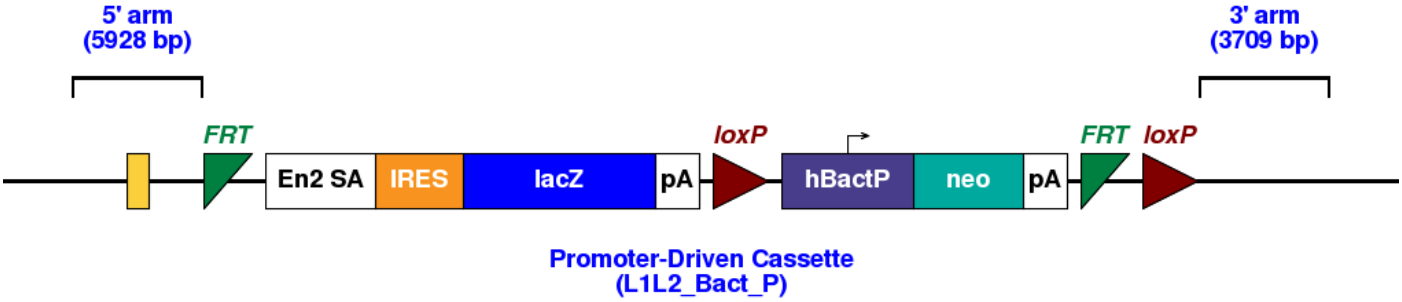
Knockout mouse lines presenting with welfare issues affecting their survival [abnormal survival [MP:0010769]] are processed through a bespoke sub-pipeline known as the "sick mouse procedure" [SMP] to maximise information collected on that mouse line. Matched wild-type controls are also processed to identify phenotypic abnormalities arising from the targeted allele.

Trex1$^{tm1(KOMP)Wtsi}$

Three prime repair exonuclease 1

Genetic Background: C57BL/6NTac;C57BL/6NTac;C57BL/6N

ES Cell Clone: EPD0296_3_C07



Affected genotypes

Homozygous (*Trex1*$^{tm1(KOMP)Wtsi/tm1([KOMP)Wtsi}$).

Alternative breeding strategy

Following initial welfare observations, wild-type x heterozygous mating strategy was employed to complete phenotyping work in standard pipeline using heterozygous mice only.

Heterozygous mice showed no significant phenotypic findings on the primary screen.

Welfare observations

Homozygous mice exhibit:

- Both sexes exhibit small body size (homozygote female 51% n=20/39, male 28% n=15/54 vs WT female 1% n=1/76, male 0% n=0/80). Decreased body size [MP:0001265].

- Exhibit eye defects (hom female 15% n=6/39, male 11% n=6/54 vs WT female 5% n=4/76, male 0% n=0/80). Eye defect manifests as increased incidence of corneal abnormalities. Both sexes had corneal eye defects. Abnormal cornea morphology [MP:0001312].

- Mice had an increased incidence of elevated respiratory rate (hom female 8% n=3/39, male 15% n=8/54 vs WT female 0% n=0/67, male 0% n=0/57). Increased pulmonary respiratory rate [MP:0005573].

- Overall deterioration of health contributed to a higher rate of loss of homozygous mice (hom female 39% n=15/39, male 28% n=15/54 vs WT female 3% n=2/67, male 2% n=1/57). Decreased survivor rate [MP:0008770].

Homozygous Viability:

All genotyped mice from het x het intercross considered. When at least 28 mice are available, viability at p14 is calculated. *[>13% = Homozygous viable; >0% and <13% = Sub-viable; 0% = Lethal]*

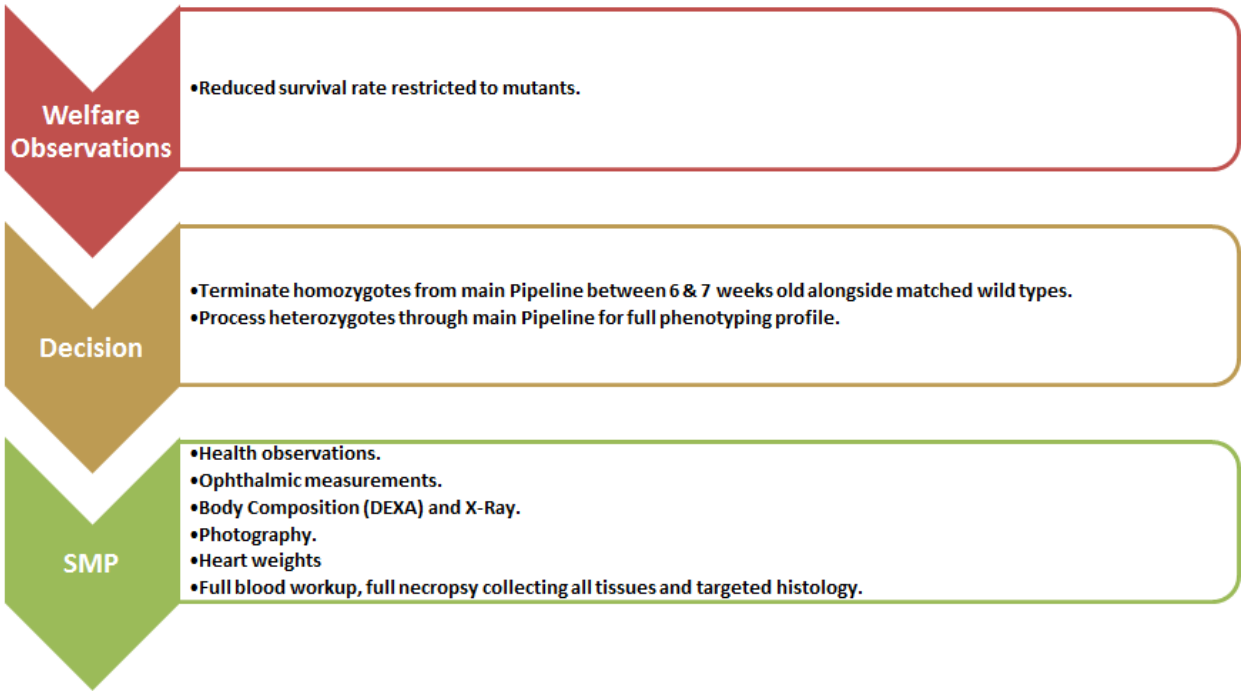
- **Viable** : 76 Homs / 370 Total = 20.5%

Sick Mouse Procedure (SMP)

Initial welfare observations were reported when the first homozygotes were born during the breeding and expansion stage. Homozygotes were still viable when issued to the phenotyping pipelines (4 weeks) but severity progressed rapidly by 6 weeks of age.

Welfare observations in homozygotes described above progressed to moderate severity between 6 and 7 weeks of age upon which SMP (see schematic below) was initiated. 7 male and 6 female homozygotes were processed alongside 7 male and 6 female matched wild-types. No further homozygotes were phenotyped due to the aforementioned alternative breeding strategy employed to reduce further welfare implications.

Schematic Outline of Bespoke SMP Pipeline



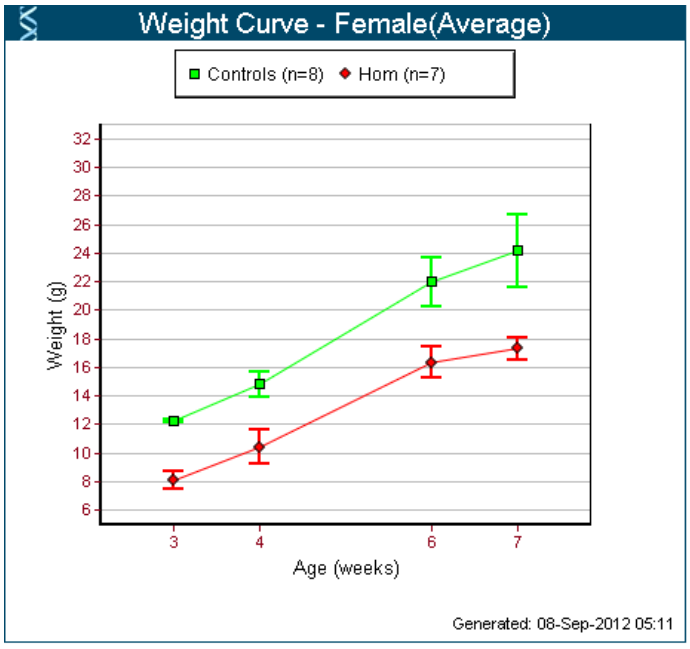
Phenotyping Heat Map

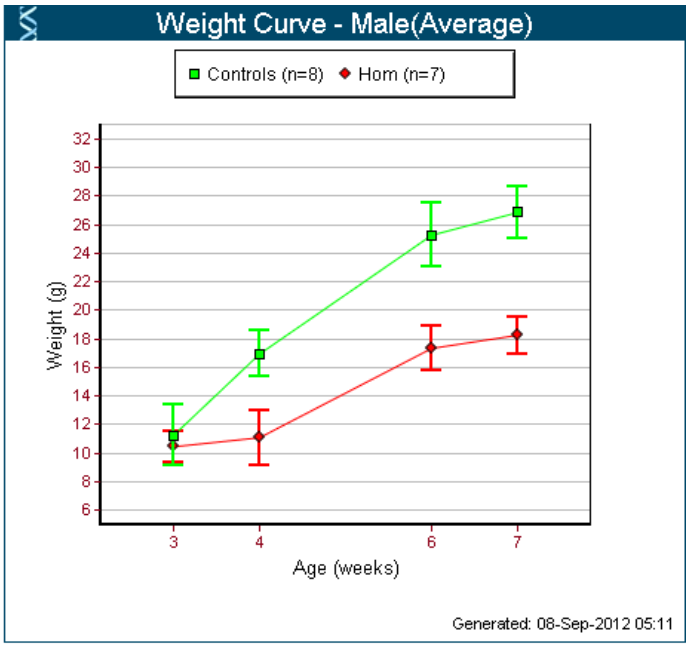
Colony Prefix	Allele Name	Genotype	Weight Curves	Ophthalmic Measurements	Body Composition (DEXA)	X-ray Imaging	Plasma Chemistry	Haematology (CBC)	Heart Weights	Peripheral Blood Leukocytes	Tissue Biobank
MAYY	Trex1tm1(KOMP)Wtsi	Homozygous									

Significant / Interesting
Not significant
Resources available

Phenotyping data of interest (significant changes)

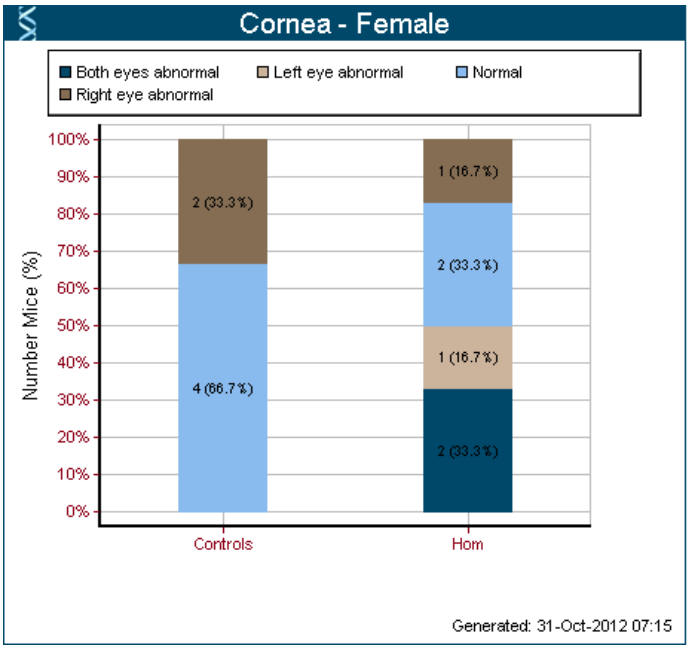
In life phenotyping

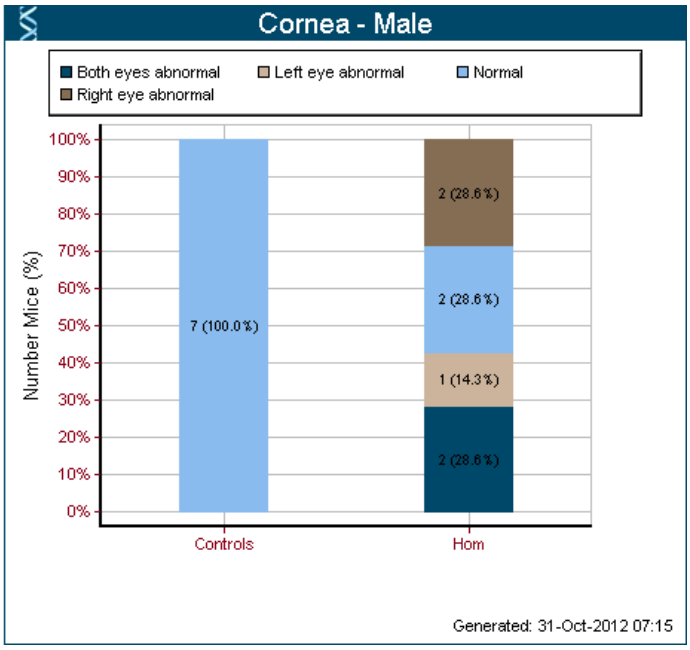




Males and Females - decreased body weight [MP:0001262]

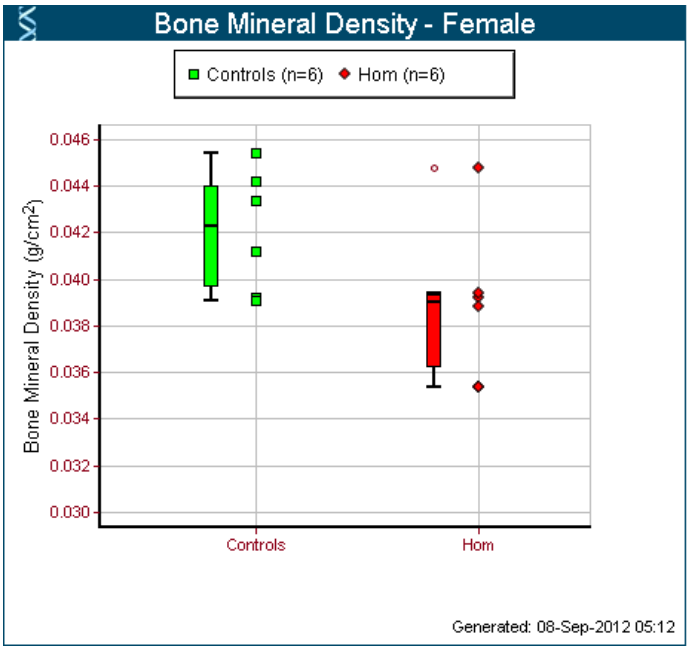
Ophthalmic Measurements

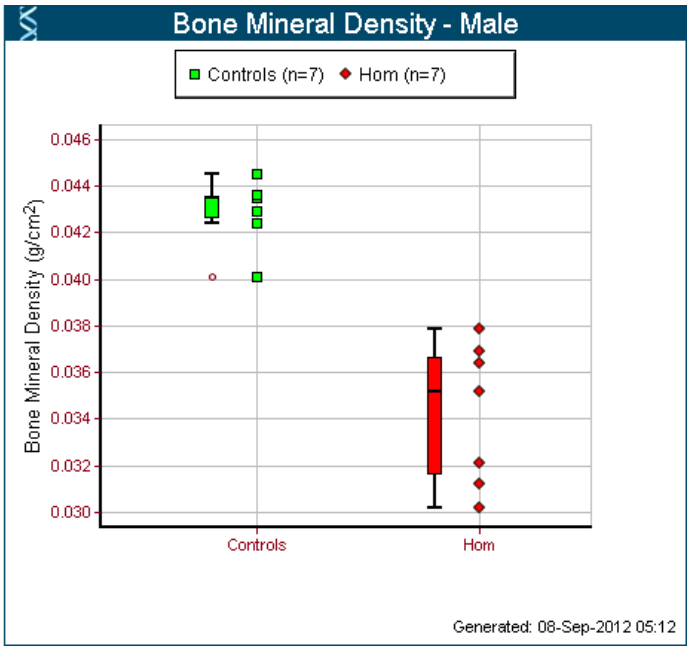




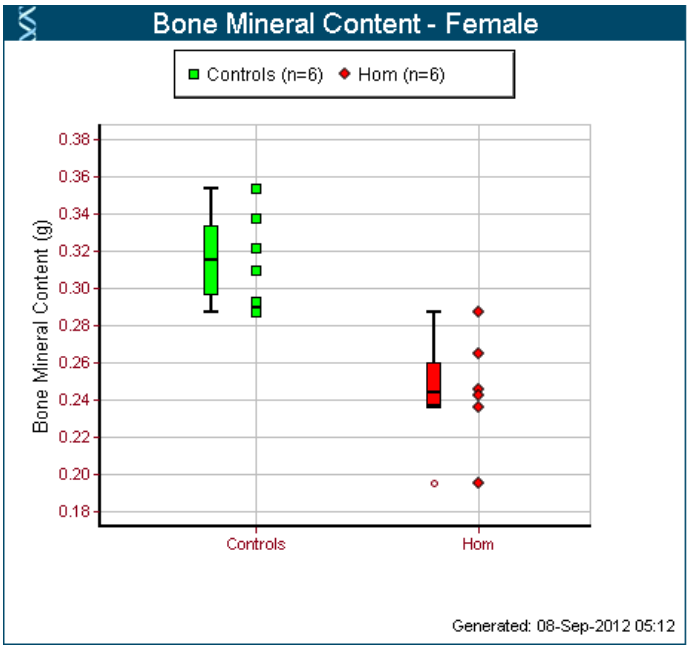
Males and Females - abnormal cornea morphology [MP:0001312]

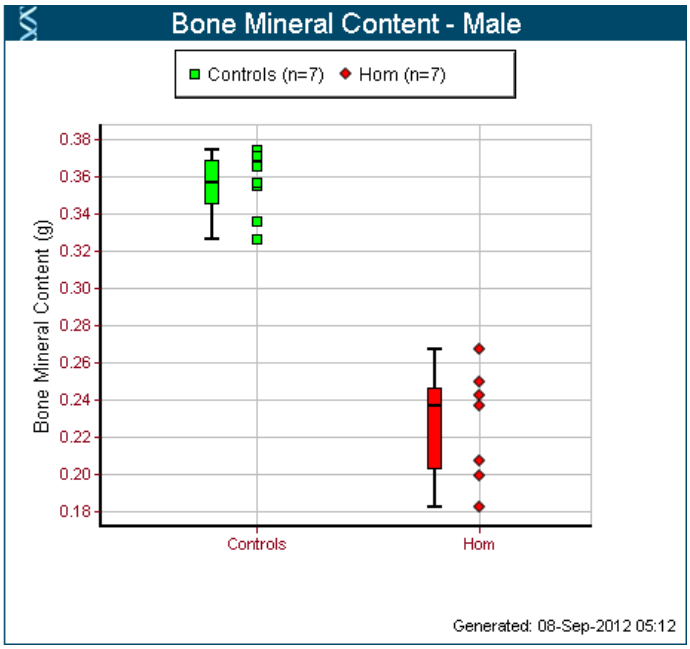
Body Composition (DEXA)



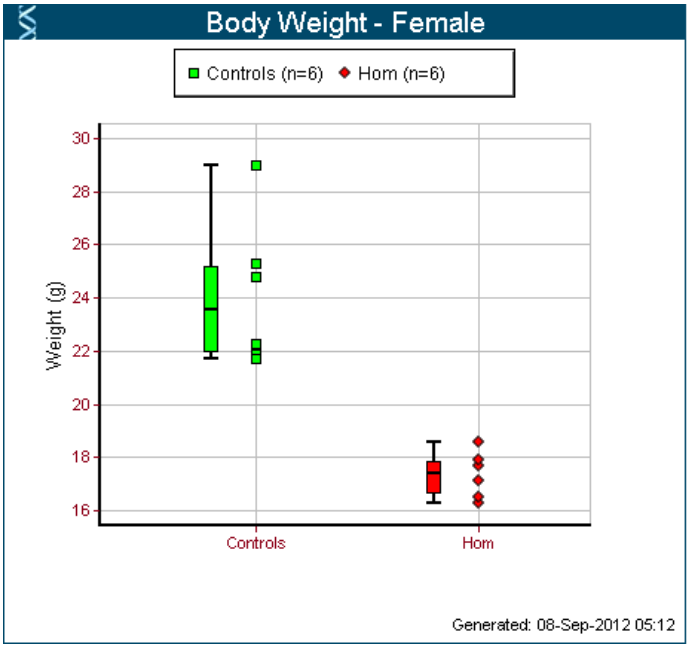


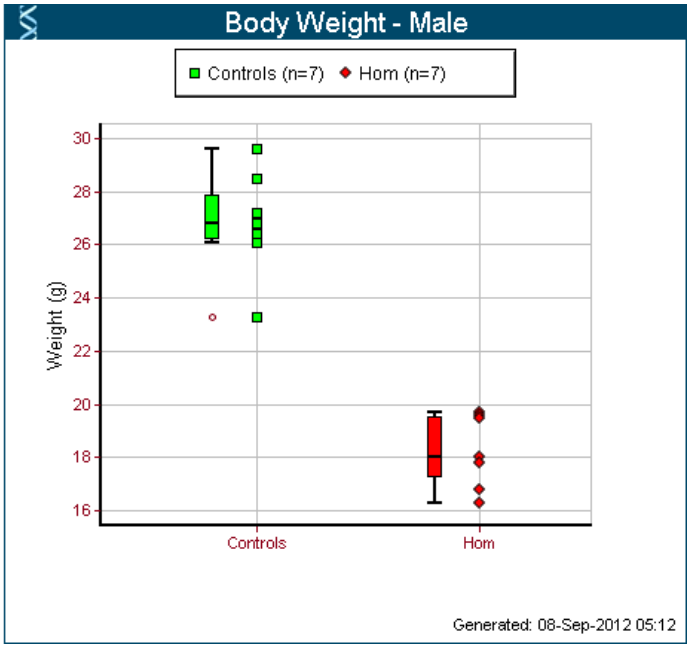
Males and Females - decreased bone mineral density [MP:0000063]



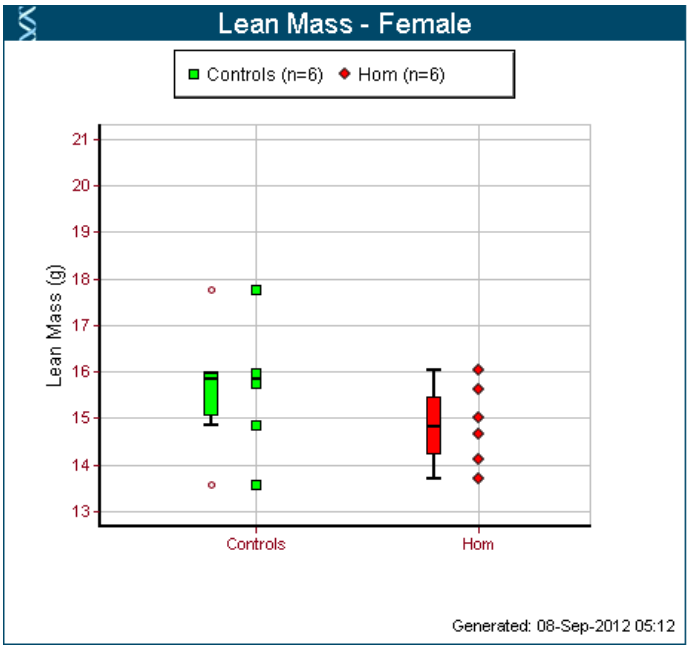


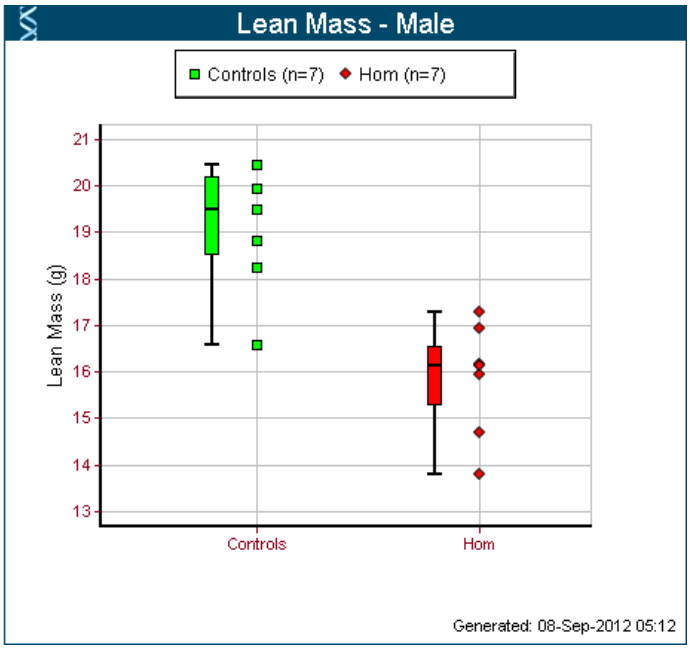
Males and Females - decreased bone mineral content [MP:0010124]



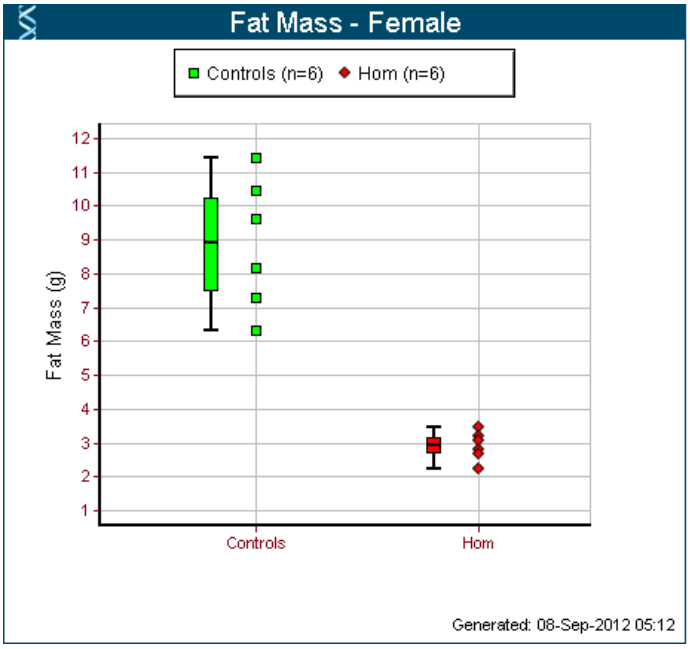


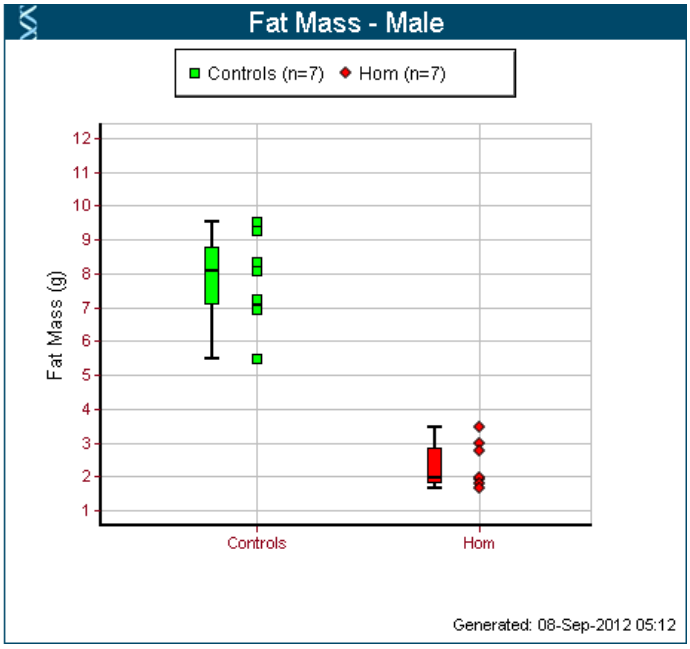
Males and Females - decreased body weight [MP:0001262]



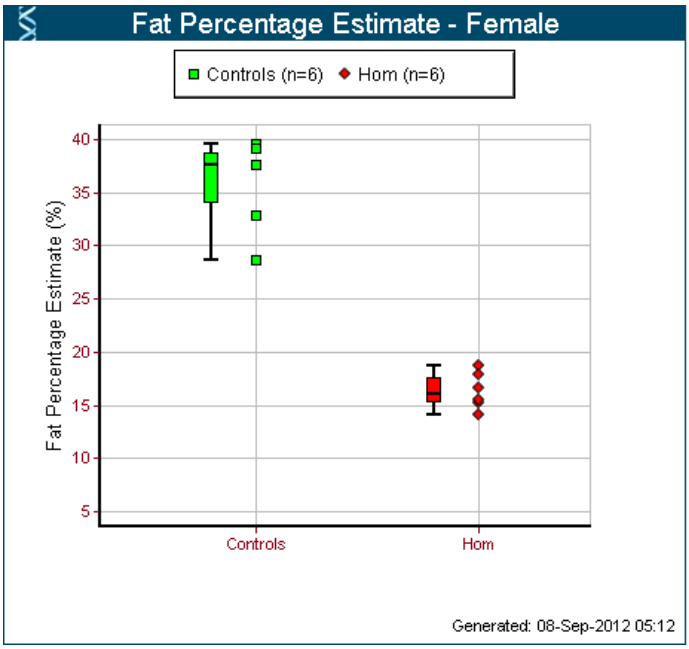


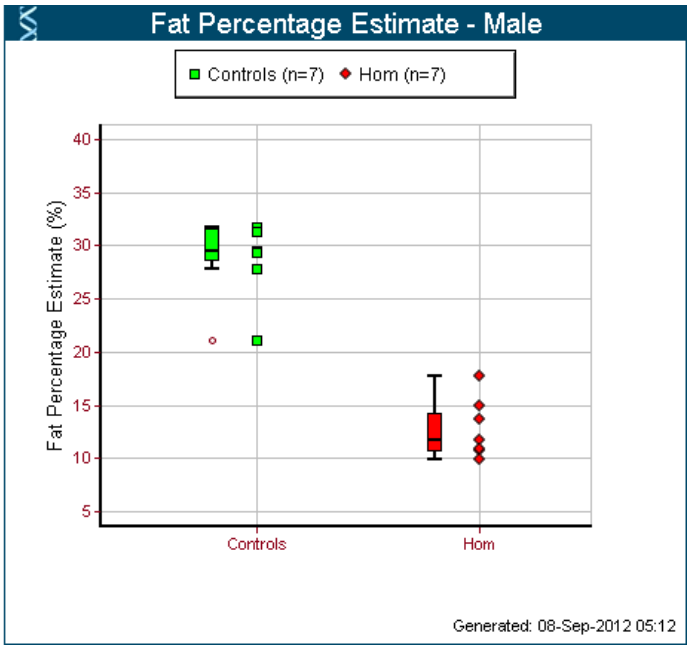
Males - decreased lean body mass [MP:0003961]





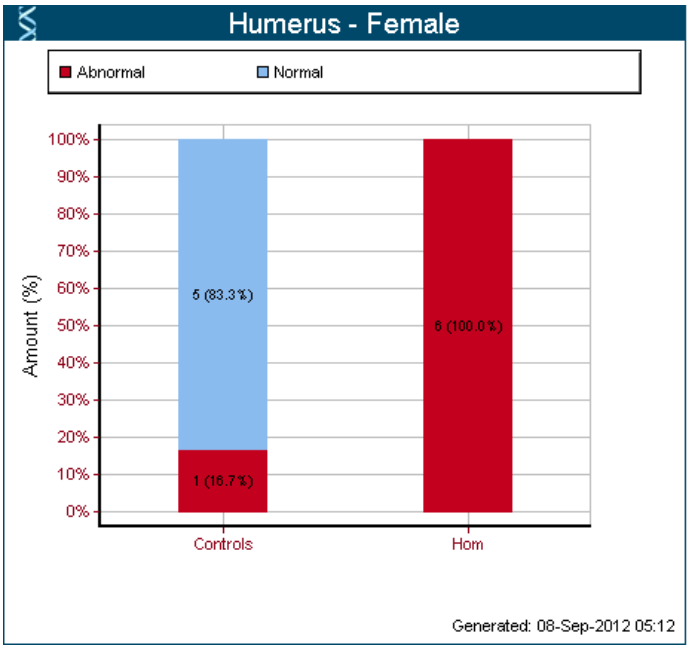
Males and Females - decreased total body fat amount [MP:0010025]

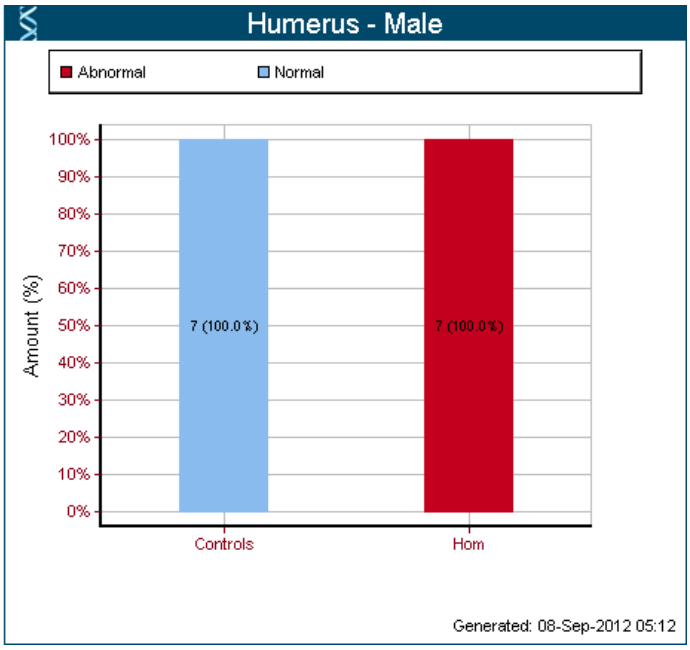




Males and Females - decreased percent body fat [MP:0005459]

X-ray Imaging





Males and Females - abnormal humerus morphology [MP:0005296]

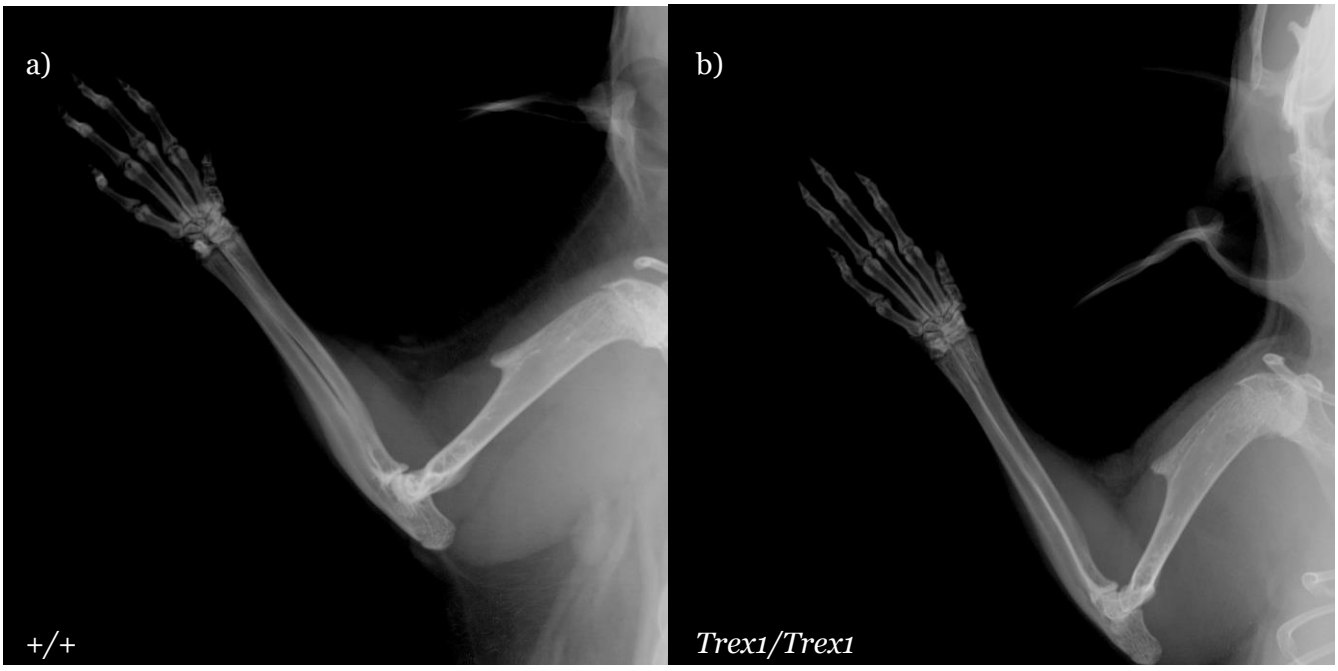


Figure 1. Dorsoventral radiograph of (a) wild-type and (b) homozygous mouse left forelimb displaying bowing of the humeral diaphysis.

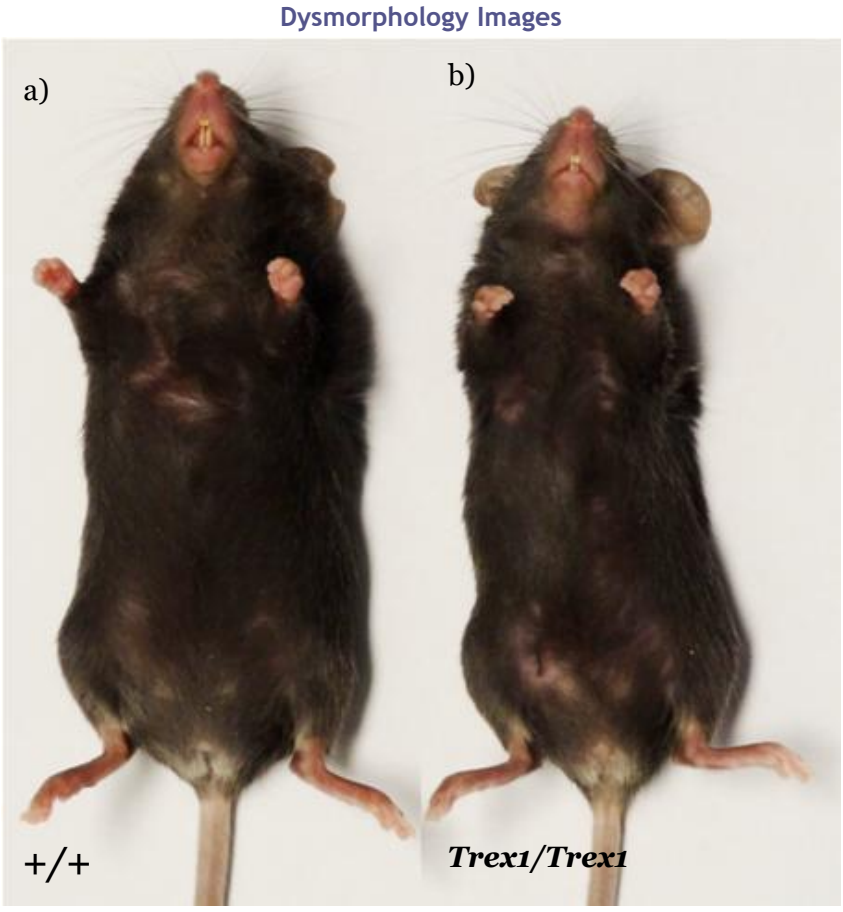
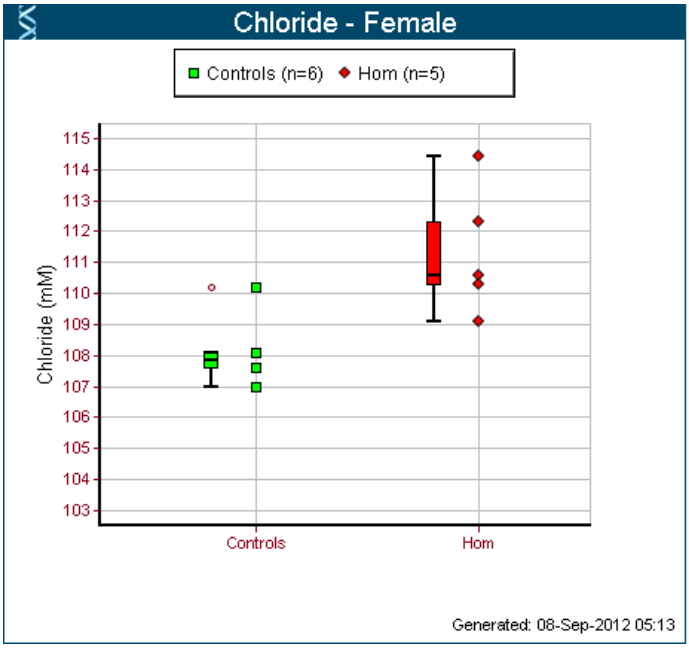
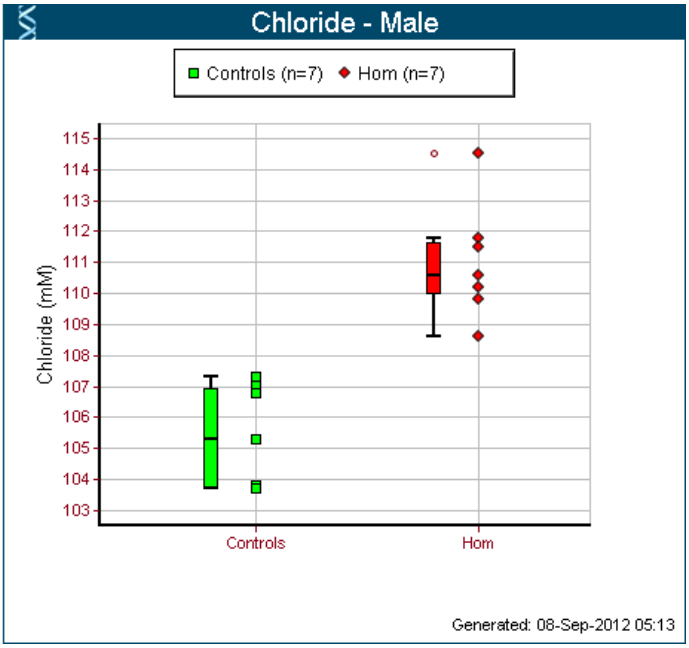


Figure 2. Ventral view of wild-type (a) and homozygous (b) mice showing small body size.

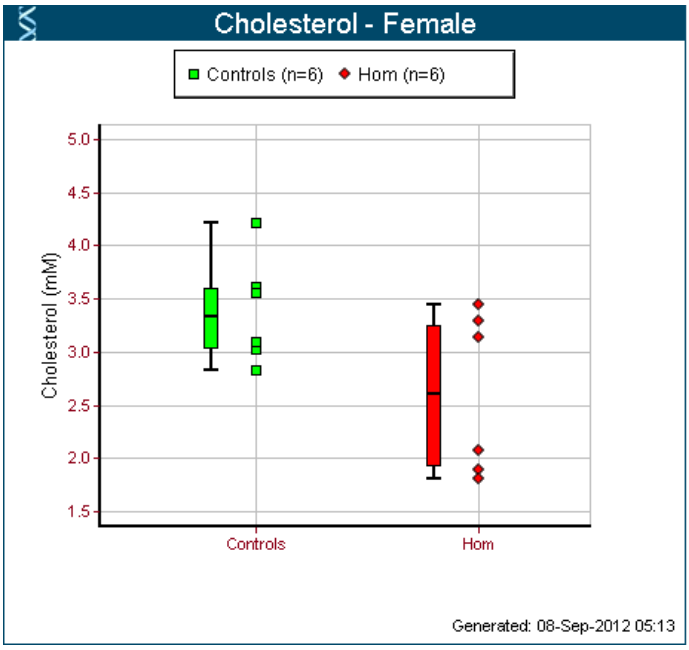
Ex vivo phenotyping

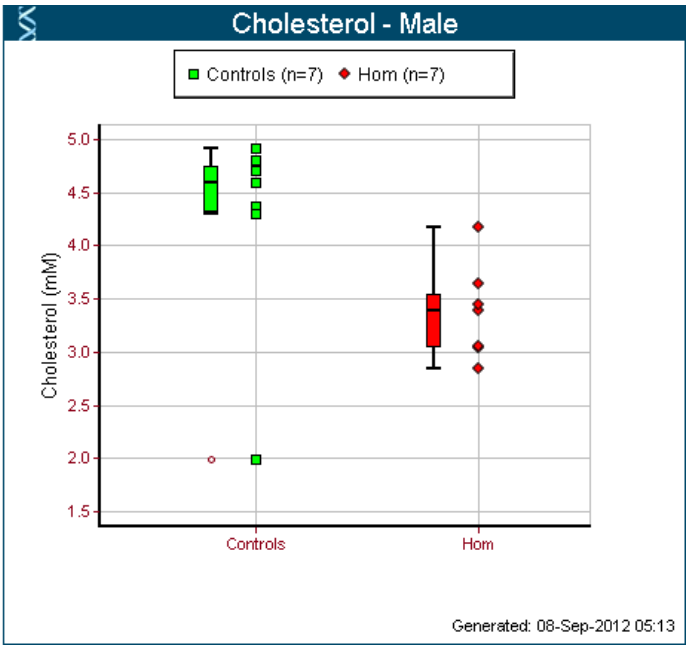
Plasma Chemistry



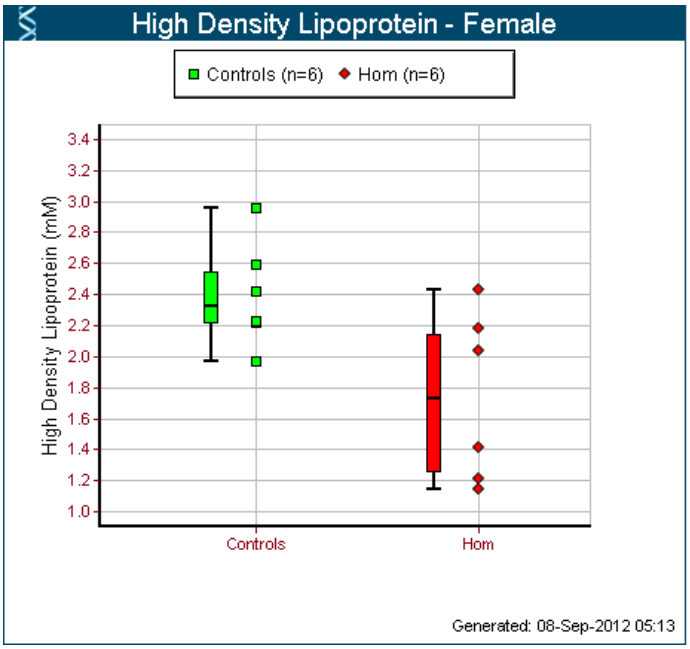


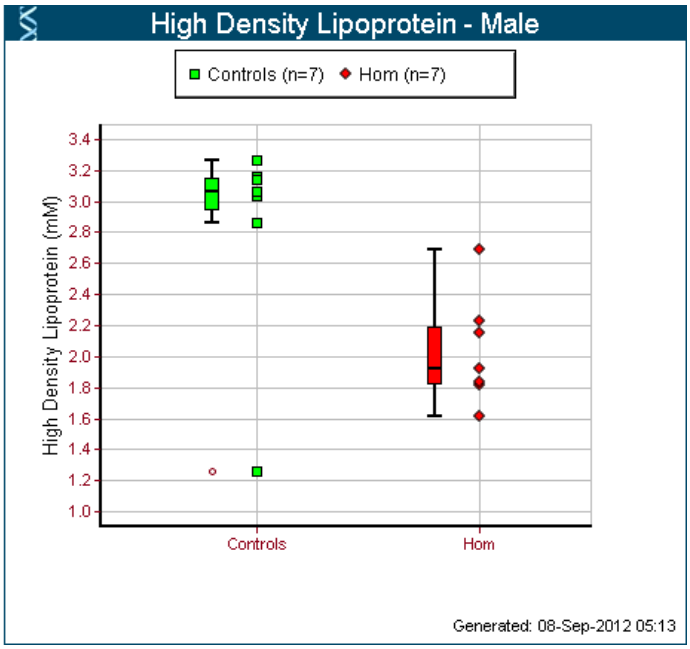
Males and Females - increased circulating chloride level [MP:0003019]



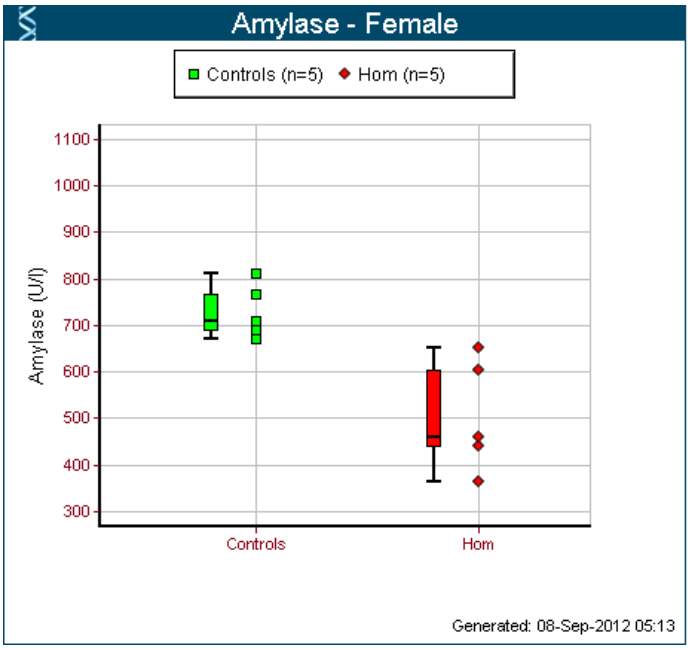


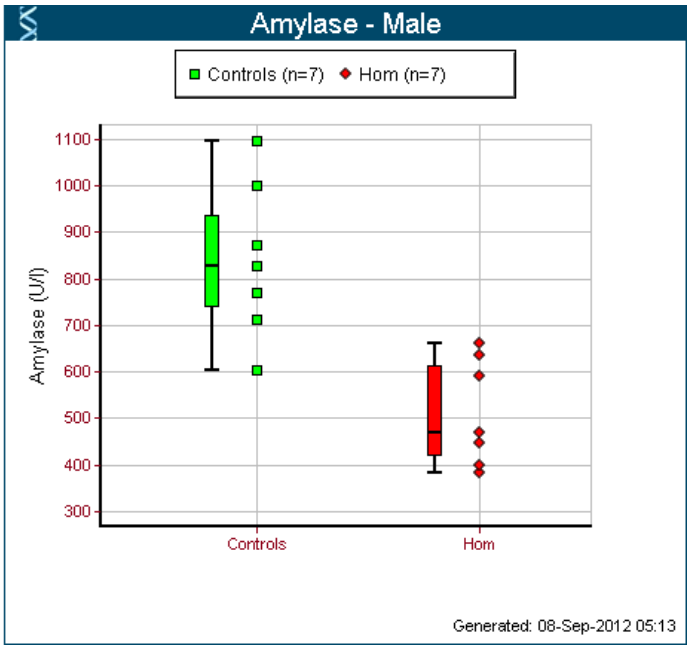
Males and Females - decreased circulating cholesterol level [MP:0005179]



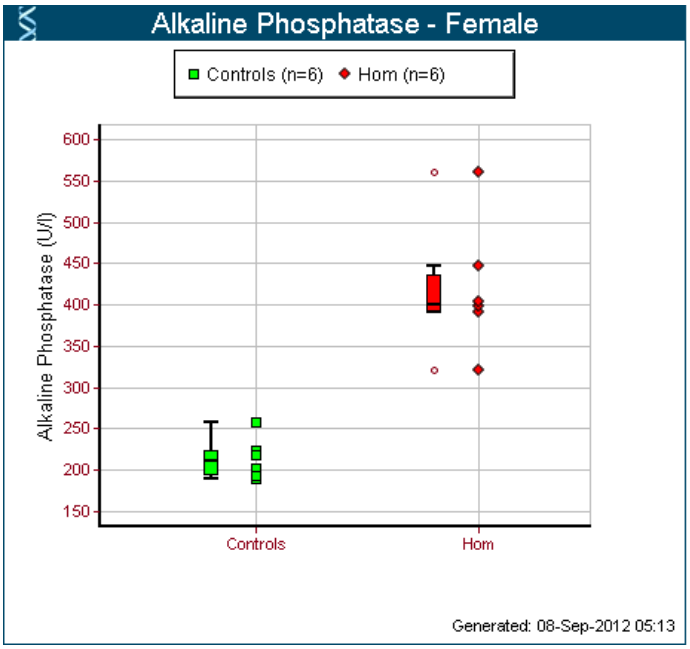


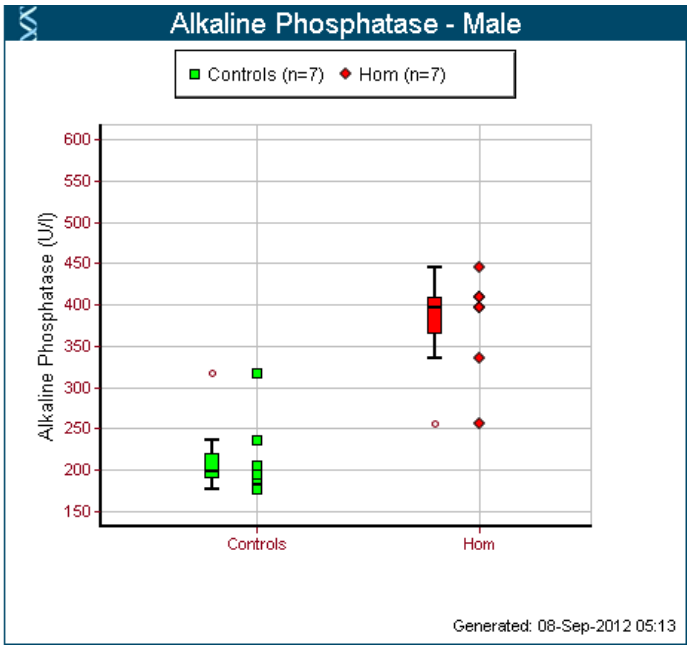
Males and Females - decreased circulating HDL cholesterol level [MP:0000186]



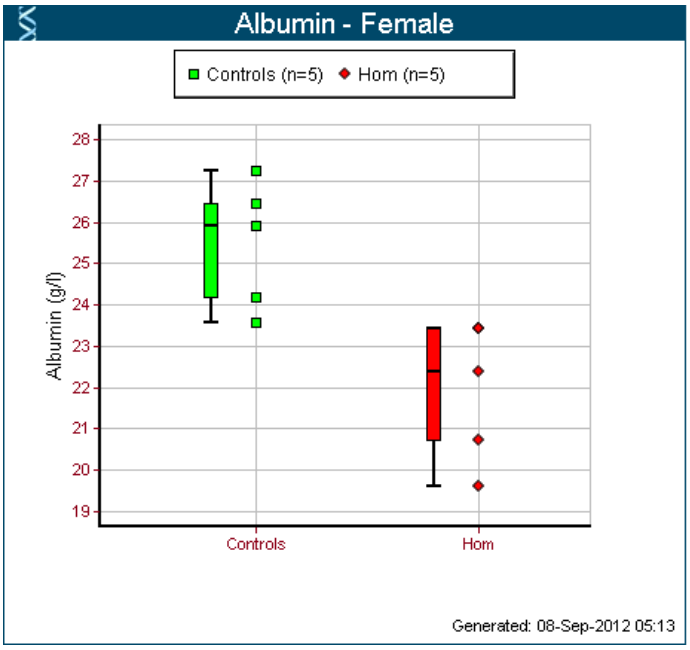


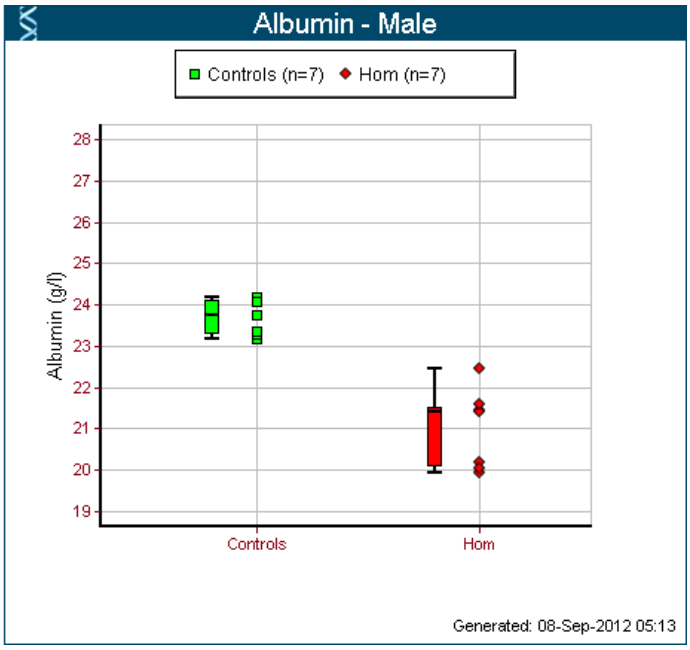
Males and Females - decreased circulating amylase level [MP:0008805]



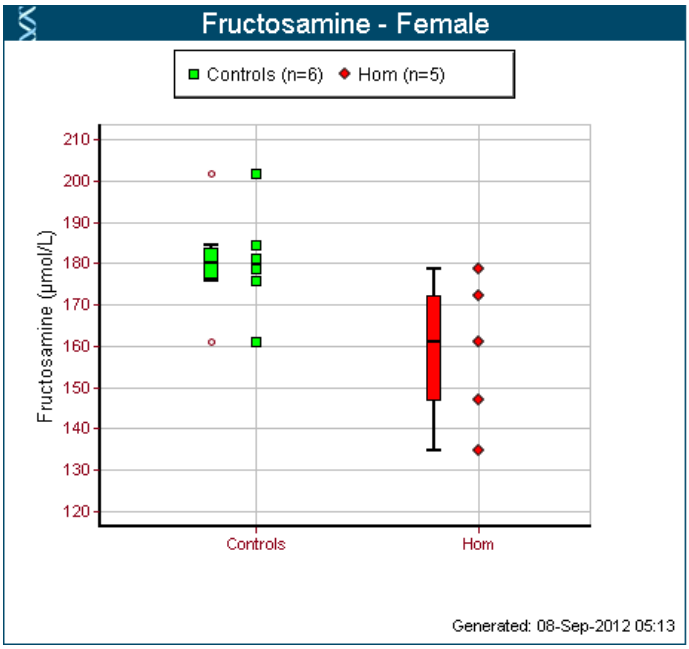


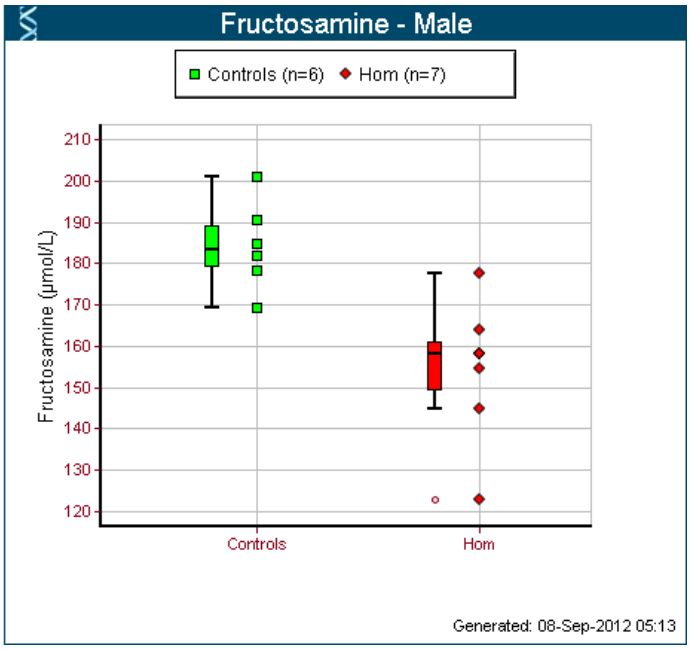
Males and Females - increased circulating alkaline phosphatase level [MP:0002968]



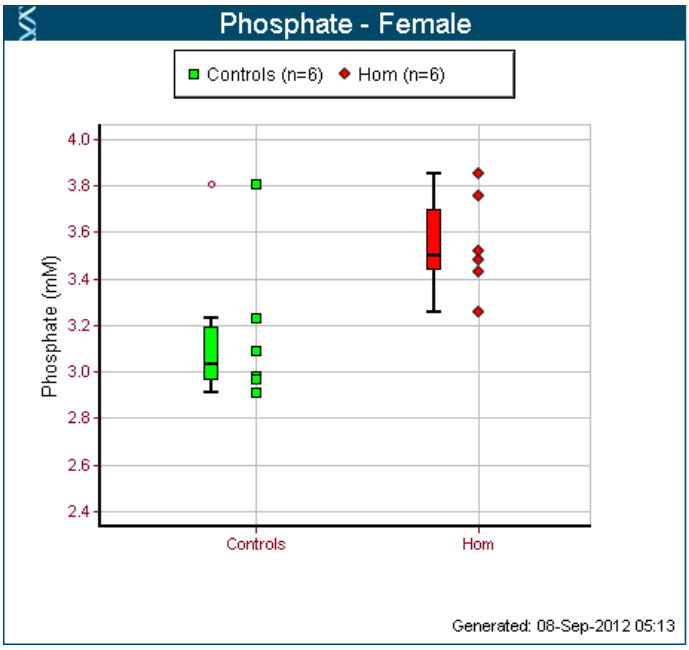


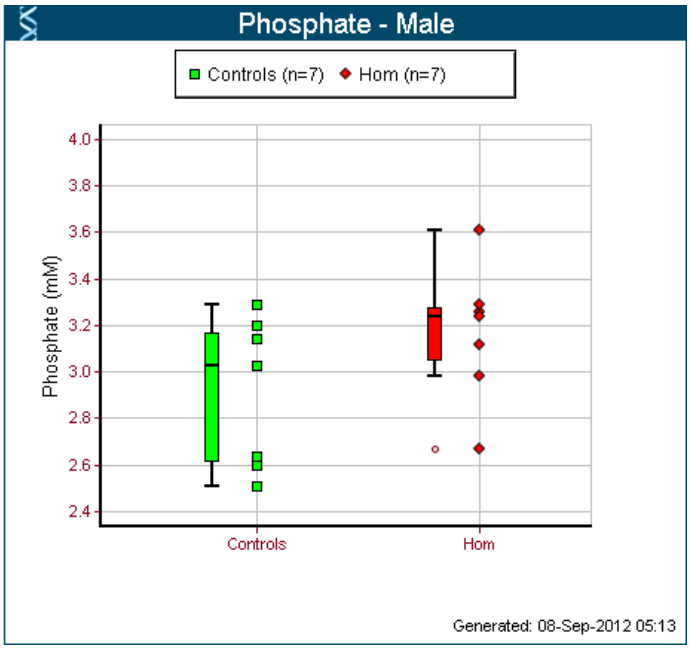
Males and Females - hypoalbuminemia [MP:0005419]



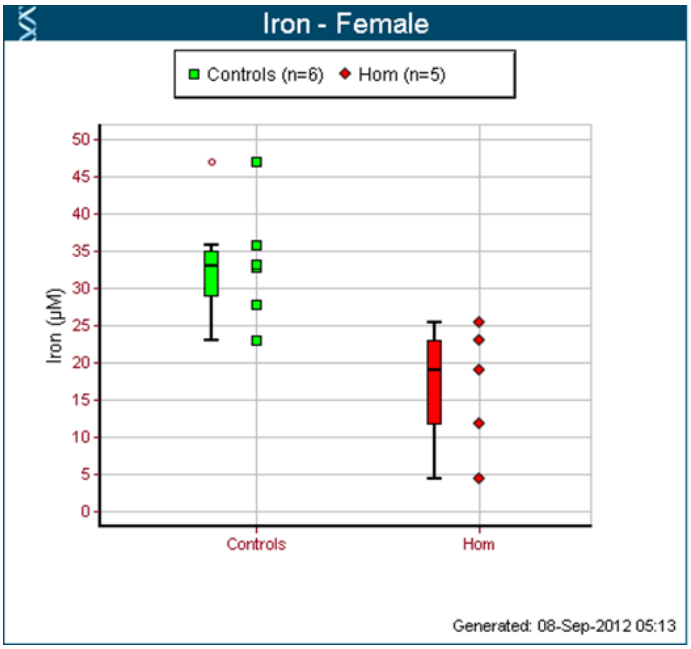


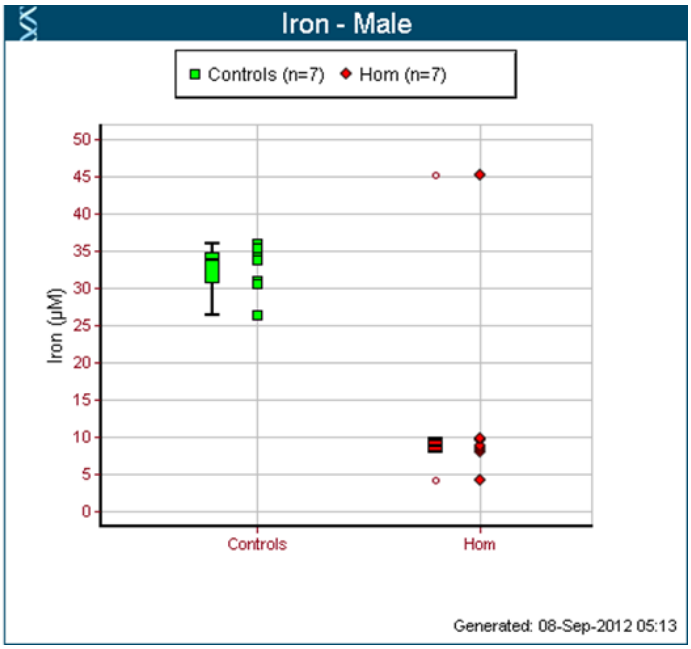
Males and Females - decreased circulating fructosamine level [MP:0010088]





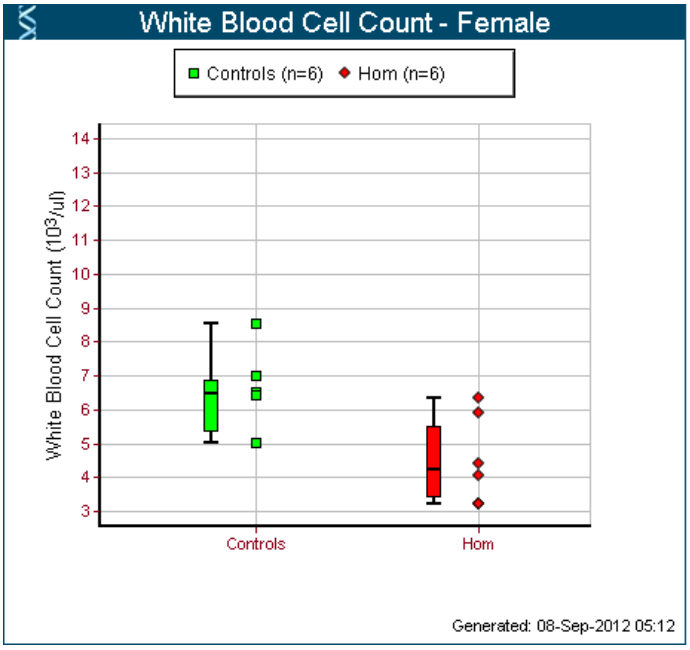
Females only - hyperphosphatemia [MP:0001566]

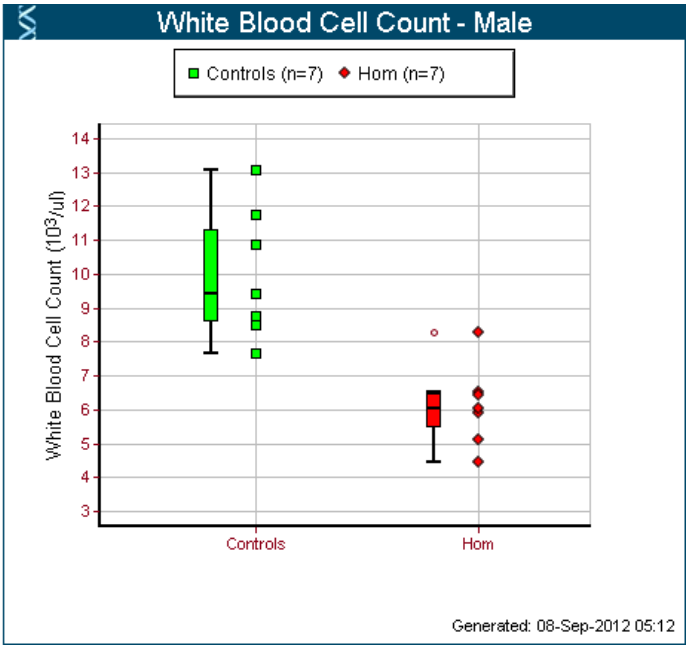




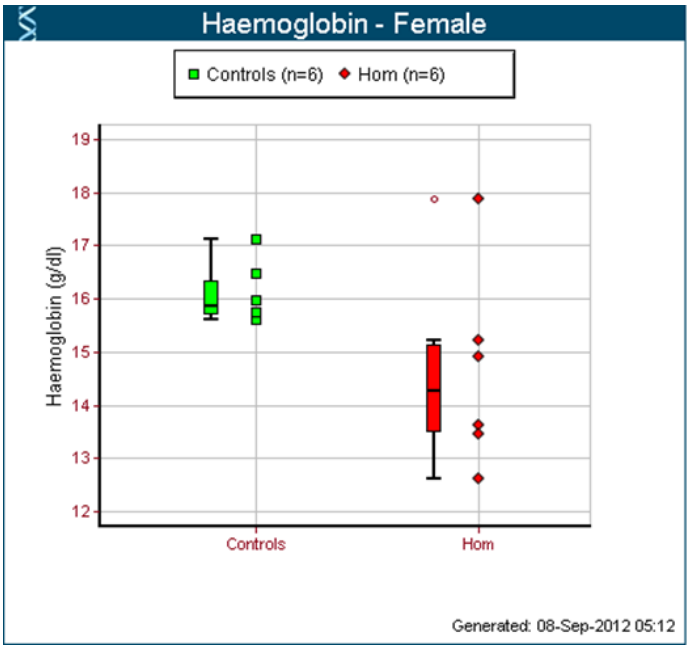
Males and Females - hypoferremia [MP:0004151]

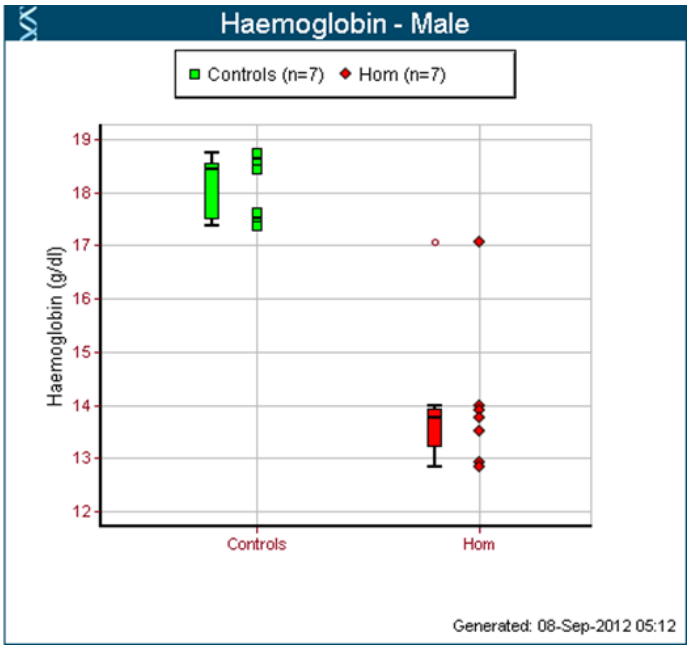
Haematology



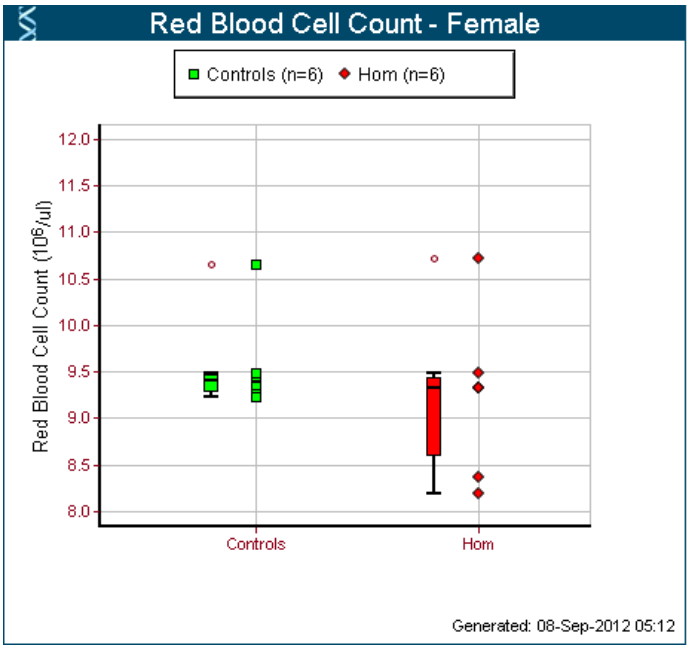


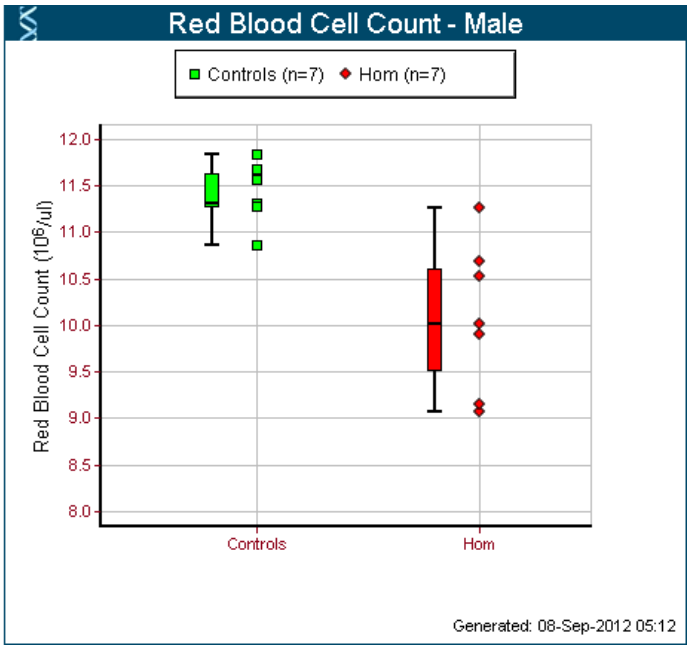
Males and Females - decreased leukocyte cell number [MP:0000221]



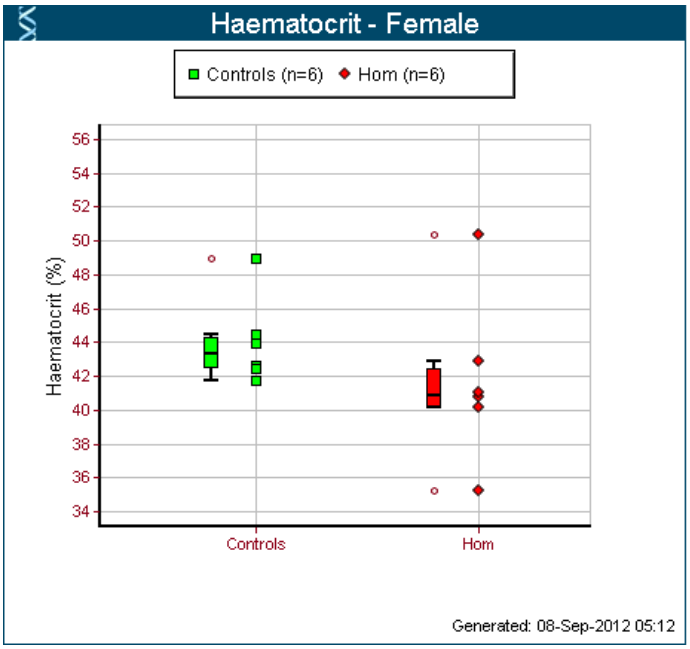


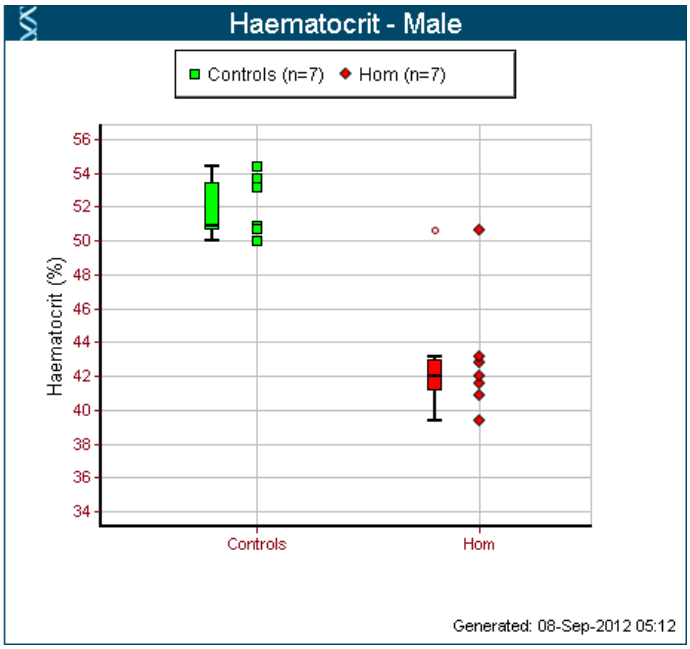
Males and Females - decreased hemoglobin content [MP:0002874]



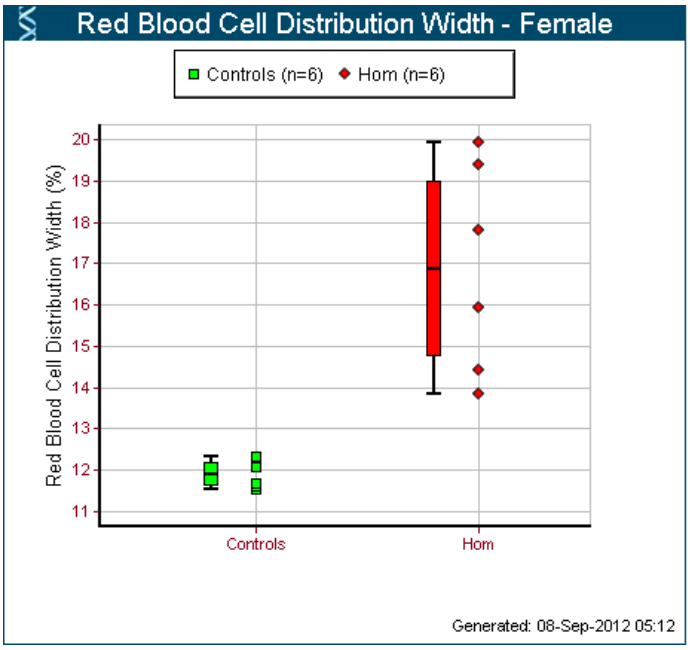


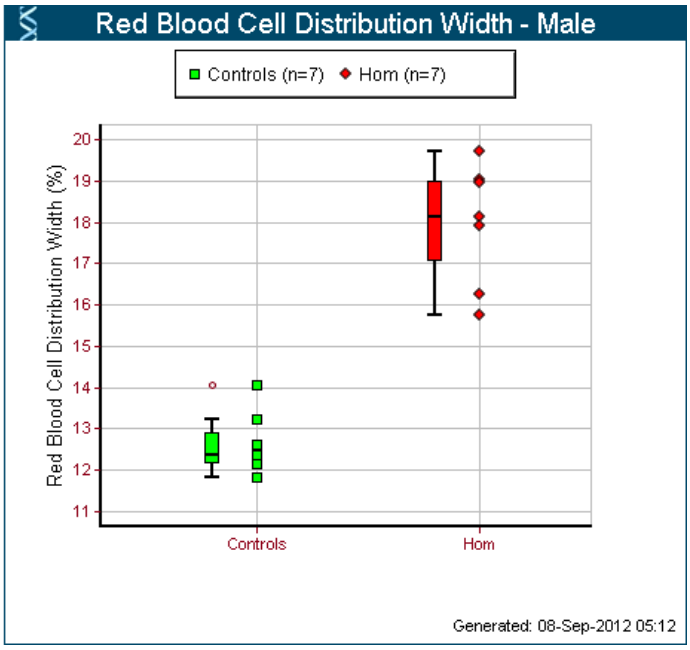
Males only - decreased erythrocyte cell number [MP:0002875]



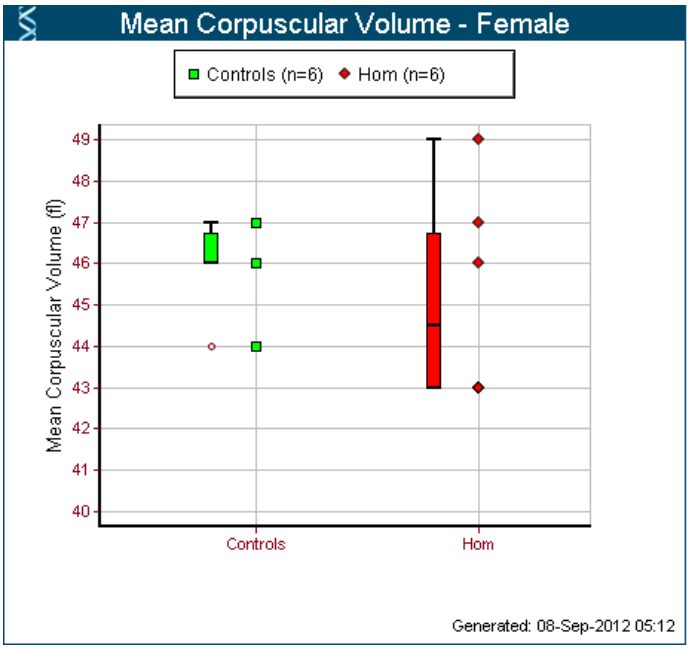


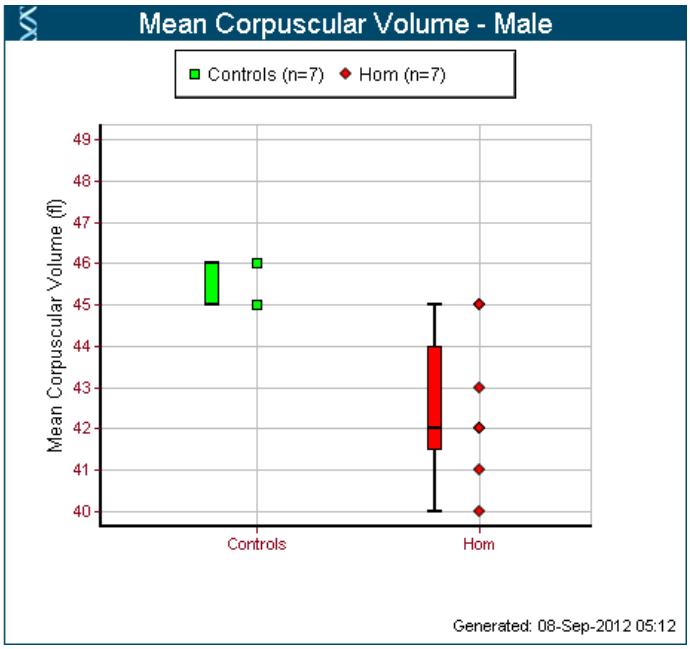
Males only - decreased hematocrit [MP:0000208]



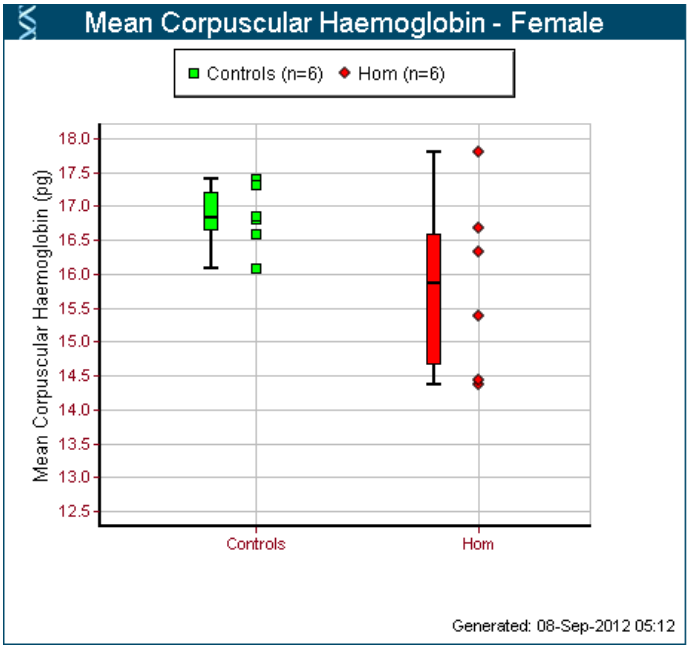


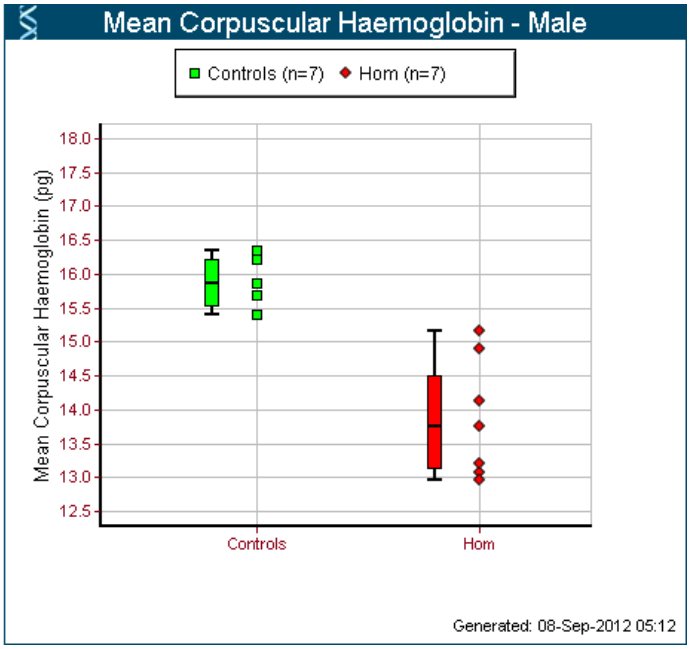
Males and Females - increased red blood cell distribution width [MP:0010067]



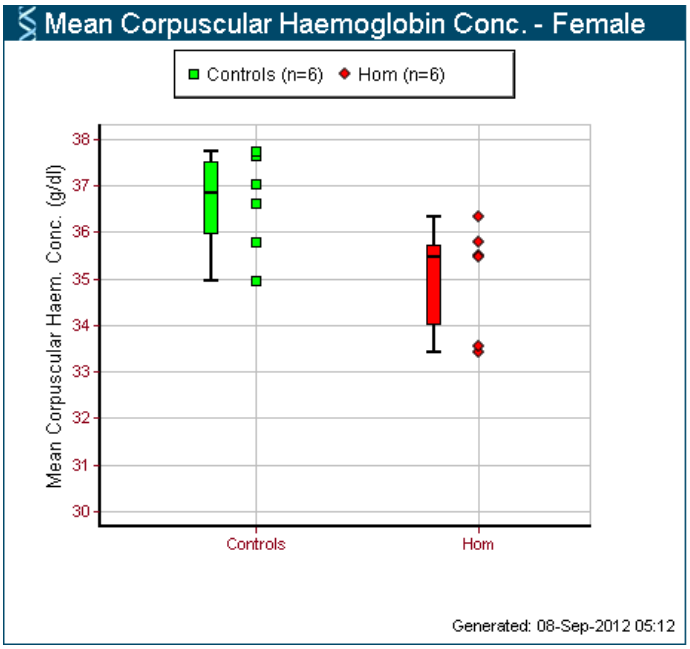


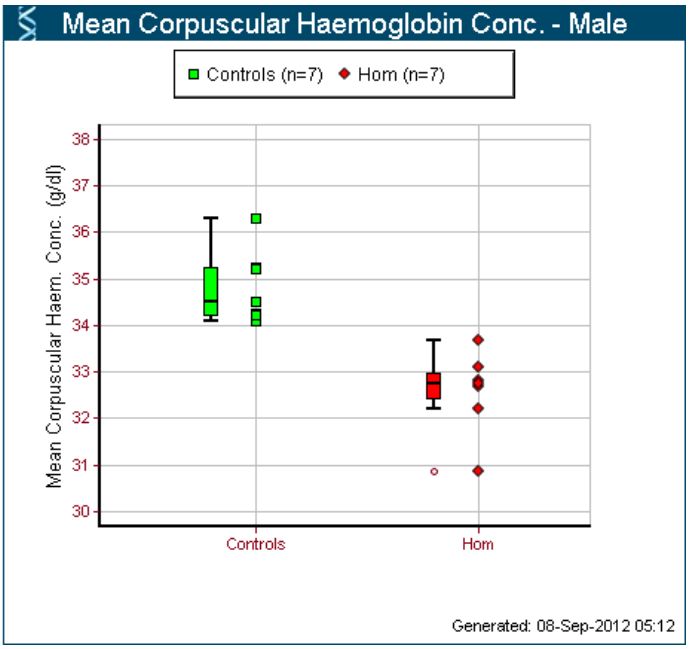
Males only - decreased mean corpuscular volume [MP:0002591]



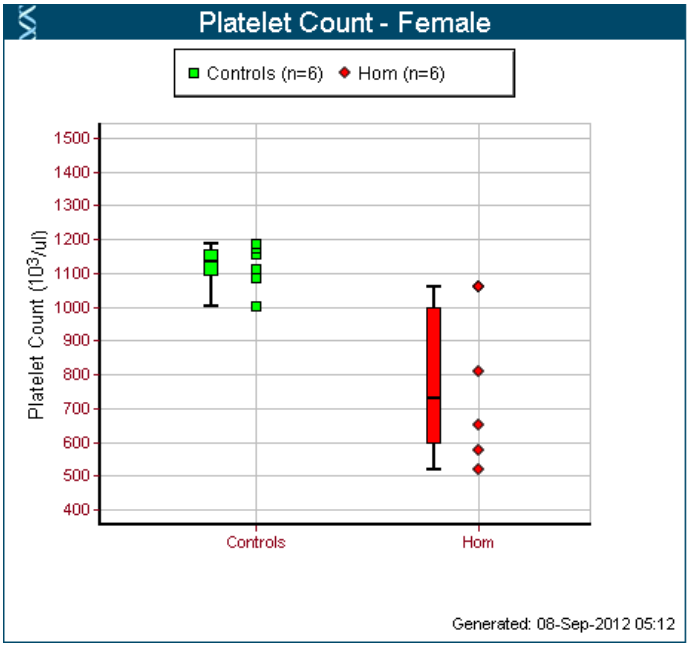


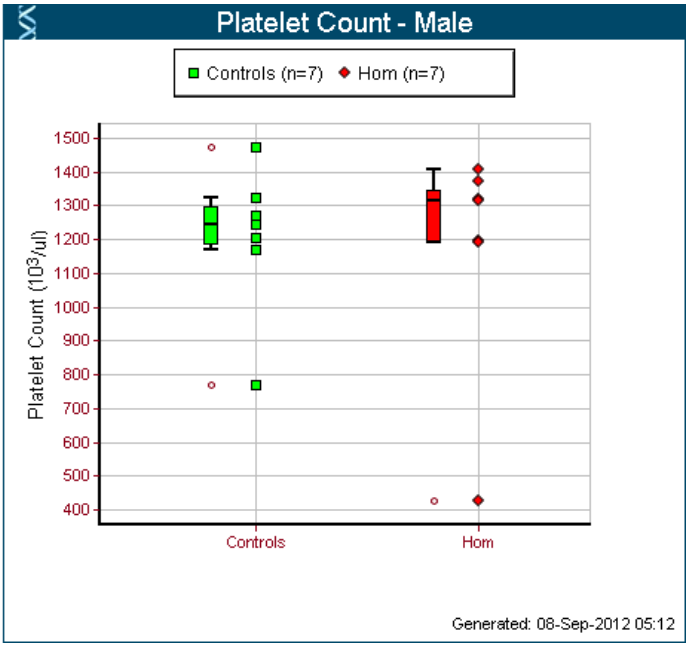
Males only - decreased mean corpuscular haemoglobin [MP:0005562]



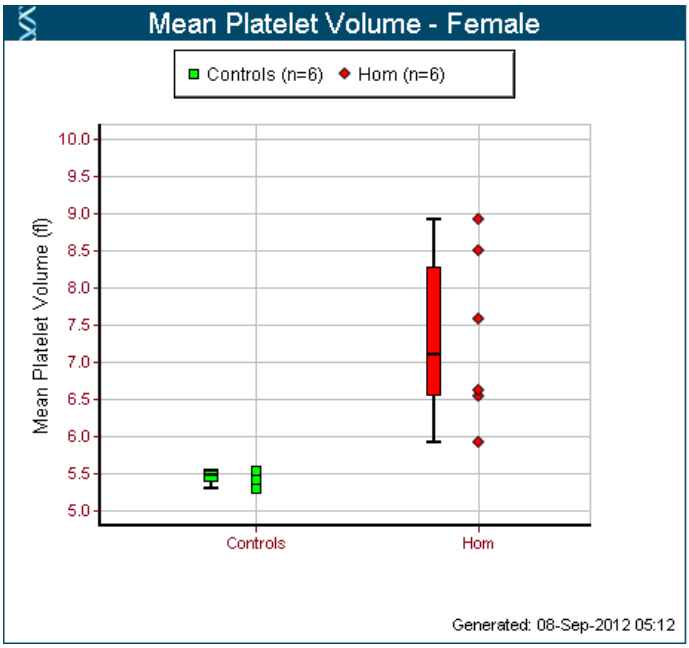


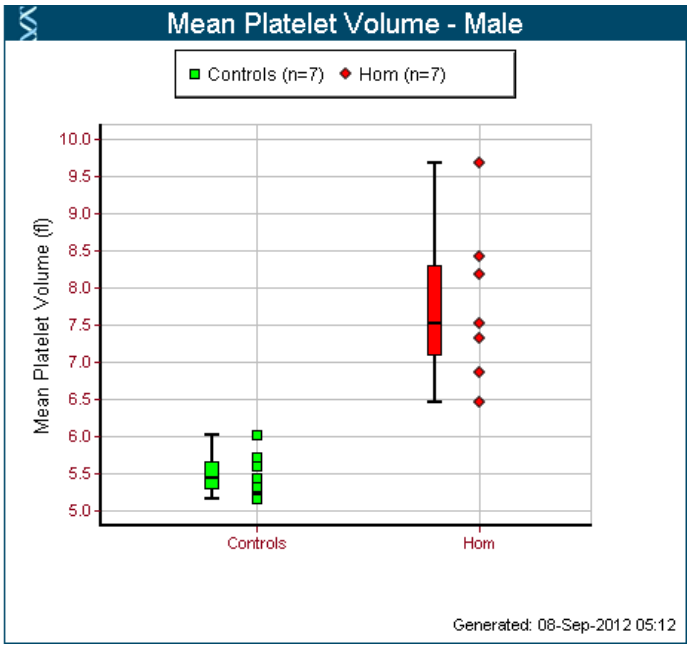
Males only - decreased mean corpuscular haemoglobin concentration [MP:0005642]





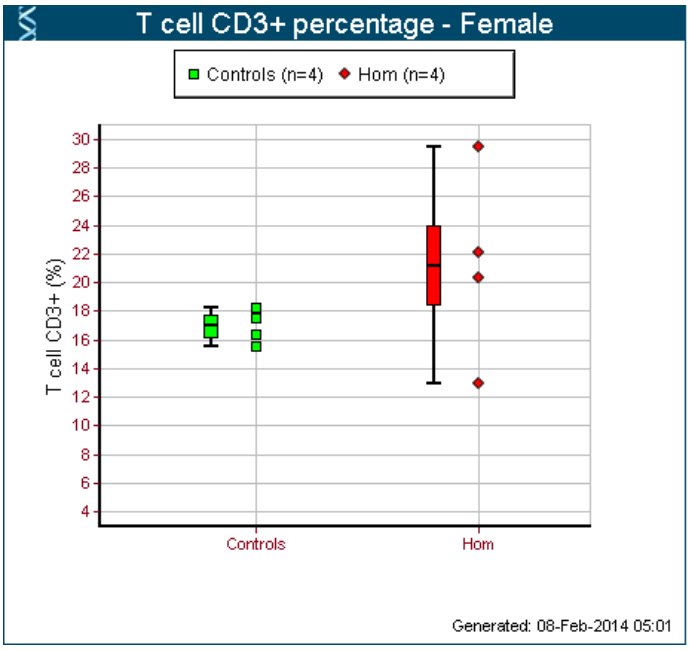
Females only - decreased platelet cell number [MP:0003179]

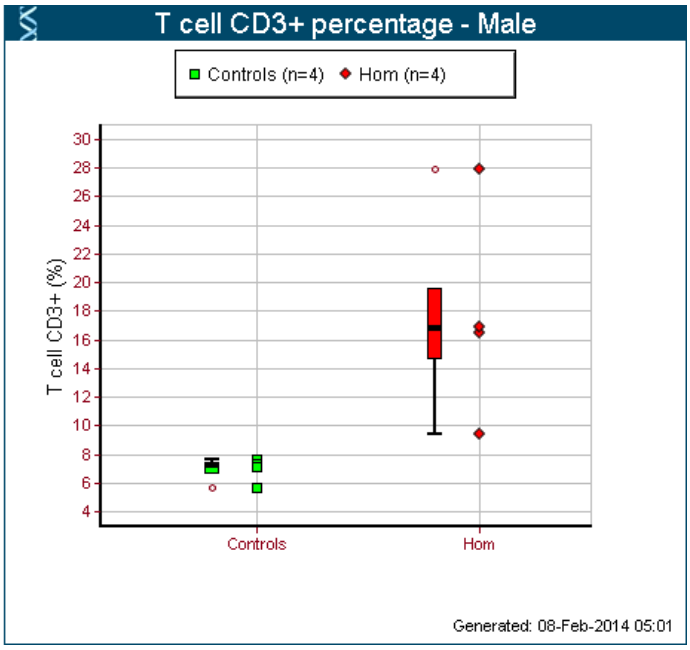




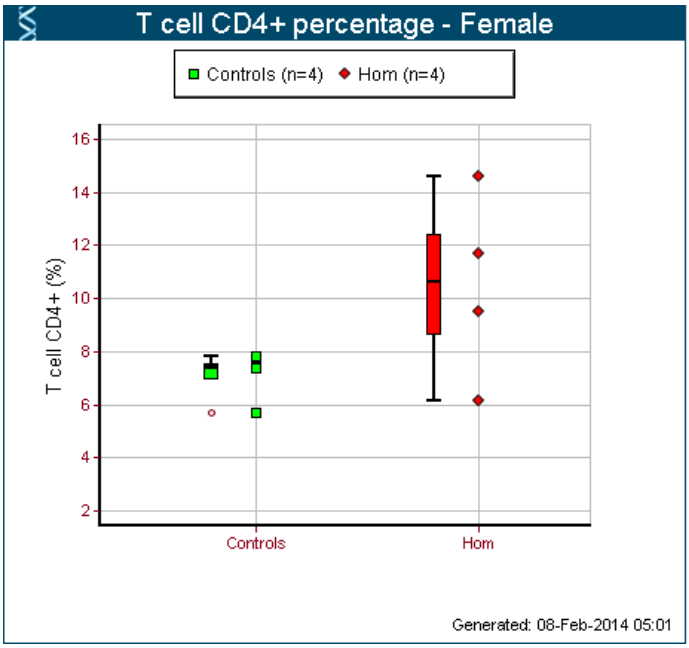
Males and Females - increased mean platelet volume [MP:0002599]

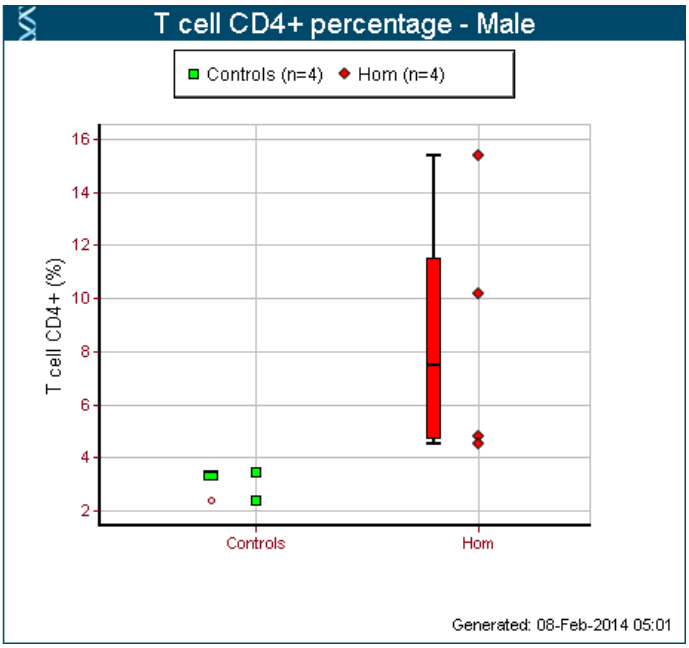
Peripheral Blood Leukocytes



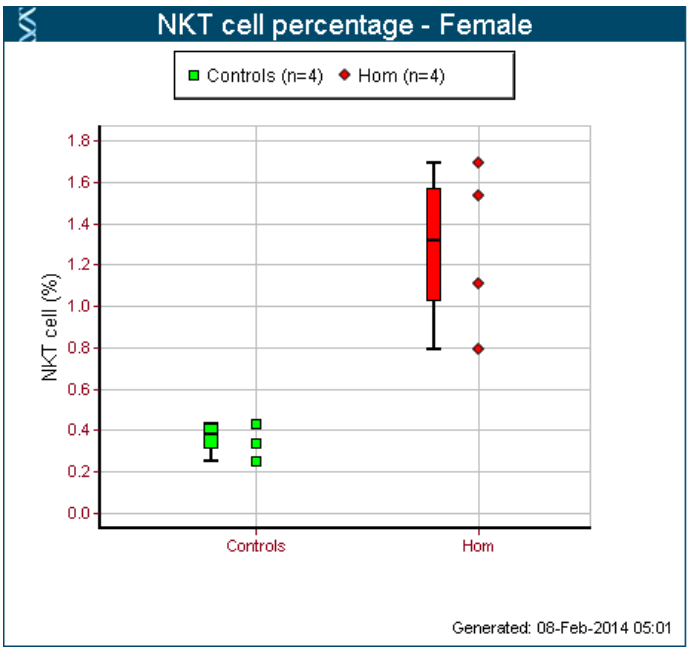


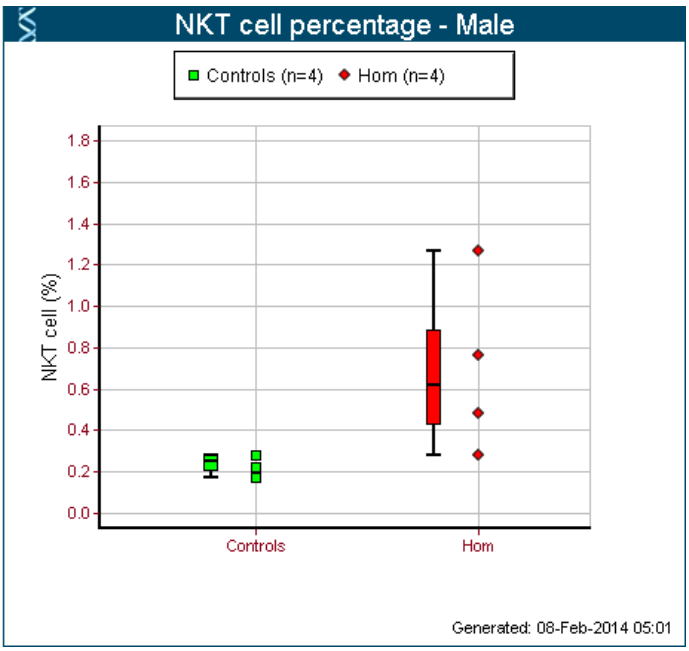
Males and Females - increased T cell number [MP:0005015]



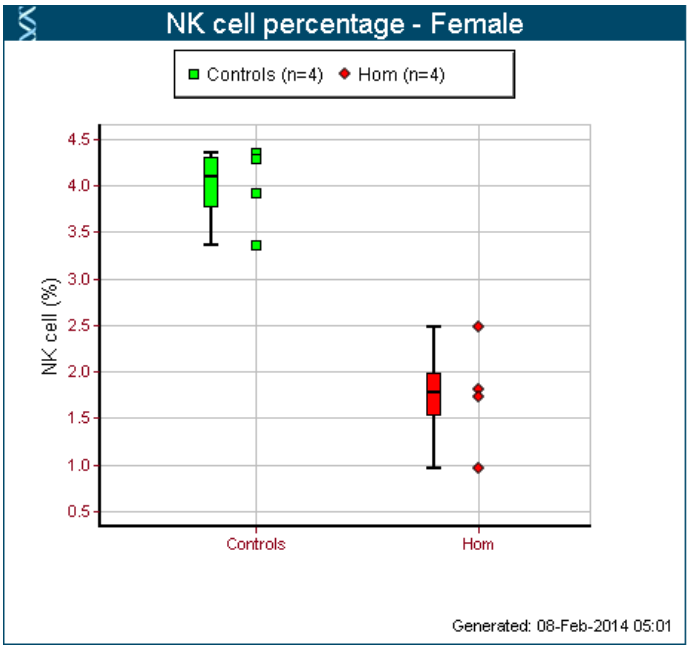


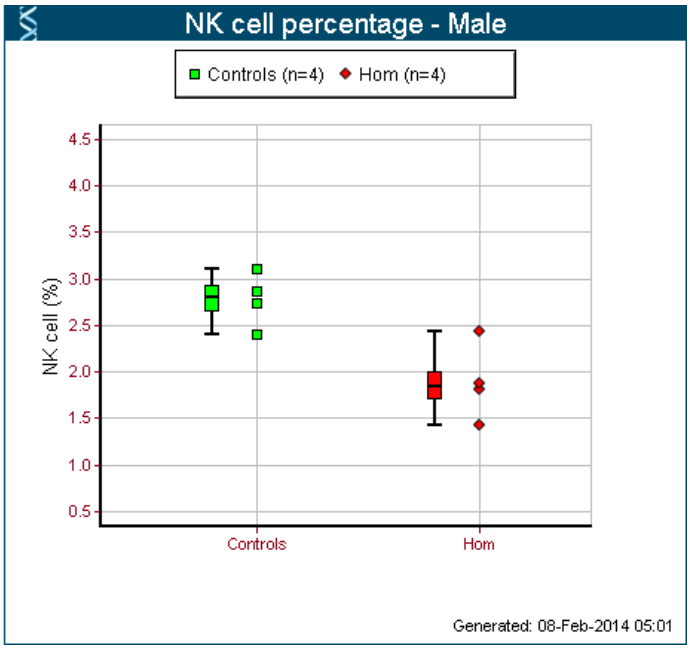
Males and Females - increased CD4+ T cell number [MP:0008074]



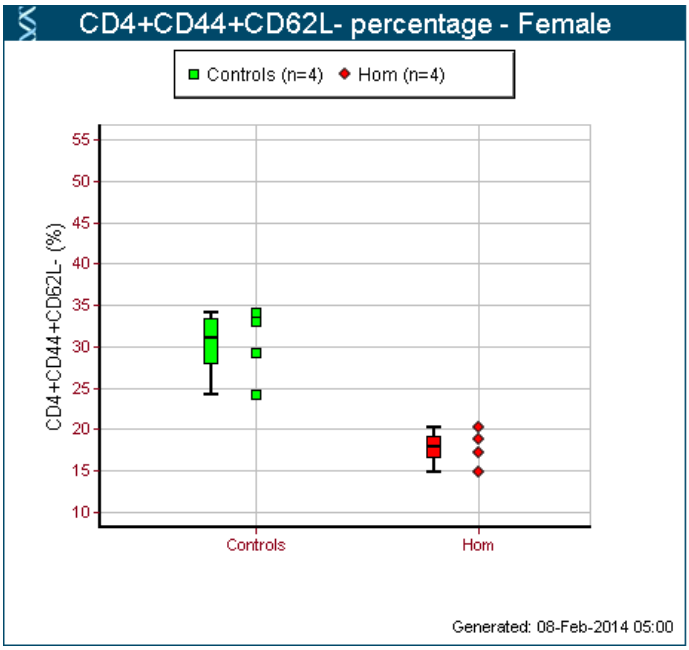


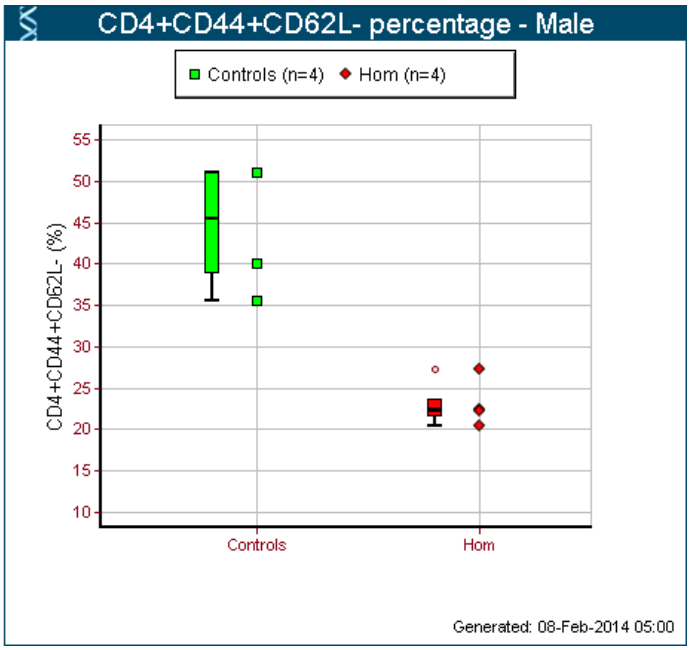
Males and Females - increased NKT cell number [MP:0008039]



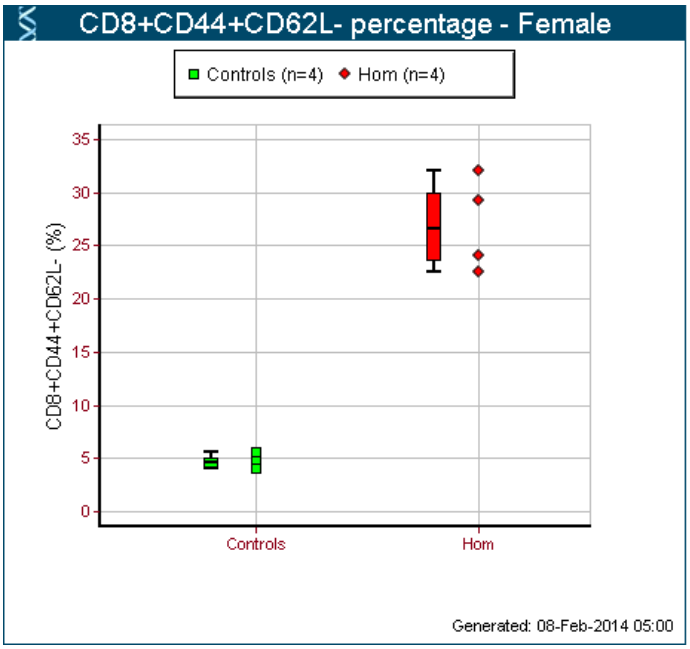


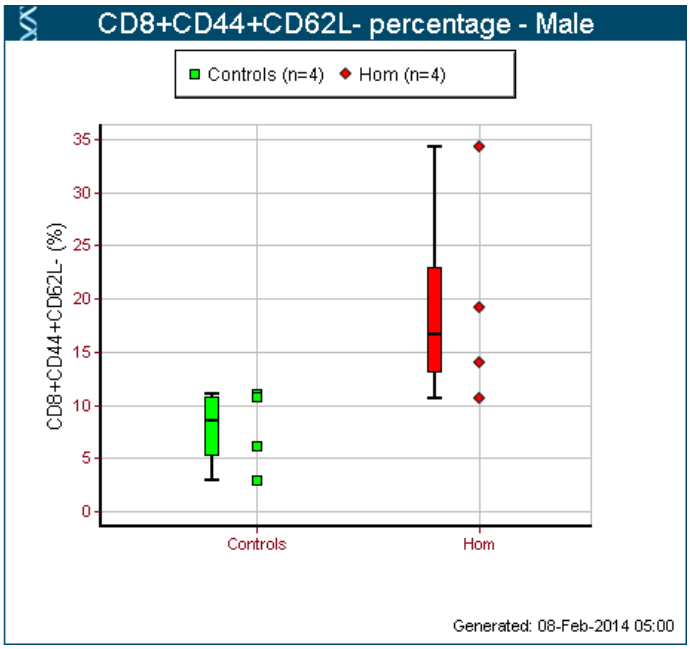
Males and Females - decreased NK cell number [MP:0008045]



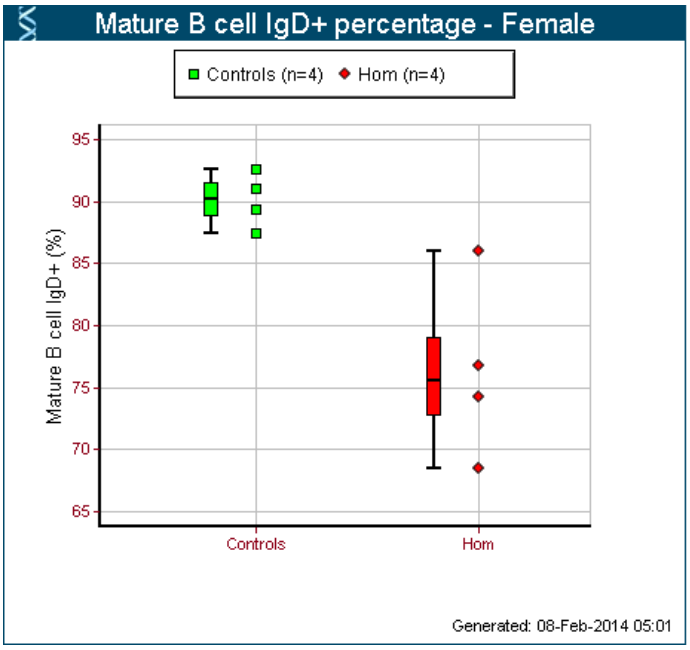


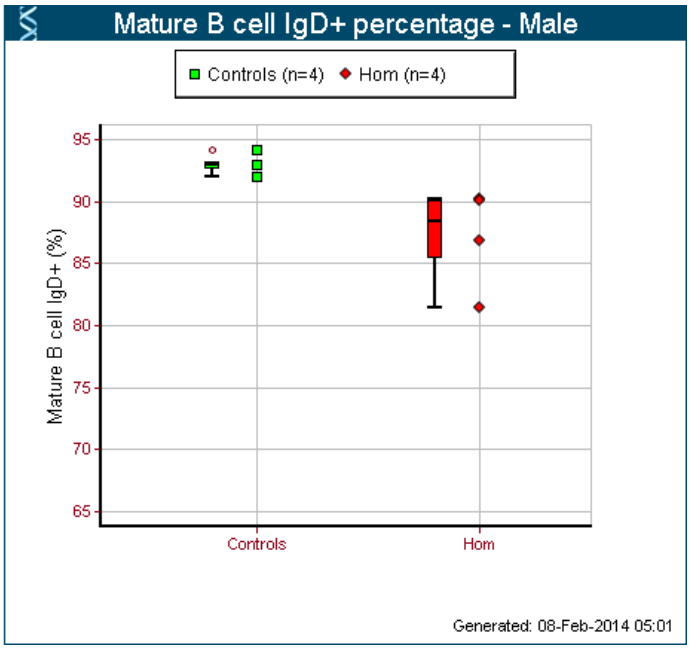
Males and Females - decreased CD4+ alpha beta memory T cell number [MP:0010836]



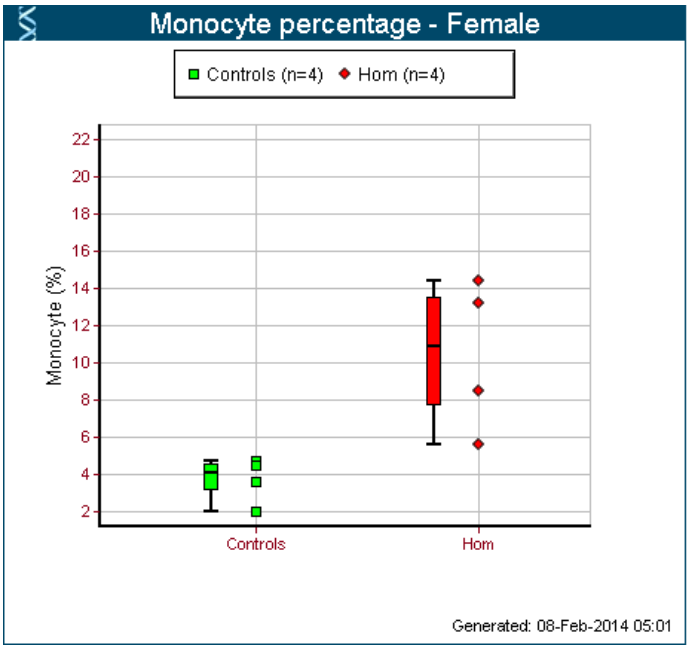


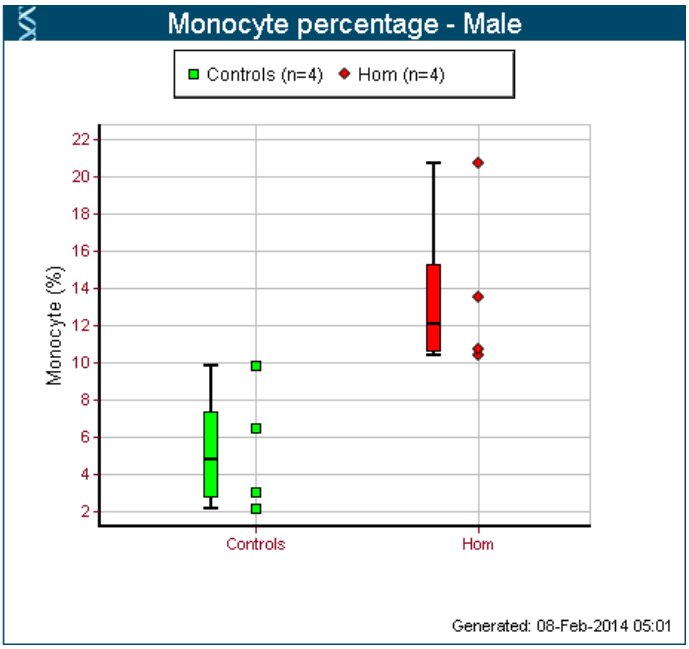
Males and Females - increased CD8+ alpha beta memory T cell number [MP:0010838]





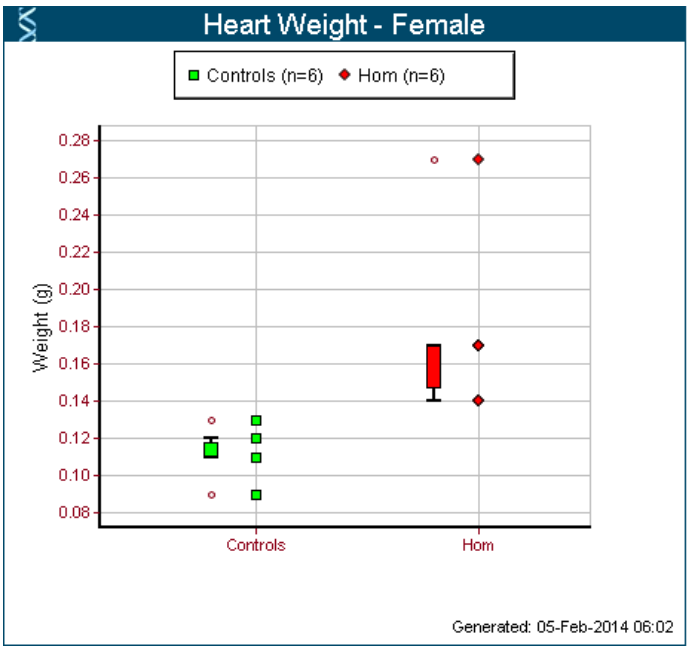
Males and Females - decreased mature B cell number [MP:0008211]

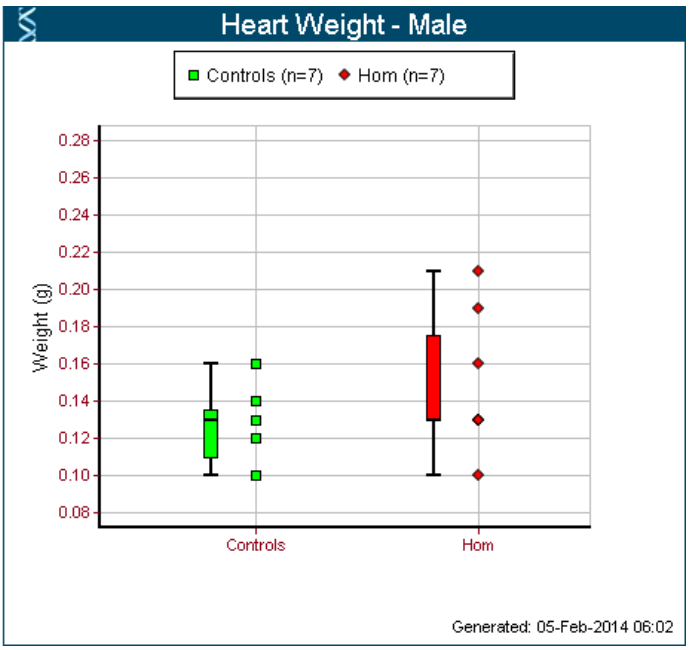




Males and Females - increased monocyte cell number [MP:0000220]

Necropsy observations





Females only – increased heart weight [MP:0002833]

Macroscopy observations in homozygote mice showed enlarged heart [MP:0000274] and enlarged spleen [MP:0000691].