

Impact case study (REF3)

Institution: University of Liverpool		
Unit of Assessment: UoA6		
Title of case study: Globally improved porcine welfare and rearing profitability by development of scientifically validated feed additive sweeteners as dietary supplements.		
Period when the underpinning research was undertaken: October 2001 to 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Prof Soraya Shirazi-Beechey Dr Jane Dyer Dr Kristian Daly Dr Andrew Moran	Role(s) (e.g. job title): Professor Postdoctoral fellow Postdoctoral fellow Postdoctoral fellow	Period(s) employed by submitting HEI: 1997-present 2000-2007 2005-present 2005-present
Period when the claimed impact occurred: 1 st August 2013 to 31 st July 2020		
Is this case study continued from a case study submitted in 2014? No		
1. Summary of the impact Post-weaning disorders, diarrhoea, dehydration and nutrient malabsorption in early weaned piglets results in approximately 30,000,000 deaths annually worldwide. Our research has addressed this problem through scientifically validated formulation of innovative plant-based sweeteners (e.g. TakTik®). We have shown that sweeteners are detected by an intestinal glucose (sweet) receptor activating a pathway leading to increased glucose, electrolyte, and water absorption (oral rehydration). University of Liverpool research findings attracted the feed additive company Pancosma/ADM who approached Shirazi-Beechey in 2008 and funded the subsequent research. This development has i) led to 22% of all piglets worldwide currently consuming a TakTik® product, ii) improved health and survival rate by increasing weight, immunity and optimisation of feed utilisation, and iii) created significant economic benefits for Pancosma/ADM with sweetener sales increasing from [text removed for publication] in 2014 to [text removed for publication] in 2018.		
2. Underpinning research In intensive pig production, piglets are weaned at 3 to 4 weeks of age when gut structure and function are not fully developed. This practice allows more piglets to be born, but leads to disorders including nutrient malabsorption, diarrhoea and consequent malnutrition and dehydration, accounting for approximately 3% mortality (equivalent to 30,000,000 piglets annually). Feed additives that improve animal health and performance are significant to animal welfare and economics. Fundamental underpinning research led by Professor Shirazi-Beechey, funded by the Wellcome Trust at the University of Liverpool, for the first time identified an intestinal glucose (sweet) receptor [3.1] that influences glucose absorptive capacity [3.2]. Activation of the receptor by sugars and non-nutritive (artificial) sweeteners results in i) enhancement in activity/expression of the intestinal glucose transporter (Na⁺/glucose cotransporter 1, SGLT1) increasing gut capacity to absorb glucose, electrolytes and water [3.2] and ii) secretion of the gut hormone, glucagon-like peptide 2, enhancing gut structural maturity [3.3]. Our subsequent research demonstrated that pig intestine expresses the glucose (sweet) receptor, and that Sucram 150 (a Pancosma brand sweetener containing saccharin and neohesperidin dihydrochalcone [NHDC]) enhances activity/expression of SGLT1 when included in feed or drinking water. Gut tissue growth is also improved, as well as its capacity to absorb glucose [3.4] thereby maximising feed utilisation and promoting weight gain. Moreover, NHDC induces propagation of gut probiotic <i>Lactobacillus</i>, enhancing immunity and gut health [3.5].		

Development of Sucram-based product range, TakTik® (1st August 2013 - present)

Restrictions imposed by the EU on the use of saccharin in animal feed has stimulated interest in developing new plant derived sweeteners for inclusion in animal feed. Our research has enabled the development of next generation Sucram sweetener and the TakTik® range incorporating stevia-based sweeteners. The novelty in the research relied on assessing the specificity of sweetener compounds in activating the intestinal glucose (sweet) receptor through species-specific amino acid sequence modifications in receptor binding sites for various artificial/natural sweeteners. These findings allowed us to develop novel plant-based sweeteners to be commercialised using similar research strategies for application to the rearing of other species including ruminants, rabbits, and fish [3.6].

3. References to the research

- 3.1 **Dyer J, Salmon KSH, Zibrik L, Shirazi-Beechey SP.** Expression of sweet taste receptors of the T1R family in the intestinal tract and enteroendocrine cells. *Biochem. Soc. Trans.* 33: 302-5, (2005); Citations = 269 <https://doi.org/10.1042/bst0330302>
- 3.2 Margolskee RF, **Dyer J**, Kokrashvili Z, **Salmon KS**, Ilegems E, **Daly K**, Mailliet EL, Ninomiya Y, Mosinger B, **Shirazi-Beechey SP.** T1R3 and gustducin in gut sense sugars to regulate expression of Na⁺/glucose cotransporter 1. *Proc Natl Acad Sci U S A.* 104:15075-80, (2007); Citations = 565 <https://doi.org/10.1073/pnas.0706678104>
This paper was highlighted as the leading edge biochemistry select paper in *Cell* (2007, 130:965-966) with a commentary entitled "Gut reaction to a sweet sensation".
- 3.3 **Moran AW, Al-Rammahi MA, Batchelor DJ, Bravo DM, Shirazi-Beechey SP.** Glucagon-Like Peptide-2 and the Enteric Nervous System Are Components of Cell-Cell Communication Pathway Regulating Intestinal Na⁺/Glucose Co-transport. *Front Nutr* 5:101 (2018); Citations = 19 <https://doi.org/10.3389/fnut.2018.00101>
- 3.4 **Moran AW, Al-Rammahi MA, Arora DK, Batchelor DJ, Coulter EA, Daly K, Ionescu C, Bravo DM, Shirazi-Beechey SP.** Expression of Na⁺/glucose co-transporter (SGLT1) is enhanced by supplementation of the diet of weaning piglets with artificial sweeteners. *Br J Nutr* 104:637-646 (2010); Citations = 74 <https://doi.org/10.1017/S0007114510000917>
- 3.5 **Daly K, Darby AC, Hall N, Wilkinson MC, Pongchaikul P, Bravo D, Shirazi-Beechey SP.** Bacterial sensing underlies artificial sweetener-induced growth of gut *Lactobacillus*. *Environ Microbiol.* 18(7):2159-71 (2016); Citations = 13 <https://dx.doi.org/10.1111/1462-2920.12942>
- 3.6 **Moran AW, Al-Rammahi MA, Daly K, Grand E, Ionescu C, Bravo DM, Wall EH, Shirazi-Beechey SP.** Consumption of a natural high-intensity sweetener enhances activity and expression of rabbit intestinal Na⁺/glucose cotransporter (SGLT1) and improves colibacillosis-induced enteric disorders. *J Agric Food Chem* 68:441-450 (2020); Citations = 3 <https://doi.org/10.1021/acs.jafc.9b04995>

4. Details of the impact**Impact on practice and knowledge**

Our research since 2013 has changed the practice of the animal feed additive industry. By applying our scientific knowledge, we have shown that there are species-specific modifications in receptor binding sites for sweeteners, allowing for the development of novel, effective and targeted products. This is a major advance from previous empirical-based approaches that were used routinely by the industry, often leading to ineffective products [5.1]. Our research has also substantially changed the fundamental understanding of the mode of action of sweeteners used in animal nutrition. Rather than being non-specific 'palatants', at low concentrations (0.01%), stevia-based sweeteners used in TakTik® products are potent activators of the intestinal glucose (sweet) receptor, approximately 1,000 fold more active than glucose.

Impact on animal health and welfare

Shirazi-Beechey's research in developing science-based and Regulatory approved sweetener products has had major impacts on increasing food intake, weight, and optimisation of food conversion ratio (i.e. quantity of feed consumed divided by weight gained), in early weaned piglets, impacting health and well-being of the animals concerned.

Figure 1 - Overview of independent field trials of the use of a sweetener* on piglet performance.

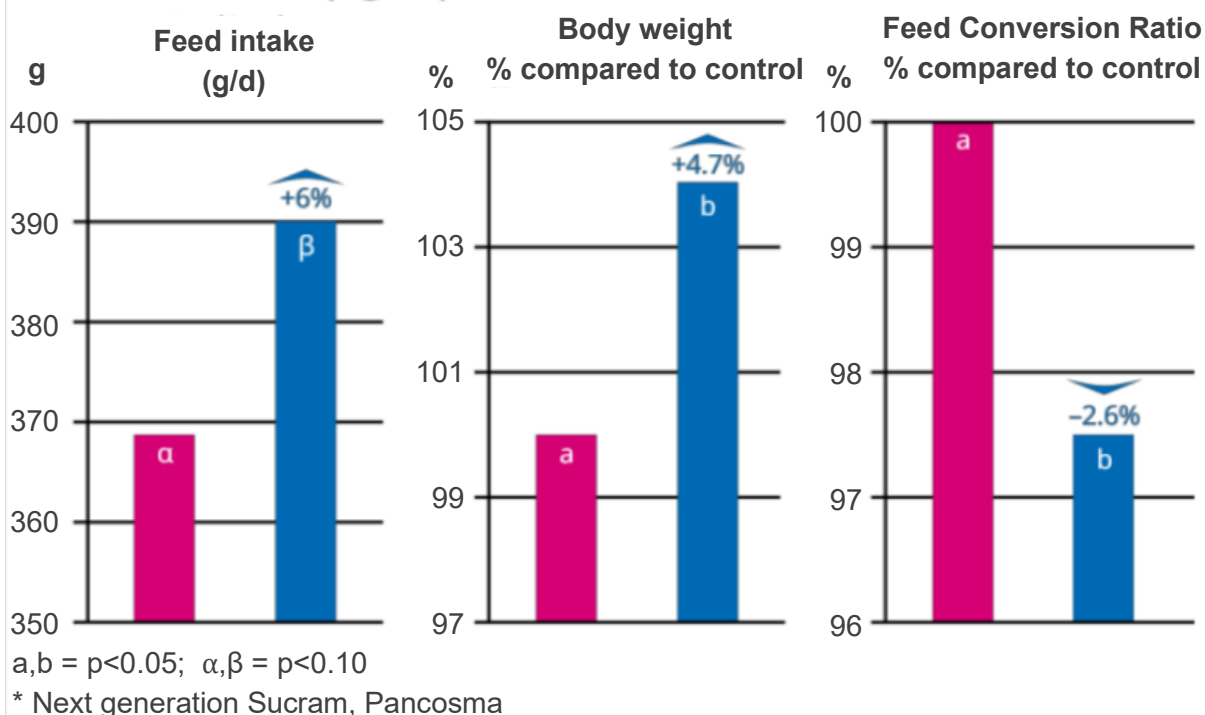


Figure 1: is an example of an independent field trial demonstrating that inclusion of the new sweetener in the feed increased feed intake and body weight gain by approximately 6% and 5% respectively, and improved feed utilisation as demonstrated by the substantial reduction in feed conversion ratio compared to controls [5.2].

In support of such impacts, the Technical Sales Manager of Pancosma, China states “many Chinese animal feed customers use TakTik® as an alternative to routine antibiotics for piglets, and based on the feedback from the Chinese market, this results in significant reduction in post-weaning diarrhoea, and improvements in health. Our customers have carried out large feeding trials of TakTik®, but they consider the data confidential and not available to the public. But the fact that we have doubled the sales figure for TakTik® in China and our Chinese customers continue purchasing TakTik® are good indications of the effectiveness of our products” [5.3].

The Director of Swine Research at the animal feed company Purina, USA, comments that “the fundamental knowledge gained through research carried out by Shirazi-Beechey, that such additives improve health and well-being of early weaned piglets, has stimulated the inclusion of sweeteners in piglet’s feed worldwide” [5.4]. A University of Illinois Professor of Applied Swine Nutrition and an authority on swine nutrient requirements states that Shirazi-Beechey’s research “has made substantive contribution to efficient production of animal source foods, and the research findings leading to rapid increase in global use of sweetener products indicate that advantages extend beyond Pancosma to pig and pig producers. Pig producers do not buy, or continue to buy, products unless they are convinced those products benefits their business” [5.5].

The importance of the role of TakTik® product on pig gut development has received wide industry recognition including high profile articles in pig industry journals [5.2,5.6].

Economic impact and impact on commercial uptake

Research carried out by Shirazi-Beechey has had significant economic impacts on the pig production industry and the feed additive company Pancosma/ADM, with whom Shirazi-Beechey has collaborated. Shirazi-Beechey's research has enhanced customers' understanding of the underlying mechanisms and benefits of new sweetener products in piglet feed, thereby increasing the sale of TakTik® product. This has had major economic benefits for Pancosma.

Pancosma has recognised the importance of the work carried out by Liverpool in promoting their products [5.2,5.6]. Since 2014, annual income due to sales of the sweetener has more than doubled from [text removed for publication] in 2014 to [text removed for publication] in 2018. In 2014 sweetener sales amounted to 80t per annum with an increase to 160t in 2018 [5.7].

Considering that each piglet consumes approximately 8kg of feed, containing 0.8g of sweetener, during the weaning period (from 21 to 42 days of age), the increase in annual sales of 80t of the sweetener amounts to an additional 100,000,000 piglets consuming TakTik® product per year.

Regarding percentage of piglets in the world consuming the sweetener in 2018; 160t of sweetener equate to a total of 200,000,000 pigs consuming TakTik® product. It is reported that in 2018, there were approximately 900,000,000 piglets born, meaning approximately 22% of all piglets worldwide currently consume TakTik® product.

Additional economic benefits

Shirazi-Beechey's fundamental research into the underlying molecular mechanisms of intestinal sweet perception has changed Pancosma's approach to delivering science-led innovations globally (Pancosma is represented in 75 countries) with a corporate focus on gut health. Pancosma CEO (until 2016) has commented on this science-led approach "*which has contributed to development of new concepts and products resulting in commercial success*" [5.8]. Whilst the more recent Pancosma CEO, states [5.8] that "*Shirazi-Beechey's research has had a tangible impact on multi-million Euro business of Pancosma products and that industry needs such scientific challenges in order to better design and develop the solution of tomorrow's challenges*". The present Pancosma Research Director for Feed Additives has commented "*the scientific support provided by Shirazi-Beechey has been a major cornerstone of palatants' range development and has promoted for the first time the gut effect of sweetener products*". She has also acknowledged Shirazi-Beechey's research contribution to the development of new Pancosma range TakTik®, as well as next generation Sucram products [5.7].

These effects are being felt more widely in the industry. Several global animal feed companies, for example CP Group (Thailand) and Grupo-Nutec (Mexico), have incorporated TakTik® into their products. The global animal feed company, Cargill, states that "*this is an excellent example of how relatively 'deep' science can have a very close connection with, and impact on, practical animal agriculture. The knowledge that sweeteners trigger molecular pathways is leading to industrial realisation that the research outputs are relevant to other major aspects of agriculture, including the dairy industry*" [5.9].

In recognition of her exceptional contributions, the American Society of Animal Science awarded Prof. Shirazi-Beechey the ASAS President's Award for International Achievement in Animal Science (2018) [5.10].

5. Sources to corroborate the impact

- 5.1 **Daly K, Moran AW, Al-Rammahi M, Weatherburn D, Shirazi-Beechey S.** Non-nutritive sweetener activation of the pig sweet taste receptor T1R2-T1R3 *in vitro* mirrors sweetener stimulation of the gut-expressed receptor *in vivo*. *Biochem Biophys Res Commun* 542:54-58 (2021) <https://doi.org/10.1016/j.bbrc.2021.01.032>
- 5.2 Pig progress article, describing independent feed trials on the impact of sweetener additive on biomarkers of piglet health and performance. Ramillien M, Faugeton J.
- 5.3 Letter from Technical Sales Manager, Pancosma China, commenting on increase in sale of new products, their use as non-antibiotic replacer and health benefits for piglets.
- 5.4 Letter from The Director of Swine Nutrition, Purina, USA comments on Shirazi-Beechey's substantive contributions to efficient production of animal-source foods.
- 5.5 Letter from Professor of Swine Nutrition, University of Illinois and an authority on swine nutrient requirements comments on the benefits of additive products on piglet health and productive performance, leading to the uptake of products worldwide.
- 5.6 Examples of inclusion of University of Liverpool research in marketing literature.
- 5.7 Letters from Pancosma Research Director for Feed Additives, and Pancosma Business Development Director, commenting on Shirazi-Beechey's research in Liverpool on the development of new products and increases to sales.
- 5.8 Letters from former (until 2016) and current Pancosma CEOs.
Former Pancosma CEO states Shirazi-Beechey's research contribution to the development of new concepts and products, and commercial success.
Pancosma CEO comments on the impact of Shirazi-Beechey's research in Liverpool on commercial success and animal performance.
- 5.9 Letter from R&D Director, Cargill Innovation Center. Confirms the connection between the science and practical animal agriculture.
- 5.10 The American Society of Animal Science President's Award bestowed to Soraya Shirazi-Beechey for her International Achievements in Animal science, July 2018; for her pioneering research that has improved health, welfare and productivity of livestock.