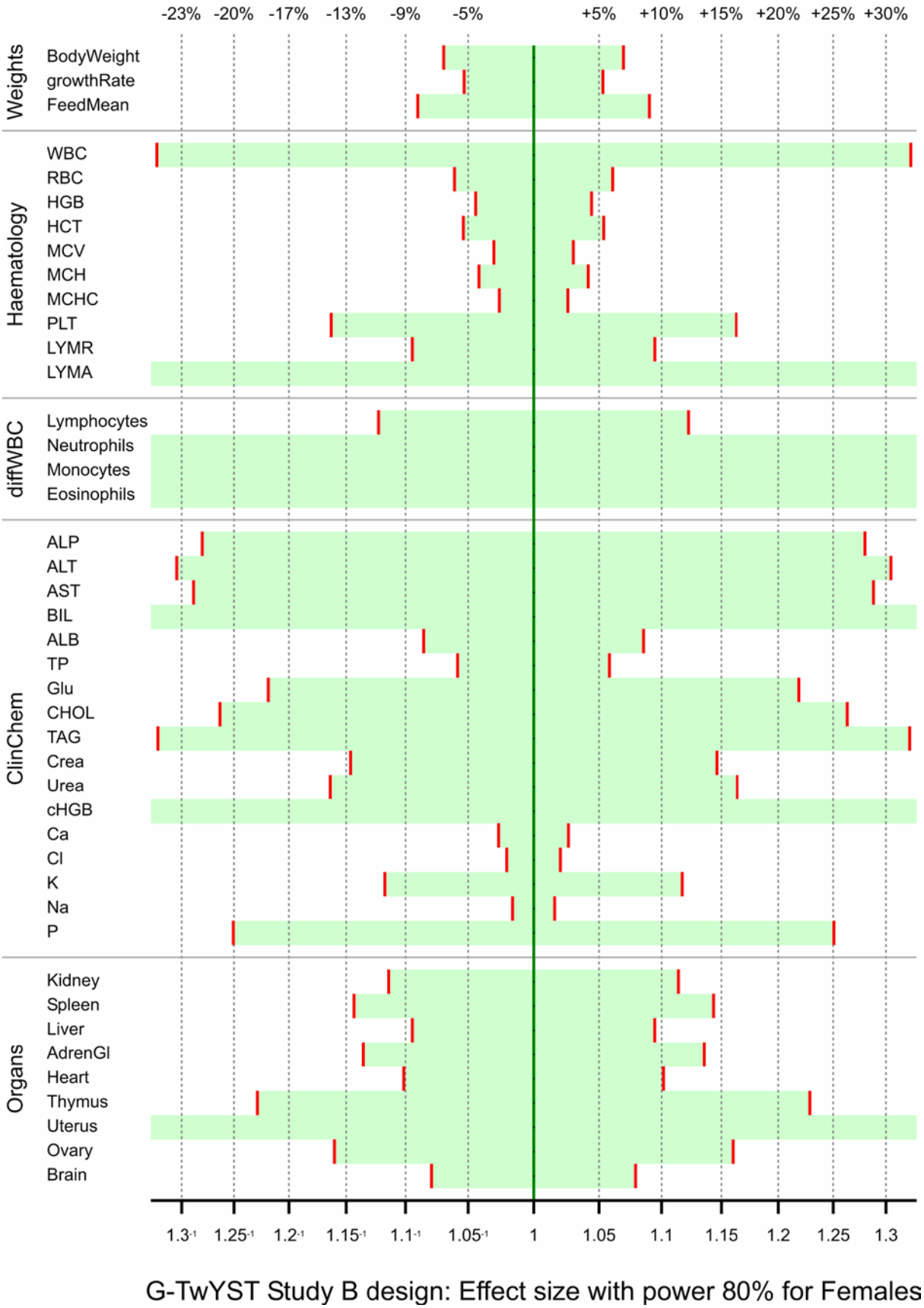

Figure 2 **Effect sizes which can be found significant by two-sided testing with power 0.80 and confidence level α=0.05 for the main endpoints in females in a 90-days study.**

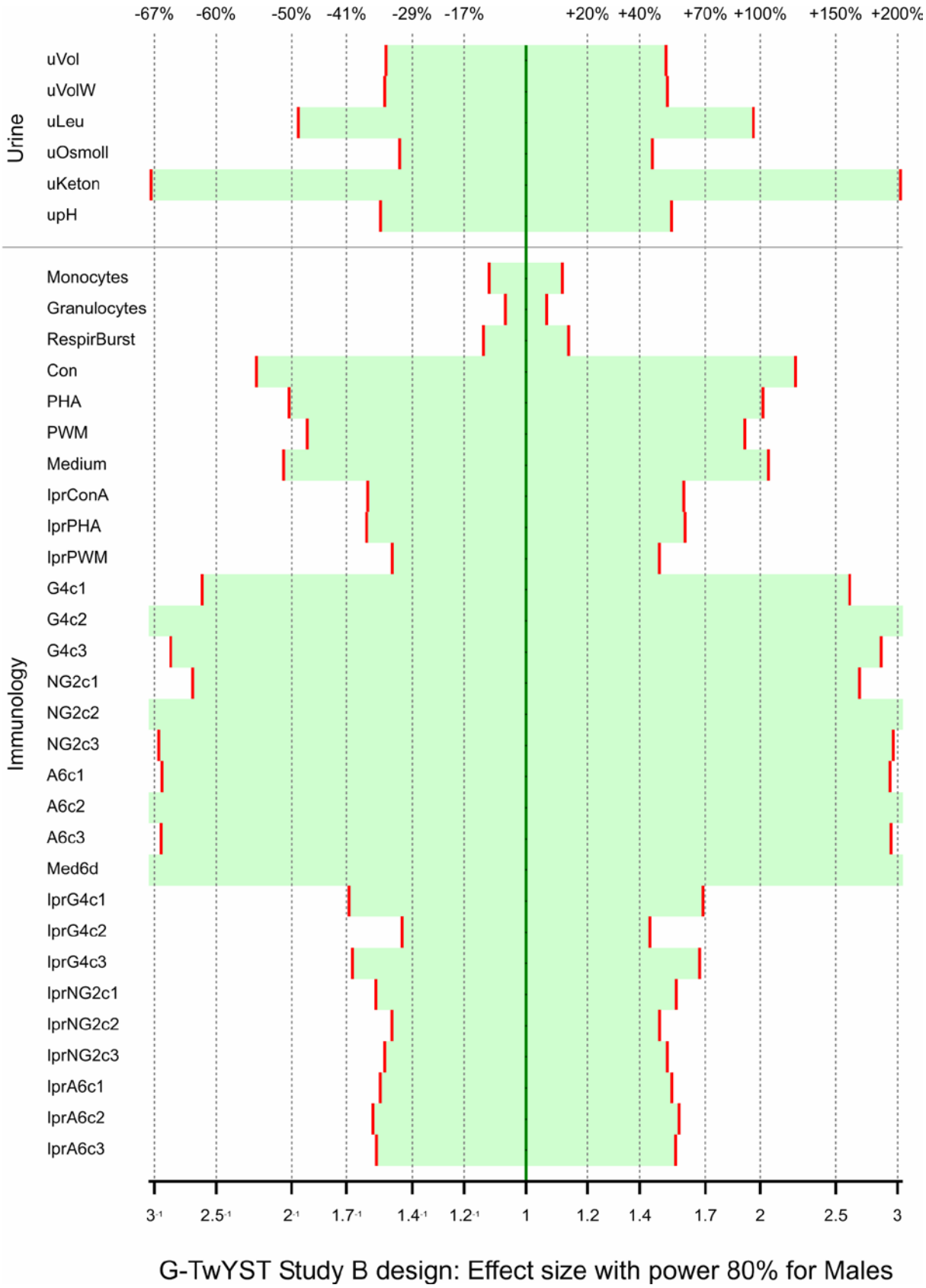

Figure 3 **Effect sizes which can be found significant by two-sided testing with power 0.80 and confidence level α=0.05 for Urine/Immunology endpoints in males in a 90-days study.**

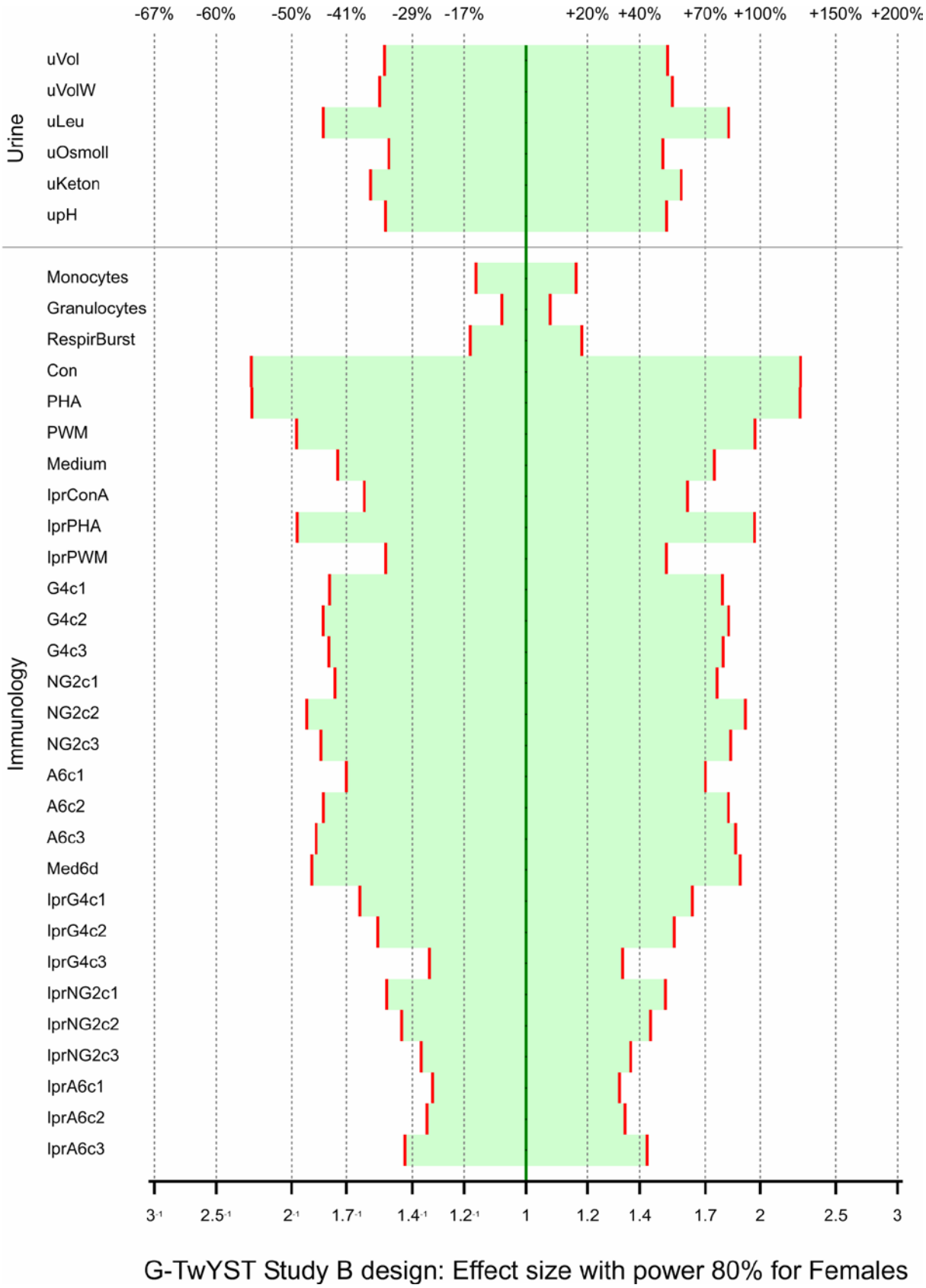

Figure 4 **Effect sizes which can be found significant by two-sided testing with power 0.80 and confidence level α=0.05 for Urine/Immunology endpoints in females in a 90-days study.**

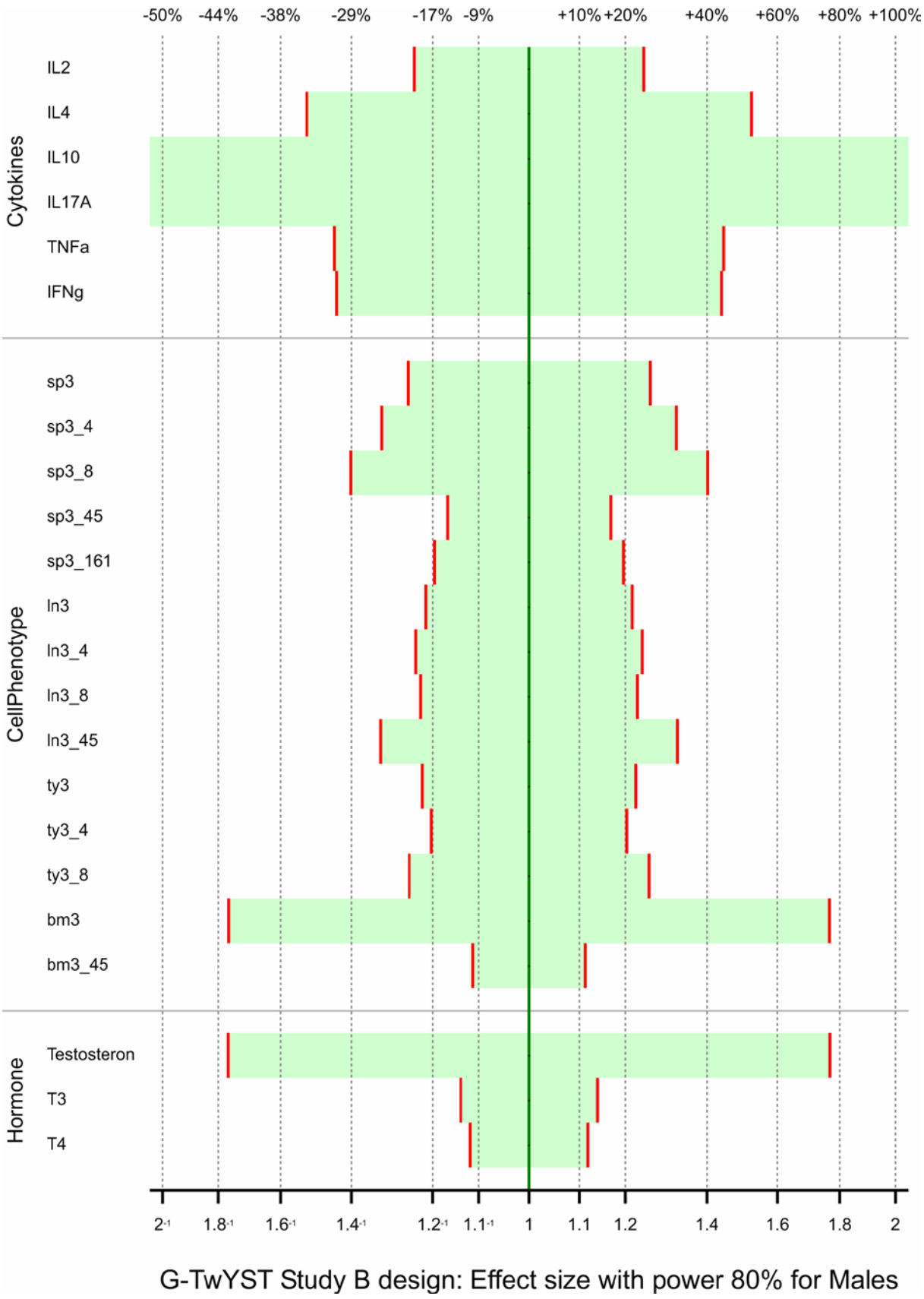

Figure 5 Effect sizes which can be found significant by two-sided testing with power 0.80 and α=0.05 for Cytokines/CellPhenotype/Hormone endpoints in males in a 90-days study.

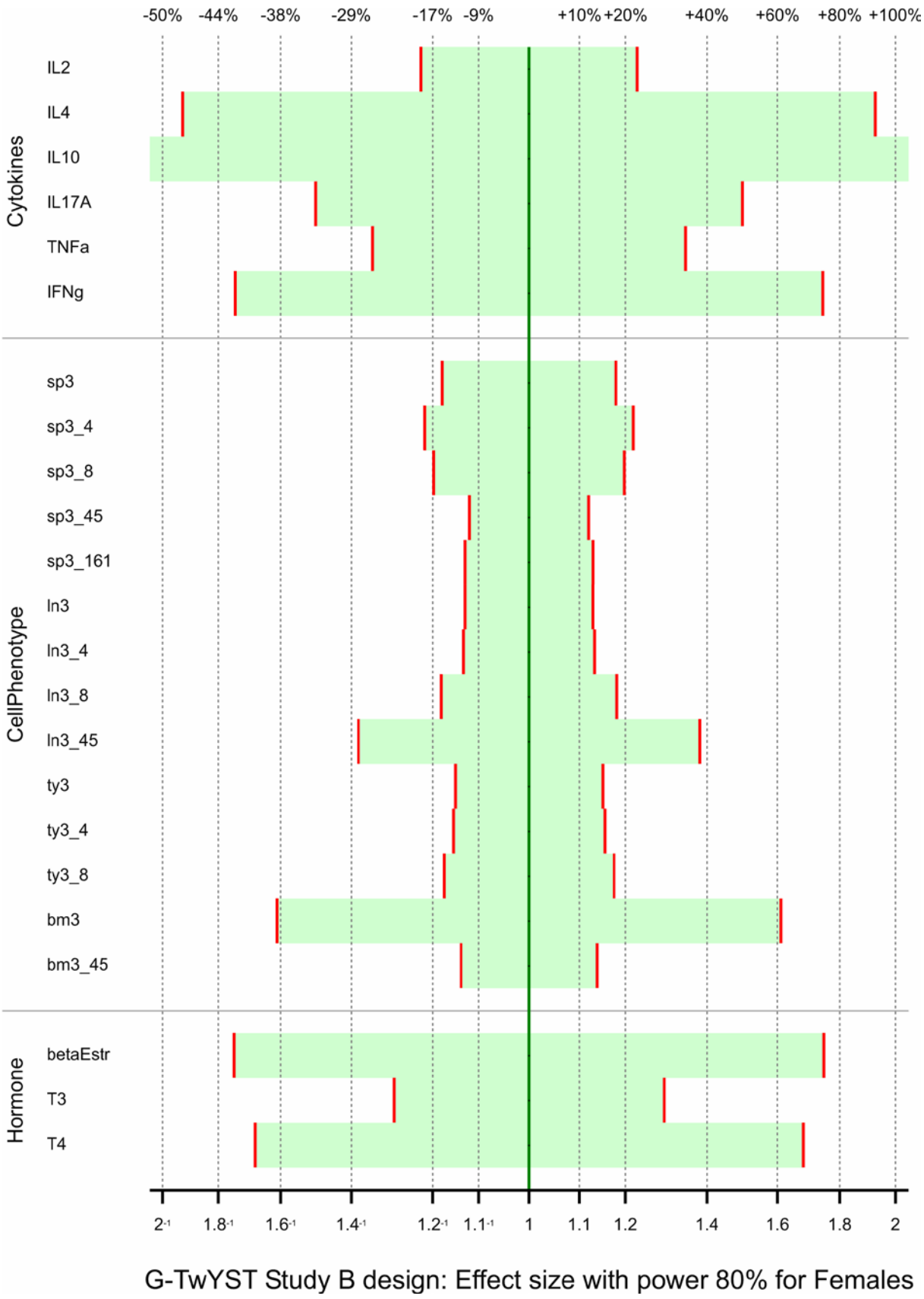

Figure 6 Effect sizes which can be found significant by two-sided testing with power 0.80 and α=0.05 for Cytokines/CellPhenotype/Hormone endpoints in females in a 90-days study.

Appendix 1. GenStat program for power of Fisher's exact test

```
" Define settings "
scalar    alpha ; 0.05
scalar    power ; 0.80
scalar    seed  ; 39352
scalar    ntimes ; 10000
variate   NN ; !(16,50,100)
variate   pControl ; !(0.1, 0.2 ... 0.9)
" Prepare "
calculate init = urand(seed ; 1)
calculate nSample, nControl = nvalues(NN, pControl)
variate   vpower ; !(#power)
pointer   [suffixes=NN] pFit, pRaw
variate   [nvalues=nControl] pFit[], pRaw[] ; deci=3
for [ntimes=nSample ; index=iSample]
  scalar    nbin, ntot ; (1,2) * NN$[iSample]
  for [ntimes=nControl ; index=iControl]
    " Simulate for Control group "
    scalar    p0 ; pControl$[iControl]
    calculate xControl = grbinomial(ntimes ; nbin ; p0)
    " Simulate for list of values for Treatment group "
    calculate p0plus = p0 + 0.005
    variate   pTreat ; !(#p0, #p0plus ... 1)
    calculate nTreat = nvalues(pTreat)
    pointer   [nvalues=nTreat] xTreat, xSum, prob, pow
    variate   [nvalues=nTreat] vpow ; deci=4
    calculate xTreat[] = grbinomial(#nTreat(ntimes) ; nbin ; #pTreat)
    " Do FisherExact and obtain power for each value of pTreat "
    calculate xSum[] = xControl + xTreat[]
    calculate prob[] = clhyper(#nTreat(xControl) ; xSum[] ; nbin ; ntot)
    calculate pow[] = mean(prob[] .lt. alpha)
    equate    pow ; vpow
    " Fit smoothing spline to power values and interpolate "
    subset    [vpow.le.0.9999] vpow, pTreat
    model     [dist=binomial] vpow ; nbin=1
    fit       [print=*] sspline(pTreat ; 4)
    rkeep     fit=fit
    interpola oldval=vpow,fit ; oldint=pTreat ; newval=vpower ; newint=p1,p2
    calculate pFit[nbin]$[iControl] = p1
    calculate pRaw[nbin]$[iControl] = p2
  endfor
endfor
print     [mis='-'] pControl, pFit[], pRaw[] ; field=10 ; deci=2
stop
```

Appendix 2. R program for power of Cox proportional hazard model

```
# Define settings
library(powerSurvEpi)
alpha <- 0.05
power <- 0.80
ratio <- seq(from=1.1, to=10, by=0.01)
pC <- rep(c(0.5, 0.6, 0.7), times=3)
pT <- rep(c(0.5, 0.6, 0.7), each=3)
NN <- c(16,50,100)
# Prepare
nRatio <- length(ratio)
nProbs <- length(pT)
result <- matrix(, nrow=length(NN), ncol=nProbs)
rownames(result) <- NN
# Calculate size in a loop by means of interpolation
for (jj in 1:nProbs) {
  ipT <- pT[jj]
  ipC <- pC[jj]
  size  <- NA*ratio
  for (ii in 1:nRatio) {
    size[ii] <- ssizeCT.default(power, ratio, ipT, ipC, ratio[ii], alpha)[1]
  }
  interpolate <- approx(size, ratio, NN)$y
  result[,jj] <- interpolate
}
pC
pT
round(result, 2)
```

Appendix 3. GenStat program for power of Weibull survival data

```
" Define settings "
scalar    seed   ; 3290128
scalar    lambda ; 2.141
scalar    kk     ; 5.38
scalar    censor ; 2
scalar    alpha  ; 0.05
scalar    power  ; 0.80
scalar    ntimes ; 1000
variate   NN     ; !(16,50,100) ; deci=0
variate   delta  ; !(1, 0.99...0.8) ; deci=2
" Initialize "
calculate init = urand(seed ; 1)
variate   vpower ; !(#power)
calculate nNN,ndelta = nvalues(NN,delta)
" Loop over values "
for [ntimes=nNN ; index=ii]
  scalar    iNN ; NN$[ii]
  variate   [nvalues=ndelta] powerTval ; deci=3
  for [ntimes=ndelta ; index=jj]
    scalar    idelta ; delta$[jj]
    " Define structures to hold simulated samples "
    factor    [nval=2*iNN*ntimes ; levels=2 ; values=#iNN(1,2)#ntimes] long
    variate   [nvalues=2*iNN*ntimes] mu, weibull, cweibull
    calculate mu = lambda * newlevels(long ; !(1, #idelta))
    pointer   [nvalues=ntimes] times, censored
    variate   [nvalues=2*iNN] times[], censored[]
    factor    [nvalues=2*iNN ; levels=2 ; values=#iNN(1,2)] treat
    " Simulate by means of inversion of CDF; do censoring "
    calculate weibull = mu * (-log(1-urand(0 ; 2*ntimes*iNN)))**(1/kk)
    calculate cweibull = weibull.ge.censor
    calculate weibull = bound(weibull ; 0 ; censor)
    equate    weibull, cweibull ; times, censored
    " Loop over ntimes datasets "
    " The null hypotheses is rejected for large treatment effect "
    variate   [nvalues=ntimes] esti,se
    for [ntimes=ntimes ; index=idata]
      rsurvival [print=* ; distribution=weibull ; times=times[idata] ; \
                 censored=censored[idata]] treat
      rkeep     esti=qesti ; se=qse
      calculate (esti,se)$[idata] = (qesti,qse)$[2]
    endfor
    calculate pval = cunormal(esti/se)
    calculate powerTval$[jj] = mean(pval.le.alpha)
  endfor
  " Interpolate to obtain effect size "
  interpola oldval=powerTval ; oldint=delta ; newval=vpower ; newint=eff[ii]
  print     iNN, eff[ii], delta, powerTval ; deci=0,3,2,3
endfor
print     NN, !(#eff) ; deci=0,2
stop
```

Appendix 4. Residual standard errors for endpoints in males

Group	Endpoint	dfResA	dfResB	dfResC	seResA	seResB	seResC	seRes
Weights	BodyWeight	136	28	49	0.0484	0.0466	0.0512	0.0488
Weights	growthRate	136	28	49	0.0184	0.0224	0.0182	0.0198
Weights	FeedMean	136	28	49	0.0442	0.0486	0.0483	0.0471
Group	Endpoint	dfResA	dfResB	dfResC	seResA	seResB	seResC	seRes
Haematology	WBC	76	28	49	0.1739	0.1744	0.1656	0.1713
Haematology	RBC	76	28	49	0.0333	0.0440	0.0212	0.0341
Haematology	HGB	76	28	49	0.0271	0.0233	0.0222	0.0243
Haematology	HCT	76	28	49	0.0305	0.0349	0.0200	0.0292
Haematology	MCV	76	28	49	0.0251	0.0205	0.0162	0.0209
Haematology	MCH	76	28	49	0.0337	0.0281	0.0221	0.0284
Haematology	MCHC	76	28	49	0.0168	0.0190	0.0133	0.0165
Haematology	PLT	76	28	49	0.1280	0.1508	0.1210	0.1339
Haematology	LYMR	76	28	48	0.0659	0.0690	0.0365	0.0590
Haematology	LYMA	76	28	49	0.1836	0.1824	0.1606	0.1759
Group	Endpoint	dfResA	dfResB	dfResC	seResA	seResB	seResC	seRes
diffWBC	Lymphocytes		28			0.0735		0.0735
diffWBC	Neutrophils		28			0.1632		0.1632
diffWBC	Monocytes		28			0.3019		0.3019
diffWBC	Eosinophils		28			0.4199		0.4199
Group	Endpoint	dfResA	dfResB	dfResC	seResA	seResB	seResC	seRes
ClinChem	ALP	76	28	49	0.1570	0.1078	0.1740	0.1489
ClinChem	ALT	76	28	49	0.1083	0.1032	0.1503	0.1225
ClinChem	AST	76	28	49	0.1498	0.1371	0.1956	0.1628
ClinChem	BIL	76	28	49	0.2871	0.1164	0.1188	0.1915
ClinChem	ALB	76	28	49	0.0388	0.0274	0.0423	0.0367
ClinChem	TP	76	28	49	0.0308	0.0186	0.0229	0.0246
ClinChem	Glu	76	28	49	0.1076	0.1048	0.1146	0.1090
ClinChem	CHOL	76	28	49	0.0997	0.0965	0.0973	0.0978
ClinChem	TAG	76	28	49	0.1939	0.1773	0.1991	0.1903
ClinChem	Crea	76	28	49	0.1112	0.0771	0.1187	0.1039
ClinChem	Urea	76	28	49	0.0907	0.0860	0.1031	0.0935
ClinChem	cHGB	76	28	49	0.4139	0.2943	0.3296	0.3496
ClinChem	Ca	76	28	49	0.0201	0.0135	0.0145	0.0163
ClinChem	Cl	76	28	49	0.0150	0.0093	0.0147	0.0132
ClinChem	K	76	28	49	0.0754	0.0451	0.0707	0.0651
ClinChem	Na	75	28	49	0.0090	0.0079	0.0101	0.0090
ClinChem	P	76	28	49	0.0817	0.0895	0.1142	0.0961

Group	Endpoint	dfResA	dfResB	dfResC	seResA	seResB	seResC	seRes
Urine	uVol	36	28	49	0.2715	0.2960	0.2888	0.2856
Urine	uVolW	36	28	49	0.2840	0.2977	0.2827	0.2882
Urine	uLeu	36	28	49	0.3940	0.5672	0.4098	0.4636
Urine	uOsmoll	36	28	49	0.2783	0.2396	0.2526	0.2573
Urine	uKeton	36	28	49	0.6068	1.0358	0.5557	0.7637
Urine	upH	36	28	49	0.2973	0.2428	0.3412	0.2965
Group	Endpoint	dfResA	dfResB	dfResC	seResA	seResB	seResC	seRes
Organs	Kidney		28	49		0.0727	0.0637	0.0683
Organs	Spleen		28	49		0.0824	0.0930	0.0879
Organs	Liver		28	49		0.0407	0.0386	0.0397
Organs	AdrenGl		28	49		0.1012	0.1032	0.1022
Organs	Heart		28	49		0.0519	0.0551	0.0535
Organs	Thymus		28	49		0.1177	0.1310	0.1245
Organs	Testis		28	49		0.0657	0.0632	0.0644
Organs	Epididymis		28	49		0.0766	0.0769	0.0768
Organs	Brain		28	49		0.0507	0.0518	0.0513
Group	Endpoint	dfResA	dfResB	dfResC	seResA	seResB	seResC	seRes
Immunology	Monocytes			31			0.0746	0.0746
Immunology	Granulocytes		16	31		0.0441	0.0402	0.0422
Immunology	RespirBurst		16	31		0.1055	0.0635	0.0871
Immunology	Con		16	31		0.3553	0.6907	0.5492
Immunology	PHA		16	31		0.2943	0.6165	0.4831
Immunology	PWM		16	31		0.4142	0.4754	0.4458
Immunology	Medium		16	31		0.3444	0.6080	0.4941
Immunology	IprConA		16	31		0.3515	0.2894	0.3220
Immunology	IprPHA		16	31		0.2931	0.3531	0.3245
Immunology	IprPWM		16	31		0.2261	0.3116	0.2722
Immunology	G4c1			31			0.6598	0.6598
Immunology	G4c2			31			0.7819	0.7819
Immunology	G4c3			31			0.7240	0.7240
Immunology	NG2c1			31			0.6797	0.6797
Immunology	NG2c2			31			0.8025	0.8025
Immunology	NG2c3			31			0.7483	0.7483
Immunology	A6c1			31			0.7419	0.7419
Immunology	A6c2			31			0.8059	0.8059
Immunology	A6c3			31			0.7437	0.7437
Immunology	Med6d			31			0.8854	0.8854
Immunology	IprG4c1			31			0.3604	0.3604
Immunology	IprG4c2			31			0.2524	0.2524
Immunology	IprG4c3			31			0.3537	0.3537
Immunology	IprNG2c1			31			0.3059	0.3059

Immunology	IprNG2c2			31			0.2727	0.2727
Immunology	IprNG2c3			31			0.2881	0.2881
Immunology	IprA6c1			31			0.2970	0.2970
Immunology	IprA6c2			31			0.3117	0.3117
Immunology	IprA6c3			31			0.3047	0.3047
Group	Endpoint	dfResA	dfResB	dfResC	seResA	seResB	seResC	seRes
Cytokines	IL2		16			0.1494		0.1494
Cytokines	IL4		16			0.2899		0.2899
Cytokines	IL10		16			0.7303		0.7303
Cytokines	IL17A		16			0.5854		0.5854
Cytokines	TNFa		16			0.2538		0.2538
Cytokines	IFNg		16			0.2511		0.2511
Group	Endpoint	dfResA	dfResB	dfResC	seResA	seResB	seResC	seRes
CellPhenotype	sp3		16	31		0.1215	0.1872	0.1578
CellPhenotype	sp3_4		16	31		0.1292	0.2390	0.1921
CellPhenotype	sp3_8		16	31		0.1360	0.2996	0.2326
CellPhenotype	sp3_45		15	31		0.0386	0.1453	0.1063
CellPhenotype	sp3_161		15	31		0.0647	0.1619	0.1233
CellPhenotype	ln3		16	31		0.1377	0.1312	0.1345
CellPhenotype	ln3_4		16	31		0.1605	0.1331	0.1475
CellPhenotype	ln3_8		16	31		0.1209	0.1591	0.1413
CellPhenotype	ln3_45		16	30		0.1463	0.2313	0.1935
CellPhenotype	ty3		16	31		0.1289	0.1487	0.1392
CellPhenotype	ty3_4		16	31		0.1219	0.1328	0.1275
CellPhenotype	ty3_8		16	31		0.1362	0.1740	0.1563
CellPhenotype	bm3			31			0.3917	0.3917
CellPhenotype	bm3_45			31			0.0733	0.0733
Group	Endpoint	dfResA	dfResB	dfResC	seResA	seResB	seResC	seRes
Hormone	Testosteron		20			0.3923		0.3923
Hormone	T3		20			0.0891		0.0891
Hormone	T4		20			0.0766		0.0766

Appendix 5. Residual standard errors for endpoints in females

Group	Endpoint	dfResA	dfResB	dfResC	seResA	seResB	seResC	seRes
Weights	BodyWeight	136	28	49	0.048	0.047	0.051	0.049
Weights	growthRate	136	28	49	0.018	0.022	0.018	0.020
Weights	FeedMean	136	28	49	0.044	0.049	0.048	0.047
Group	Endpoint	dfResA	dfResB	dfResC	seResA	seResB	seResC	seRes
Haematology	WBC	76	28	49	0.174	0.174	0.166	0.171
Haematology	RBC	76	28	49	0.033	0.044	0.021	0.034
Haematology	HGB	76	28	49	0.027	0.023	0.022	0.024
Haematology	HCT	76	28	49	0.031	0.035	0.020	0.029
Haematology	MCV	76	28	49	0.025	0.020	0.016	0.021
Haematology	MCH	76	28	49	0.034	0.028	0.022	0.028
Haematology	MCHC	76	28	49	0.017	0.019	0.013	0.017
Haematology	PLT	76	28	49	0.128	0.151	0.121	0.134
Haematology	LYMR	76	28	48	0.066	0.069	0.036	0.059
Haematology	LYMA	76	28	49	0.184	0.182	0.161	0.176
Group	Endpoint	dfResA	dfResB	dfResC	seResA	seResB	seResC	seRes
diffWBC	Lymphocytes		28			0.073		0.073
diffWBC	Neutrophils		28			0.163		0.163
diffWBC	Monocytes		28			0.302		0.302
diffWBC	Eosinophils		28			0.420		0.420
Group	Endpoint	dfResA	dfResB	dfResC	seResA	seResB	seResC	seRes
ClinChem	ALP	76	28	49	0.157	0.108	0.174	0.149
ClinChem	ALT	76	28	49	0.108	0.103	0.150	0.122
ClinChem	AST	76	28	49	0.150	0.137	0.196	0.163
ClinChem	BIL	76	28	49	0.287	0.116	0.119	0.192
ClinChem	ALB	76	28	49	0.039	0.027	0.042	0.037
ClinChem	TP	76	28	49	0.031	0.019	0.023	0.025
ClinChem	Glu	76	28	49	0.108	0.105	0.115	0.109
ClinChem	CHOL	76	28	49	0.100	0.096	0.097	0.098
ClinChem	TAG	76	28	49	0.194	0.177	0.199	0.190
ClinChem	Crea	76	28	49	0.111	0.077	0.119	0.104
ClinChem	Urea	76	28	49	0.091	0.086	0.103	0.094
ClinChem	cHGB	76	28	49	0.414	0.294	0.330	0.350
ClinChem	Ca	76	28	49	0.020	0.013	0.014	0.016
ClinChem	Cl	76	28	49	0.015	0.009	0.015	0.013
ClinChem	K	76	28	49	0.075	0.045	0.071	0.065
ClinChem	Na	75	28	49	0.009	0.008	0.010	0.009
ClinChem	P	76	28	49	0.082	0.090	0.114	0.096

Group	Endpoint	dfResA	dfResB	dfResC	seResA	seResB	seResC	seRes
Urine	uVol	36	28	49	0.272	0.296	0.289	0.286
Urine	uVolW	36	28	49	0.284	0.298	0.283	0.288
Urine	uLeu	36	28	49	0.394	0.567	0.410	0.464
Urine	uOsmoll	36	28	49	0.278	0.240	0.253	0.257
Urine	uKeton	36	28	49	0.607	1.036	0.556	0.764
Urine	upH	36	28	49	0.297	0.243	0.341	0.296
Group	Endpoint	dfResA	dfResB	dfResC	seResA	seResB	seResC	seRes
Organs	Kidney		28	49		0.073	0.064	0.068
Organs	Spleen		28	49		0.082	0.093	0.088
Organs	Liver		28	49		0.041	0.039	0.040
Organs	AdrenGl		28	49		0.101	0.103	0.102
Organs	Heart		28	49		0.052	0.055	0.054
Organs	Thymus		28	49		0.118	0.131	0.125
Organs	Uterus		28	49		0.066	0.063	0.064
Organs	Ovary		28	49		0.077	0.077	0.077
Organs	Brain		28	49		0.051	0.052	0.051
Group	Endpoint	dfResA	dfResB	dfResC	seResA	seResB	seResC	seRes
Immunology	Monocytes			31			0.075	0.075
Immunology	Granulocytes		16	31		0.044	0.040	0.042
Immunology	RespirBurst		16	31		0.105	0.064	0.087
Immunology	Con		16	31		0.355	0.691	0.549
Immunology	PHA		16	31		0.294	0.616	0.483
Immunology	PWM		16	31		0.414	0.475	0.446
Immunology	Medium		16	31		0.344	0.608	0.494
Immunology	IprConA		16	31		0.351	0.289	0.322
Immunology	IprPHA		16	31		0.293	0.353	0.325
Immunology	IprPWM		16	31		0.226	0.312	0.272
Immunology	G4c1			31			0.660	0.660
Immunology	G4c2			31			0.782	0.782
Immunology	G4c3			31			0.724	0.724
Immunology	NG2c1			31			0.680	0.680
Immunology	NG2c2			31			0.803	0.803
Immunology	NG2c3			31			0.748	0.748
Immunology	A6c1			31			0.742	0.742
Immunology	A6c2			31			0.806	0.806
Immunology	A6c3			31			0.744	0.744
Immunology	Med6d			31			0.885	0.885
Immunology	IprG4c1			31			0.360	0.360
Immunology	IprG4c2			31			0.252	0.252
Immunology	IprG4c3			31			0.354	0.354
Immunology	IprNG2c1			31			0.306	0.306

Immunology	IprNG2c2			31			0.273	0.273
Immunology	IprNG2c3			31			0.288	0.288
Immunology	IprA6c1			31			0.297	0.297
Immunology	IprA6c2			31			0.312	0.312
Immunology	IprA6c3			31			0.305	0.305
Group	Endpoint	dfResA	dfResB	dfResC	seResA	seResB	seResC	seRes
Cytokines	IL2		16			0.149		0.149
Cytokines	IL4		16			0.290		0.290
Cytokines	IL10		16			0.730		0.730
Cytokines	IL17A		16			0.585		0.585
Cytokines	TNFa		16			0.254		0.254
Cytokines	IFNg		16			0.251		0.251
Group	Endpoint	dfResA	dfResB	dfResC	seResA	seResB	seResC	seRes
CellPhenotype	sp3		16	31		0.122	0.187	0.158
CellPhenotype	sp3_4		16	31		0.129	0.239	0.192
CellPhenotype	sp3_8		16	31		0.136	0.300	0.233
CellPhenotype	sp3_45		15	31		0.039	0.145	0.106
CellPhenotype	sp3_161		15	31		0.065	0.162	0.123
CellPhenotype	ln3		16	31		0.138	0.131	0.135
CellPhenotype	ln3_4		16	31		0.161	0.133	0.147
CellPhenotype	ln3_8		16	31		0.121	0.159	0.141
CellPhenotype	ln3_45		16	30		0.146	0.231	0.194
CellPhenotype	ty3		16	31		0.129	0.149	0.139
CellPhenotype	ty3_4		16	31		0.122	0.133	0.127
CellPhenotype	ty3_8		16	31		0.136	0.174	0.156
CellPhenotype	bm3			31			0.392	0.392
CellPhenotype	bm3_45			31			0.073	0.073
Group	Endpoint	dfResA	dfResB	dfResC	seResA	seResB	seResC	seRes
Hormone	Testosteron		20			0.392		0.392
Hormone	T3		20			0.089		0.089
Hormone	T4		20			0.077		0.077