

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.

Tk1^{tm1Brd}

Thymidine kinase 1

Genetic Background: C57BL/6N C57BL/6Ntac

Relevant section of sequence:

```

Wild-Type  105  AGGTGATTCTCGGGCCCATGTTCTCAGGGTAAAGGTTAATGAAGCTTTGGGCCTTCGGGG 164
           |||
Tm1Brd    105  AGGTGATTCTCGGGCCCATGTTCTCAGGGAAAAGGT-AATGAA----TGGGCCTTCGGGG 159

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This is a non-standard allele created by transposon excision rather than a cassette insertion. Alterations were made at base pairs 134, 141 and 148-151 as annotated by XM_006533150 (according to [NCBI](#)).

Affected genotypes

Homozygous (Tk1^{tm1Brd})

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:

- 3/3 litters born to homozygous parents were found dead between Po-P10 (100%) [MP:0011100].
- Rapid welfare deterioration [MP:0008770].

Colony mice (irrespective of genotype) exhibit:

- Increased loss before weaning 213/898 (23.7%) [MP:0011110].
- Of those lost before weaning, increase in deaths due to being culled sick, found dead or missing 168/213 (78.8%). The majority of these due to being found dead 149/213 (70%) [MP:0011110].

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*]

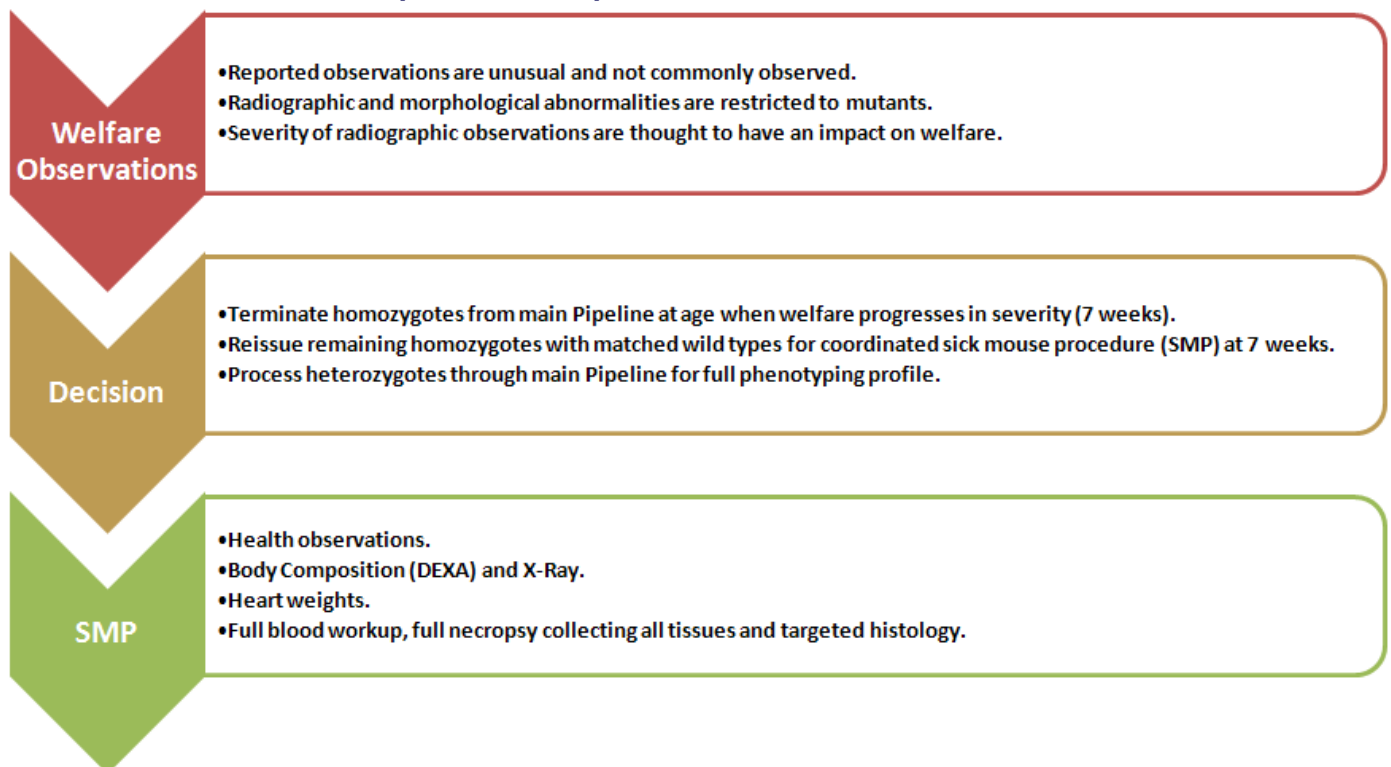
- **Subviable** : 33 Homs / 337 Total = 9.79%

Sick Mouse Procedure (SMP)

Initial welfare observations were reported when the homozygotes were noticed to have a reduced survival rate during the pipeline. Homozygotes were still viable when issued to the phenotyping pipelines (4 weeks), but severity progressed around 7 weeks of age.

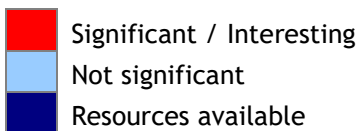
Welfare observations in homozygotes described above progressed to moderate severity around 7 weeks of age upon which SMP (see schematic below) was initiated. Six male and 7 female homozygotes were processed alongside 7 male and 7 female matched wild-types. No further homozygotes were phenotyped due to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

Schematic Outline of Bespoke SMP Pipeline



Phenotyping Heat Map

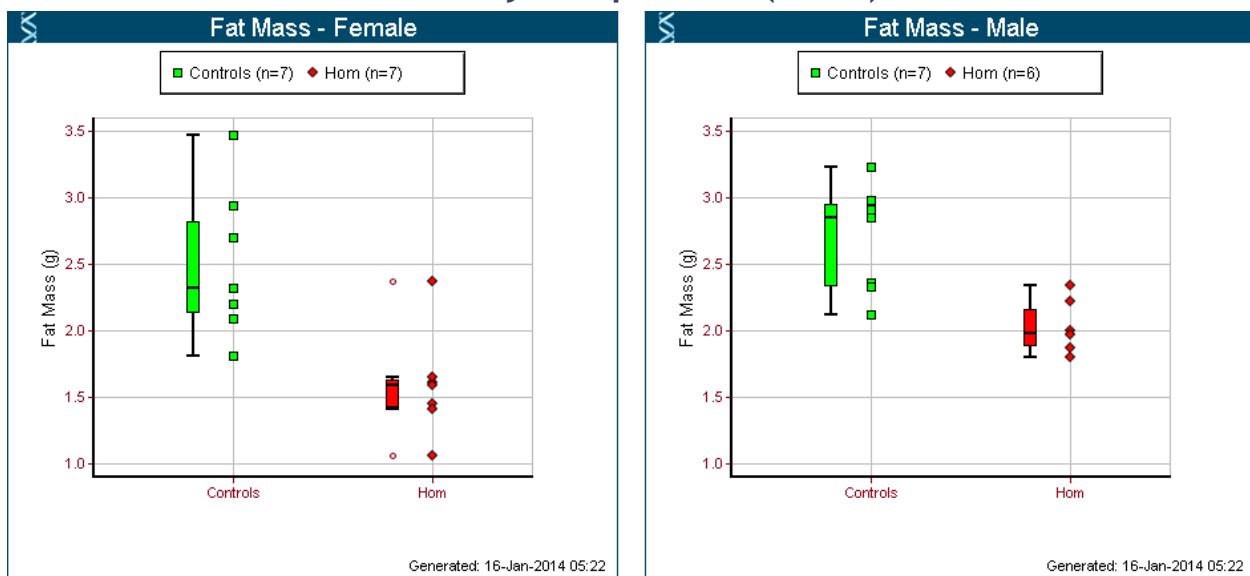
Colony Prefix	Allele Name	Genotype	Weight Curves	Body Composition (DEXA)	X-ray Imaging	Plasma Chemistry	Haematology (CBC)	Heart Weights	Peripheral Blood Leukocytes	Tissue Biobank
MTKB	Tk1tm1Brd	Homozygous	Not significant	Significant / Interesting	Not significant	Significant / Interesting	Significant / Interesting	Not significant	Significant / Interesting	Resources available



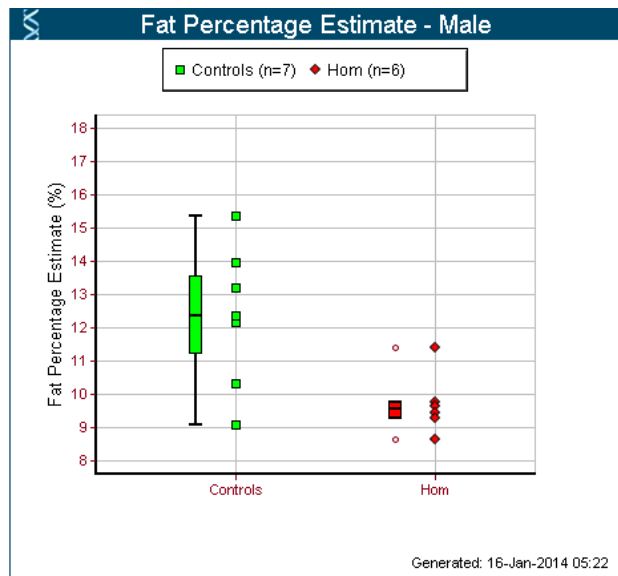
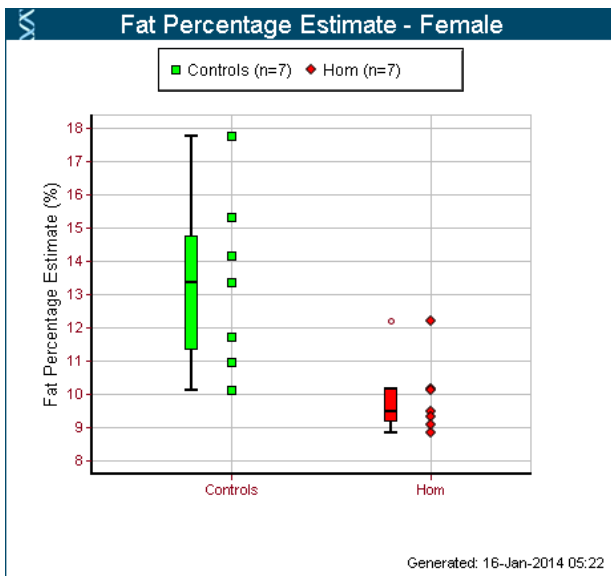
Phenotyping data of interest (significant changes)

In life phenotyping

Body Composition (DEXA)



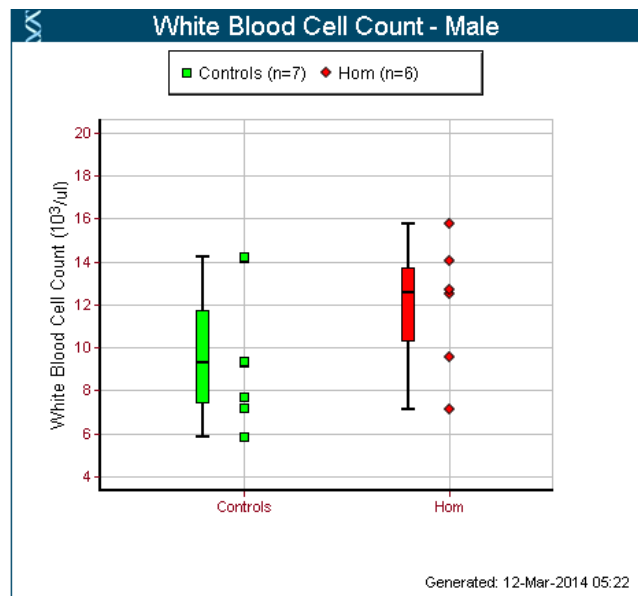
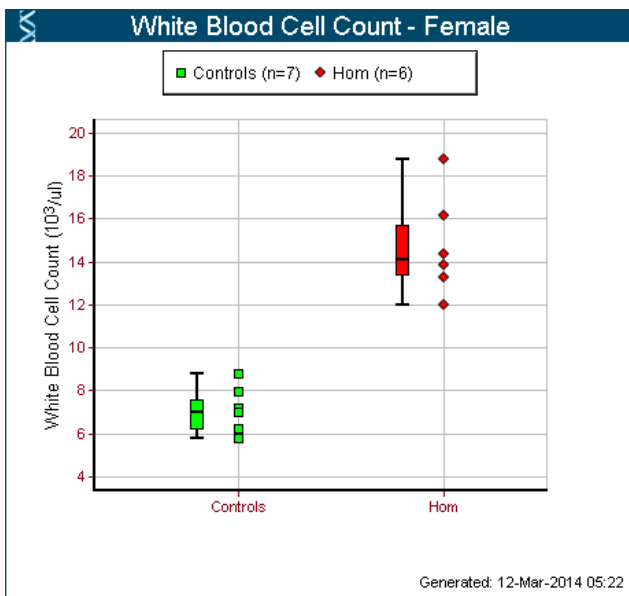
Males and females – decreased total body fat amount [MP:0010025]



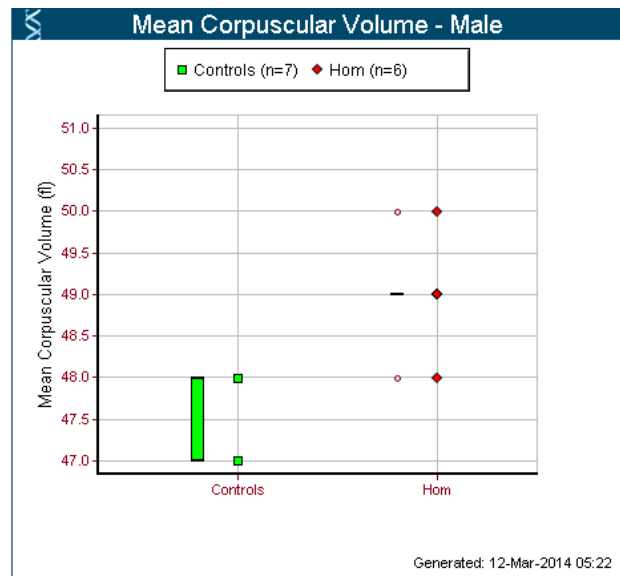
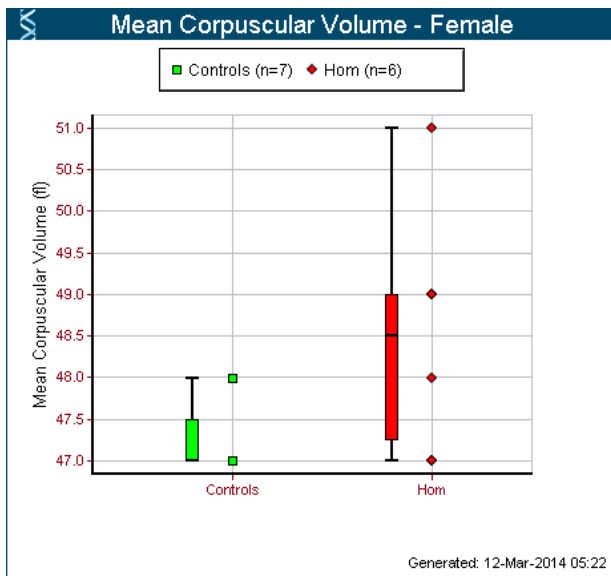
Males and females – decreased percent body fat [MP:0005459]

Ex Vivo Phenotyping

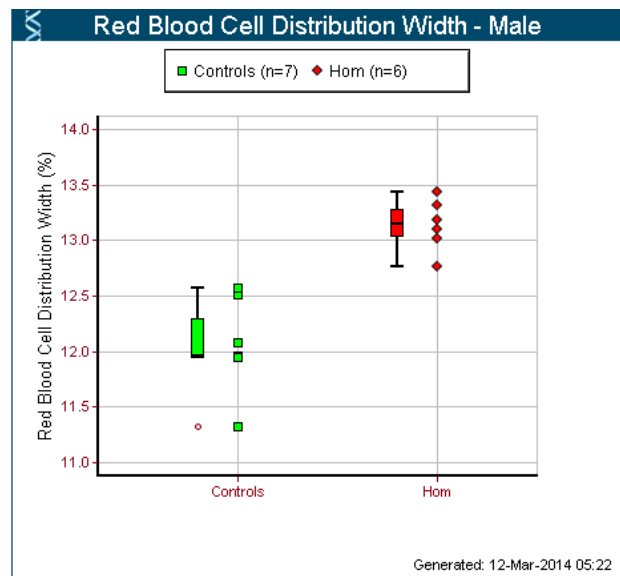
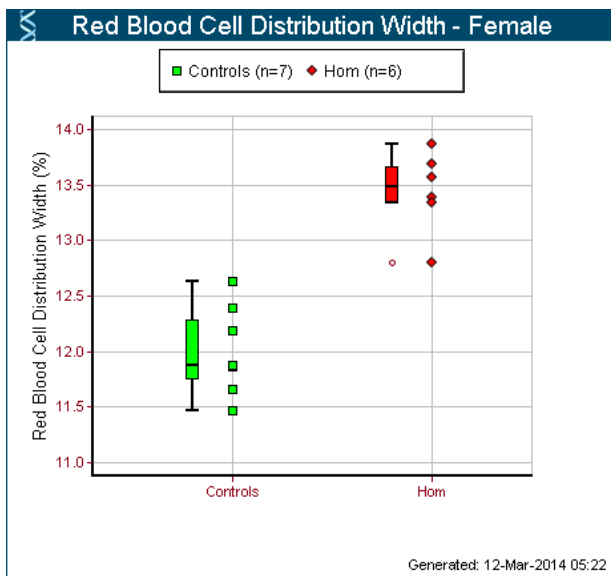
Haematology



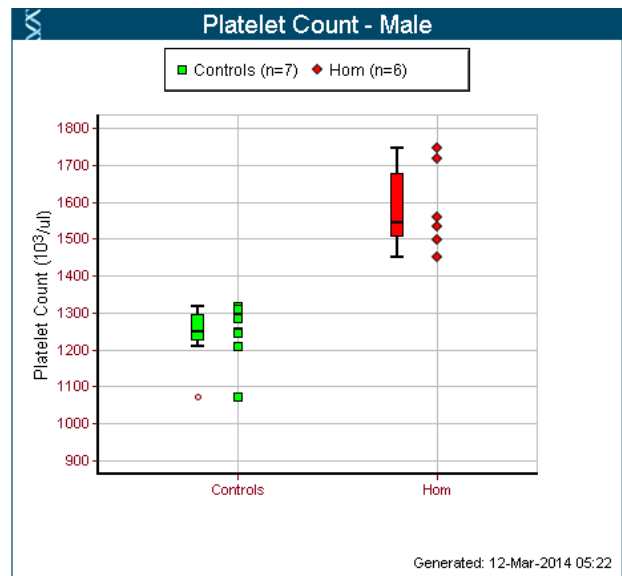
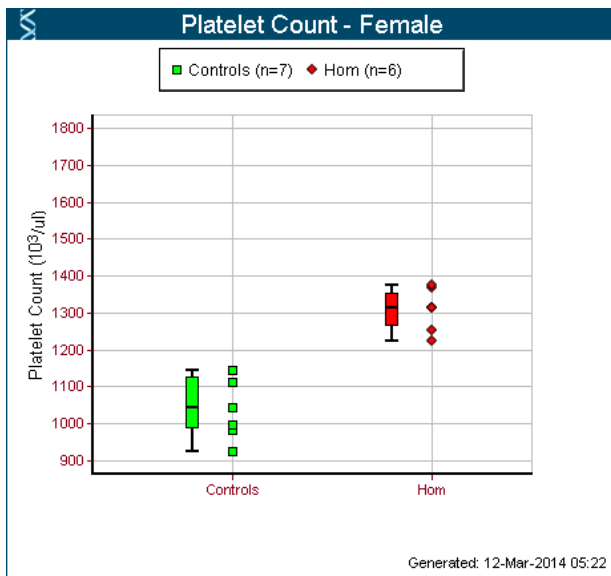
Females Only – increased leukocyte cell number [MP:0000218]



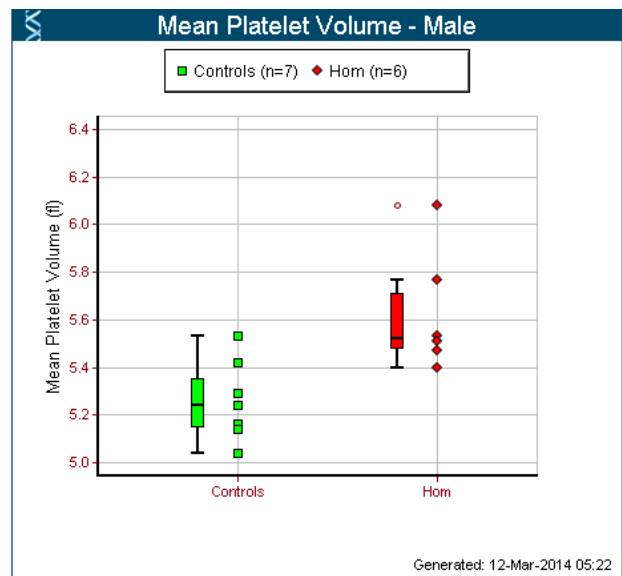
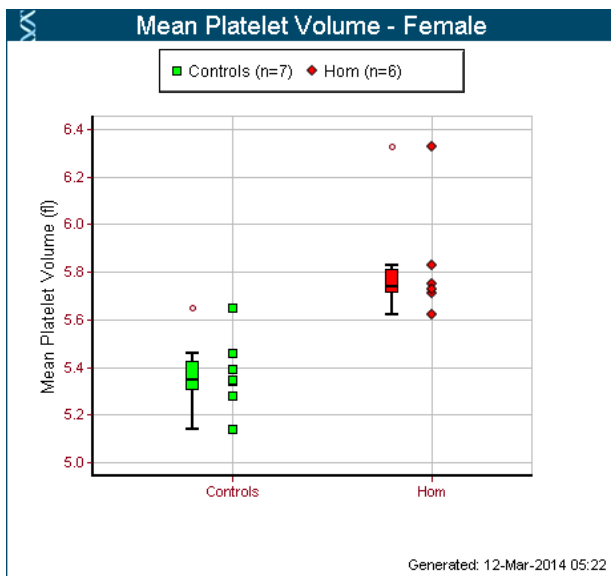
Males and females – increased mean corpuscular volume [MP:0002590]



Males and females – increased red blood cell distribution width [MP:0010067]

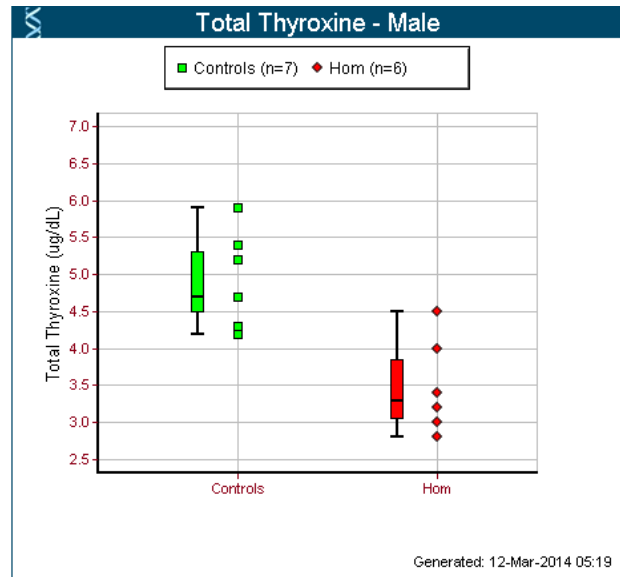
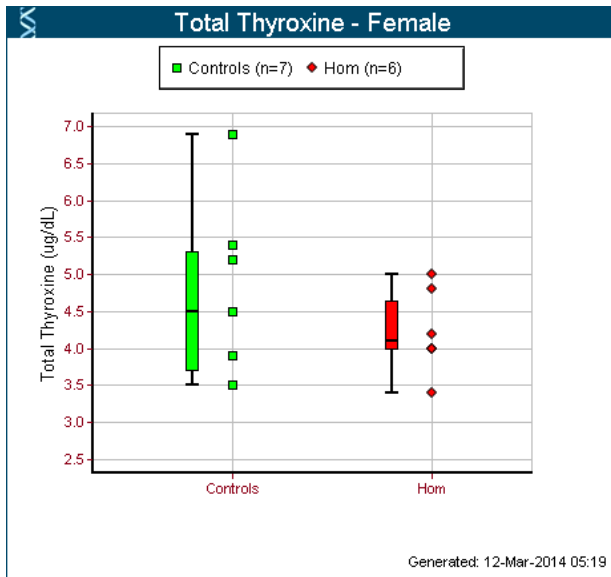


Males and females – increased platelet cell number [MP:0005505]



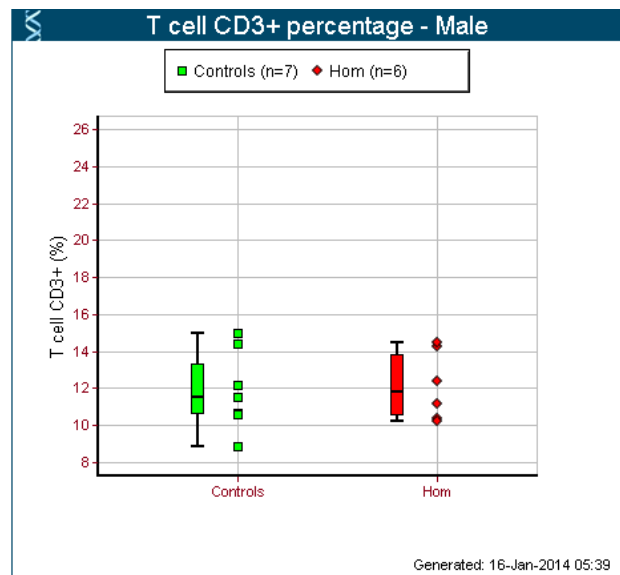
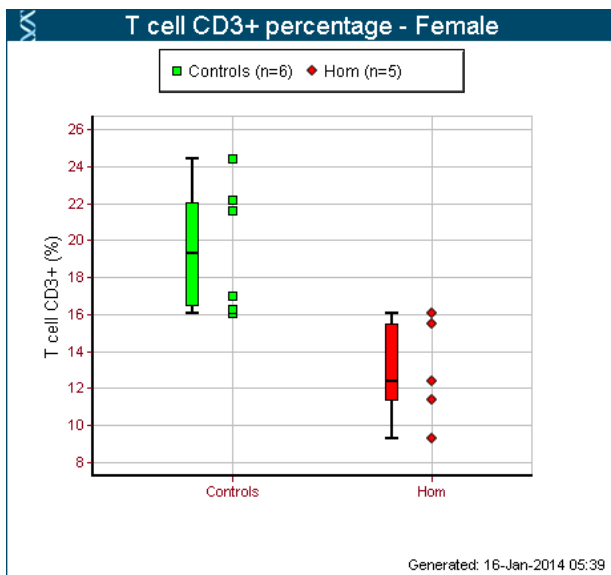
Males and females – increased mean platelet volume [MP:0002599]

Plasma Chemistry

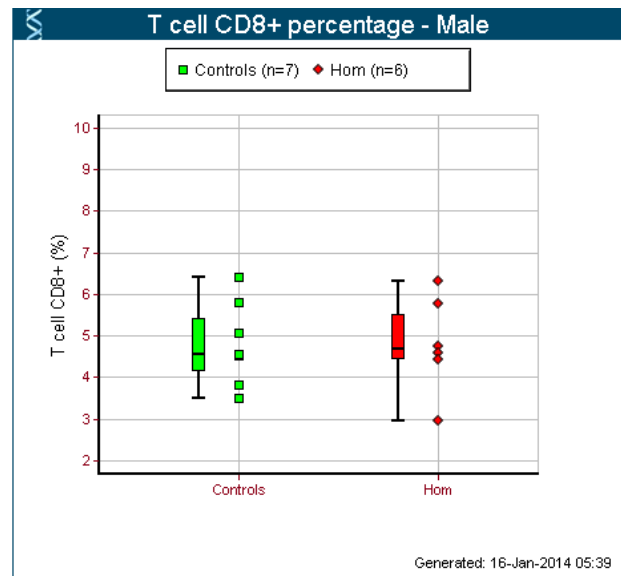
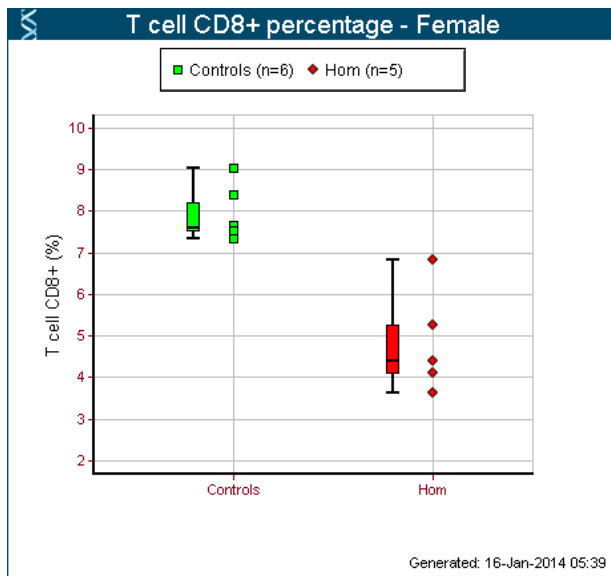


Males only – decreased circulating thyroxine level [MP:0005478]

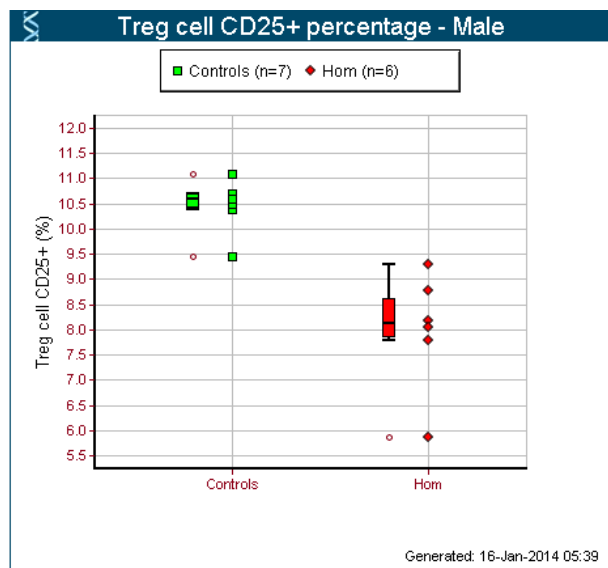
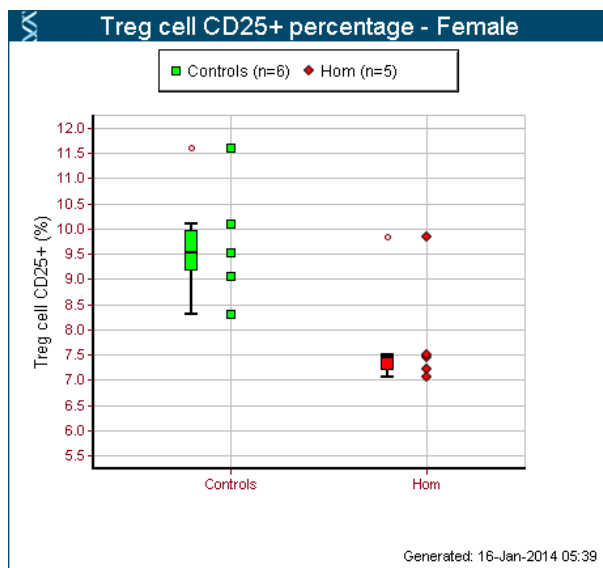
Peripheral Blood Lymphocytes



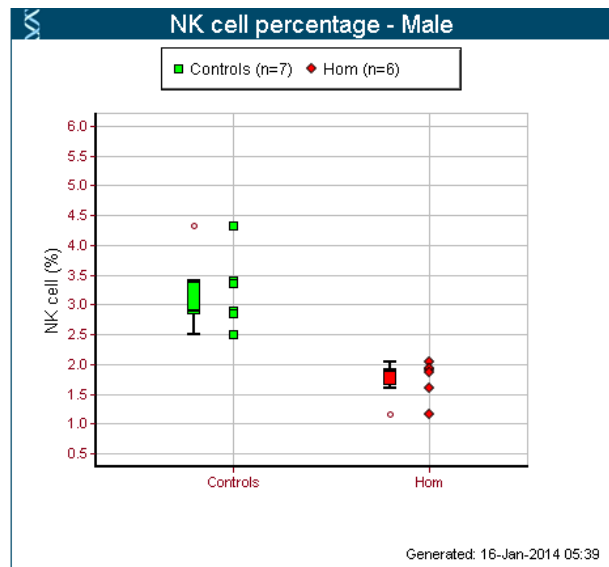
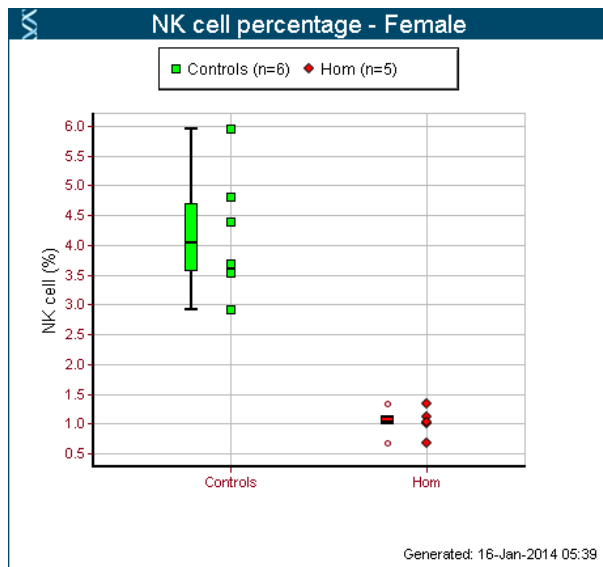
Females only – decreased T cell number [MP:0005018]



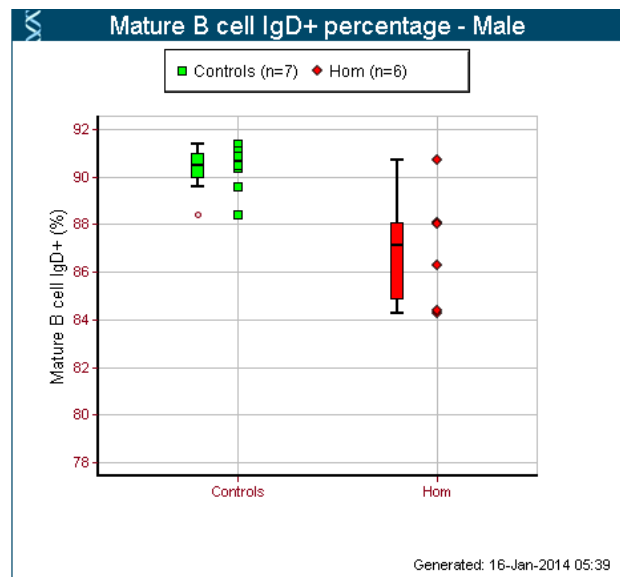
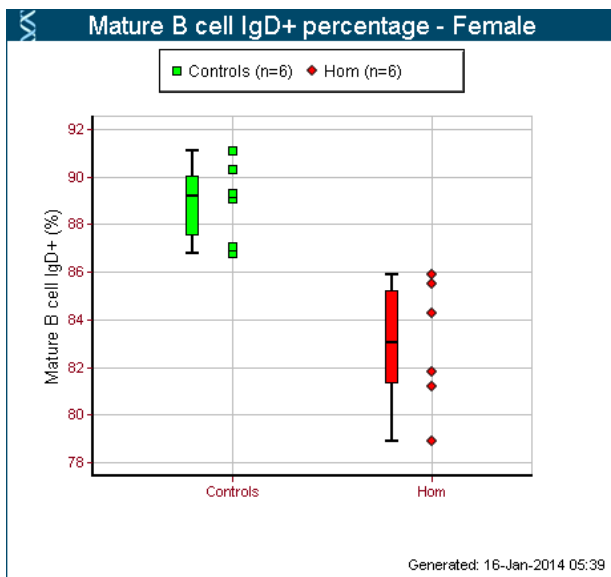
Females only – decreased CD8-positive T cell number [MP:0008079]



Males and females - decreased regulatory T cell number [MP:0010169]



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



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

Necropsy observations

Small amounts of white adipose tissue and small amounts of brown adipose fat or none at all 2/11 homs both culled sick (18%) [MP: 0001783] [MP: 0001780].