Home Office

FD-S 221603

PPL Standard Condition 18 Notification Form

Please use this form to notify the Animals in Science Regulation Unit (ASRU) of procedural-related adverse effects that have exceeded or are likely to exceed the severity limitations or controls described in the project licence. ASRU will use this information to determine whether any further action is required.

Do not use to report:

- adverse effects that are due to non-procedural issues;
- potential non-compliance (report by other means);
- issues without adverse welfare consequences.

If you are in doubt whether or not you need to fill in this form, please contact your assigned Inspector.

Please clearly title your document: **'ASRU_establishment name_PPL number_PPLh surname_date_sc18'** and send to your Inspector (e.g. using cjsm) with the subject heading 'PPL SC 18 Notification PPL [Number]

Establishment Licence name	University of Cambridge
Establishment Licence number	X81BD37B1
Name of PPL holder	Maria P. Alcolea
PPL number	PP7037913
Protocol no	06
Protocol title	Changes in epithelial cell behaviour over time
Severity classification	Moderate

1. Date of incident	24/06/2022
2. Species	Mouse
3. Brief details of study and how the limits or constraints have been breached	In study plan SP127897, a litter of 7 animals was administered a transgene inducing agent (tamoxifen) subcutaneously, at postnatal day 8 (15th June). Animals were going to be collected at different time points after induction, after weaning. However, nine days after tamoxifen induction, four of the pups (animal IDs: M00823626, M00823628, M00823629, M00823630) were found dead and partially cannibalised. These animals were in the same cage as two pups that had been reported to be found dead on the 14th June also cannibalised by one of the two female breeders (the male had been separated).
4. Have you taken advice from the Named Animal Care and Welfare Officer/Named Veterinary Surgeon/others?	We had previously discussed with Michiel Plugge about the adverse effects encountered after injecting the K14Cre-Sox9flox line with Tamoxifen. Together we had designed a strategy to reduce the volume and dose of tamoxifen and included subcutaneous route administration in all protocols as a refinement. To avoid cannibalism, we decided to limit neonatal experiments to the breeders that have littered before, to be able to predict their behaviour upon littering, and thoroughly monitor the growth and appearance of the animals. However, after this las event, we will meet again to discuss if additional measures or limitations need to be added to this type of studies when using this mouse line.
5. Cause of Problem, if known	Although it is suspected that the pups were cannibalised by one of the breeders, we will investigate if this could be related to a delayed development of the pups due to the phenotype induced in this line after tamoxifen injection.

6. Action that has been or will be taken *(For example, formulation of drug changed, supportive treatment given, study design modified). If no action needed, indicate why (for example, none required as study has been terminated and will not be repeated)*	Although in the sc18 report for these animals (ASRU_University of Cambridge_PP7037913_Alcolea_20220615_sc18) we considered the most likely cause of death was cannibalism by one of the breeder females, after finding four more dead pups today we decided to totally stop this study plan, and cull the rest of the induced animals (three more animals in the same litter, and three animals from a different litter) to further investigate the impact of the induction in these animals. In the past we had adjusted the dose of tamoxifen to have a sufficient gene induction in this model, and found that two subcutaneous injections instead of IP injections, at 5mg/20g was the optimal gene induction and well tolerated. However, we will not proceed with similar studies inducing this animal model at perinatal stages until further discussed with the NVS. If we confirm that the deaths are associated to the induction of this line's phenotype, animals in future experiments that need to be induced before weaning will be thoroughly monitored after tamoxifen injection (daily weighing and observation) and culled within 72h of induction date.
7. Reported by (name)	Maria T Bejar
8. Date	24/06/2022

**********For official use**********

Inspector's comments and recommendations:

Comments and recommendations	• Thank you for this SC18 report. • **Death** is considered to be a severe severity classification and as **protocol 6** is denoted of moderate severity there has been **a breach of protocol severity, triggering** a SC18 report. • Your actions and proposals in response to this incident are appropriate and welcomed. • I consider this case **closed**.

Inspector name	Mark Dagleish BVM&S, PhD, MRCVS, FRCPath
Date	20th July 2022