Institution: University of Lincoln		
Unit of Assessment: 6 – Agriculture, Veterinary and Food Sciences		
Title of case study: Improved Pet Welfare through Effective Evidence-based Animal Behaviour Interventions		
Period when the underpinning research was undertaken: 2000 - 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): MILLS Daniel	**Role(s) (e.g. job title):** Professor of Veterinary Behavioural Medicine	**Period(s) employed by submitting HEI:** 18 Apr 94 to date
Period when the claimed impact occurred: 2013 - 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact (indicative maximum 100 words)

The pioneering research of veterinary behaviourist Professor Daniel Mills (University of Lincoln) has led to global shifts in evidence-based advances for the treatment of problem animal behaviour by owners and professionals, with consequent commercial impacts and changes to professional practice and professional body policy. Mills' work on clinical indications, technologies and intervention efficacy underpins moves by multinational (e.g. development of imepitoin by *Boehringer Ingelheim* for veterinary behaviour indications) and smaller veterinary health companies into this sector, alongside the development and refinement of existing products, particularly with *Ceva Sante Animale* in the management of stress-related disorders in pets using synthetic analogues of naturally occurring chemical signals (Pheromonatherapy).

2. Underpinning research (indicative maximum 500 words)

Evidence-based advances for the assessment and treatment of problem animal behaviour:

Professor Mills' research **[3.1]** developed and validated the first suite of clinical instruments for assessing fearfulness in dogs (Positive and Negative Activation Scale -PANAS), the Lincoln Sound Sensitivity Scale (LSSS) and the Lincoln Canine Anxiety Scale (LCAS), which have been used by Mills' and others [*detailed in evidence 5.1, 5.2*] to scientifically evaluate potential interventions ranging from commercial sound desensitisation products (desensitisation recordings), dietary, pheromone-related and pharmaceutical interventions for fear-related issues.

Research with Boehringer Ingelheim (BI) (leaders in the field of veterinary neuropharmaceuticals, but with no behaviour portfolio) examined potential behaviour indicators for their antiepileptic medication, "imepitoin". An initial clinical case series **[3.2]**, alongside collaboration with CanCog (Canada) developing a preclinical laboratory dog model of noise fears **[3.3]** was followed by the use of LCAS for the objective assessment of noise sensitivities in relation to fireworks. This was the first multicentric double-blind randomised placebo-controlled study of imepitoin for problem behaviour to demonstrate its efficacy for noise phobias **[3.4]**.

Research improving current interventions and extending behavioural indications.

Continuing industry funded (Ceva Sante Animale) research at Lincoln explores pheromonal interventions to reduce stress in pets (previously detailed in a REF2014 case). This research is summarised in the research anthology "Adaptil Feliway Comprehensive References" **[3.5]**, in which Mills contributes at least twice as many publications on Dog Appeasing Pheromone (DAP) and three times the number of publications relating to Feline Facial Fraction F3 compared to any other academic. Research since 2000 has resulted in the development of a diffuser technology for the delivery of these mixtures, and the specific research contributions **[**see **3.5]** include:

- The first first peer-reviewed evidence for both F3 (2001), and DAP (2003) of the efficacy of the diffuser technology.

- The first peer-reviewed journal publication (2006) demonstrating the efficacy of DAP delivered via impregnated collar, based on work undertaken the previous year. This publication was also the first to statistically describe the diversity of psychological states underlying travel-related problems, providing important insights into the potential mechanism of action of DAP.

- The first publications for the following indications (double-blinded placebo-controlled studies):

  - adaptation to the new home by puppies (2003), providing further insights into mechanism and limitations, based on differential effects.
  - anxiety in the veterinary clinic (2003).

- The first blinded parallel randomised trial comparing DAP and Cat Appeasing Pheromone for the management of social stress in mixed-species homes - a new indication, and first published evidence of species-specificity of these products **[3.6]**.

- Four journal publications and the only clinical trials on noise phobias in dogs (2003-2008), one of the biggest markets for DAP in the UK.

- The first meta-analysis of any intervention for problem behaviour in companion animals (2009), which provides the most definitive evidence of F3 efficacy beyond placebo (level 1a - http://www.cebm.net/?o=1025).

3. References to the research (indicative maximum of six references)

3.1 https://ipstore.lincoln.ac.uk/product/online-canine-behaviour-calculators this site hosts both the instruments, instructions for their use and associated references.

3.2 McPeake, K. J., & Mills, D. S. (2017). The use of imepitoin (Pexion™) on fear and anxiety related problems in dogs–a case series. *BMC veterinary research*, *13*(1), 1-14. https://doi.org/10.1186/s12917-017-1098-0

3.3 Engel, O., Masic, A., Landsberg, G., Brooks, M., Mills, D. S., & Rundfeldt, C. (2018). Imepitoin shows benzodiazepine-like effects in models of anxiety. *Frontiers in pharmacology*, *9*, 1225. http://dx.doi.org/10.3389/fphar.2018.01225

3.4 Engel, O., Müller, H. W., Klee, R., Francke, B., & Mills, D. S. (2019). Effectiveness of imepitoin for the control of anxiety and fear associated with noise phobia in dogs. *Journal of veterinary internal medicine*, *33*(6), 2675-2684. https://doi.org/10.1111/jvim.15608

3.5 Adaptil Feliway Comprehensive References, Ceva, Animal Health; updated 2019, available from University of Lincoln. This Ceva publication contains a digest of all studies published using pheromone-related products.

3.6 Prior, M. R., & Mills, D. S. (2020). Cats vs. Dogs: The Efficacy of FeliwayFriends™ and Adaptil™ Products in Multispecies Homes. *Frontiers in veterinary science*, *7*, 399. https://doi.org/10.3389/fvets.2020.00399

4. Details of the impact (indicative maximum 750 words)

Professor Mills' impact strategy centralises close collaboration with commerce, professional organisations and end-users, and this has produced new evidence-based treatments to ameliorate animal suffering. Mills' research has generated a series of pivotal changes

necessary for improved animal welfare primarily via the development of novel, high quality, evidence-based products, leading to deep **commercial impacts** for sector leaders, and **changes to professional practice and professional body policy**.

Commercial Impacts.
Product development and market expansion: During the census period, this research has been integral to the development, registration, launch and marketing of veterinary behaviour-related products by both BI and Ceva. In the latter case **[5.1],** Mills' research underpins and is cited in marketing materials for 56 countries and national television advertising campaigns for Feliway™ and Adaptil™. For both, the novel delivery systems developed with Lincoln attract more global sales for Ceva than the original spray (evidence via Ceva contact if required). The simplicity and convenience of these delivery systems for pheromonatherapy, have been an integral part of the development of an "off the shelf" market for these and related products using our technological innovations. For example, Ceva have made a new cat pheromone product (FeliwayFriends™ – delivering the cat appeasing pheromone) available only in diffuser form; the AdaptilJunior™ range for puppies available through pet shops uses the DAP-impregnated collar originally developed for adults. [text removed for publication]

Industrial research strategy: Both BI **[5.2]** and Ceva **[5.1]** have made major strategic shifts on the basis of Mills' research insights. His research with BI underpinned the exceptional dual recognition by both US and European veterinary drug registration authorities of behavioural indication for imepitoin **[5.3],** enabling BI to enter the veterinary behaviour field with the first enteric medication for noise phobias in dogs and place imepitoin into the US market for the first time as a result. [text removed for publication] Clinical research practitioners internationally are now using Mills' fundamental research into the assessment and diagnosis of negative emotional states to enable other companies to produce evidence-based interventions for veterinary behaviour similarly aimed at improving animal welfare **[5.4, 5.5]**.

Professional Practice and Policy Impacts.
The significance of Mills' research has extended beyond direct industry beneficiaries and into professional development for practitioners and the sector more widely. Through his sector collaborations with industry and both veterinary and behaviour associations, Mills has mobilised his research to enhance the knowledge, skills and attitudes of both behaviour specialists and the wider veterinary professions in this field.

Mills authored the standard text "Stress and Pheromonatherapy", which is used by Ceva Animal Health to upskill both practitioners and staff new to the field of pheromonatherapy **[5.1]**. This training of the profession has underpinned sustained growth of pheromonatherapy during the census period, with new markets opening in important geographic regions globally, including Central and South America, New Zealand and most recently China; alongside increased use where the products were already available **[5.1]**. The professional impact of the pheromone research has reached the point that it is routinely included in standard reference texts for the profession **[5.6]** as well as specialist texts **[5.7]**.

Mills' research on the efficacy of pheromonatherapy and imepitoin for noise phobias (affecting 20-50% dogs in industrialised countries), also contributes materially to the opinion of professional bodies on this matter. For example, BSAVA's position statement relating to fireworks **[5.8]** recommends that veterinary surgeons use "*evidence-based therapies*", with specific references to the "*use of pheromones*" and "*short term medication*". Imepitoin is currently one of only two licensed medications for this indication.

Mills' research establishing that dogs are less stressed when exposed to DAP in the vet clinic provides the evidence for pheromonatherapy becoming an integral part of the international veterinary "FearFree" movement founded in 2016 [5.9]. Fear Free provides evidence-based online and in-person education to veterinary professionals, pet professionals, animal welfare communities, and pet owners to prevent and help alleviate fear, anxiety, and stress in pets. Since its launch, Fear Free has provided more than 490,000 hours of free continuing education,

with over 82,000 individuals registered and 54,000 certified through their courses. FearFree claims to be "one of the single most transformative initiatives in the history of companion animal practice", and Fear Free certification is now commonplace as a mark of assurance for pet owners seeking veterinary care. Mills' research has both informed FearFree's standpoint on best practice for minimising animal distress and been translated into FearFree training content and pet owner recommendations. Both the Founder/CEO of FearFree and their Head of Research state that "*Professor Mills' research in clinical animal behaviour has been central in cementing a position on the value of pheromonatherapy. Most powerfully, his research demonstrating that dogs are less stressed when exposed to dog appeasing pheromones in the veterinary clinic and during travel have been fundamental in Fear Free advocating for Pheromonatherapy as an integral part of good veterinary practice, and his many other research publications in this field underpin many of the recommendations on good pet owner practices for preventing and alleviating fear, anxiety and stress and creating Fear Free Happy Home environments (fearfreehappyhomes.com)……Professor Mills' work on pheromonatherapy has shaped our organisational standpoint and educational content engaged with across the world*." **[5.9].**

In summary, University of Lincoln research led by Professor Mills has had both broad and deep impact on the development and adoption of new demonstrably effective methods for the management of stress that have improved animal well-being and secured the commercial success of related products with evidence-based claims.

5. Sources to corroborate the impact (indicative maximum of 10 references)

5.1 [text removed for publication]

5.2 [text removed for publication]

5.3 EMA opinion May 28 2018: https://www.ema.europa.eu/en/documents/smop/cvmp-post-authorisation-summary-positive-opinion-pexion_en.pdf and USFDA CVM update: https://www.fda.gov/animal-veterinary/cvm-updates/fda-approves-pexion-treating-noise-aversion-dogs

5.4 [text removed for publication]

5.5 [text removed for publication]

5.6 Standard reference text example: Allerton F. (ed) (2020) BSAVA Small Animal Formulary. 10th edn BSAVA, Gloucester; Tilley, L. P., & Smith Jr, F. W. (Eds.). (2015). Blackwell's five-minute Veterinary consult: canine and feline. John Wiley & Sons

5.7 Specialist text example: Horwitz D.F. & Mills D.S., (2009) BSAVA Manual of Canine and Feline Behavioural Medicine 2nd edn BSAVA, Gloucester; Landsberg, G., Hunthausen, W., & Ackerman, L. (2013). Behavior Problems of the Dog and Cat-E-Book. Elsevier Health Sciences; Horwitz, D. F. (Ed.). (2018). Blackwell's Five-Minute Veterinary Consult Clinical Companion: Canine and Feline Behavior. John Wiley & Sons.

5.8 BSAVA position statement on management and treatment of firework phobias. Available from https://www.bsava.com/Resources/Veterinary-resources/Position-statements/Fireworks

5.9 [text removed for publication]