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| **Institution: University of the West of England, Bristol** | | |
| **Unit of Assessment: 3** | | |
| **Title of case study: Novel and improved oral healthcare products and practices from precise modelling and monitoring of microbial volatiles** | | |
| **Period when the underpinning research was undertaken:** 2001 – 2020 | | |
| **Details of staff conducting the underpinning research from the submitting unit:** | | |
| **Name(s):** | **Role(s) (e.g. job title):** | **Period(s) employed by submitting HEI:** |
| Dr Saliha Saad | Senior Research Fellow | 2001 – present |
| John Greenman | Professor and Professor Emeritus | 1979 – 2016 |
| Aniko Varadi | Professor | 2004 – present |
| **Period when the claimed impact occurred:** 01.08.2013 – 2020 | | |
| **Is this case study continued from a case study submitted in 2014?** No | | |

## 1. Summary of the impact

Halitosis, or unpleasant odour in the breath, impacts nearly a third of the population worldwide. Its effects include negative psychological impact and reduced quality of life. UWE's research in halitosis resulted in (i) the development and launch of a new oral care technology; (ii) the development and launch of a reformulated oral-care product with new, evidence-based claims; (iii) repurposing an existing technology to healthcare via robust validation and identifying unique features for oral care applications leading to time and cost savings in repurposing the technology and accelerating the time to market through bringing healthcare providers together; and (iv) improving patient diagnosis, classification and treatment.

## 2. Underpinning research

Halitosis, or oral malodour, is a common condition affecting about one third of the population worldwide (NICE 2019). Its potential complications include reduced self-confidence, social stigma, embarrassment, social isolation, anxiety and depression. Oral malodour is caused by volatile organic compounds (VOCs), 90% of which originate from bacteria in the mouth. Oral malodour is considered a hallmark of gum disease and VOCs are increasingly recognised as an indicator for a range of diseases including cancer, rheumatoid arthritis and Diabetes Mellitus. Understanding the mechanisms behind oral VOC production in both healthy and disease states has underpinned the invention of non-invasive systems that can detect VOC profiles that are indicative of a disease state. It has also supported the development of comprehensive oral care products. In collaboration with industry and academia, Dr Saad has conducted research and clinical trials to develop better oral care for people with oral malodour. Initial research on oral VOCs was led by Dr Saad (**R1**-**6**, **G1**-**10**) and Emeritus Professor Greenman (**R1**-**6**, **G2**, **G4**, **G7**). Subsequently, Dr Saad initiated new research with Professor Varadi on the VOCs in type 2 diabetic patients (**G6**, **G9**, **G10**).

**Improving the utility of the organoleptic intensity scale for measurement, characterisation and standardisation of oral malodour**

Halitosis is traditionally investigated by organoleptic breath assessment using a 0-to-5 scale. Saad's research demonstrated that this scale is exponential, rather than linear, which changed the way clinical trials are designed for testing the efficacy of anti-odour agents (**R1, G1**-**10**).

**Integrated oral VOCs testing through the use of a novel in vitro biofilm model and selected-ion flow-tube mass spectrometry (SIFT-MS)**

Saad's research led to the development of an *in vitro* flat-bed biofilm model **(R2**-**4, G2**-**10)**, which uses oral mixed culture samples obtained from participants, inoculated onto a

cellulose matrix perfused with a saliva-like medium. Real-time, continuous monitoring showed that the model maintains a dynamic equilibrium that is comparable to real mouth conditions for a number of weeks (**R4**). The model enables the study of various oral formulations/treatment approaches to reduce oral malodour, which is not possible to investigate in a clinical trial alone. The flat cellulose matrix has a tongue-like surface, which allows the efficacy of malodour products to be compared (**R3**, **R4**). Saad combined this new *in vitro* model and SIFT-MS (Syft™ Technologies, New Zealand) technology for the measurement of VOCs. This allowed direct comparison of parameters obtained from the model following administration of various oral formulations with those measured *in vivo* (**R2**-**R4**).

**Expansion of VOC detection to clinical trials**

Saad combined the *in vitro* testing environment and organoleptic analysis with clinical studies to test the efficacy of (i) a sonic tongue brush (**R5, G8**) and (ii) a Dual Zinc plus Arginine toothpaste formulation on halitosis (**R6, G9**). These studies were conducted with the involvement of human participants as part of randomised clinical trials designed and conducted by Saad.

## 3. References to the research

**R1** Greenman, J., Duffield, J., Spencer, P., Rosenberg, M., Corry, D., Saad, S., Lenton, P., Majerus, G., Nachnani, S. and El-Maaytah, M. (2004) Study on the organoleptic intensity scale for measuring oral malodour. *Journal of Dental Research.* 83(1), pp. 81-85 https://doi.org/10.1177%2F154405910408300116

**R2** Greenman, J., McKenzie, C., Saad, S., Wiegand, B. and Zguris, J.C. (2008) Effects of chlorhexidine on a tongue-flora microcosm and VSC production using *in vitro* biofilm perfusion model. *Journal of Breath Research* 2(4);046005 https://doi.org/10.1088/1752-7155/2/4/046005

**R3** Saad, S., Hewett, K. and Greenman, J. (2012) Effect of mouth-rinse formulations on oral malodour processes in tongue-derived perfusion biofilm model. *Journal of Breath Research* 6(1);016001 https://doi.org/10.1088/1752-7155/6/1/016001

**R4** Saad S, Hewett K. and Greenman J. (2013) Use of an *in vitro* flat-bed biofilm model to measure biologically active anti-odour compounds. *Applied Microbiology and Biotechnology* 97(17), pp. 7865-7875 https://doi.org/10.1007/s00253-013-5084-6

**R5** Saad, S, Gomez-Pereira, P, Hewett, K, Horstman, P, Patel, J and Greenman, J. (2016) Daily reduction of oral malodor with the use of a sonic tongue brush combined with an antibacterial tongue spray in a randomized cross-over clinical investigation. *Journal of Breath Research* 10(1), pp. 13-16. https://doi.org/10.1088/1752-7155/10/1/016013

**R6** Saad S., Fitzgerald M., Hewett K., Greenman, J., Vandeven, M., Trivedi, H.M. and Masters, J.G. (2018) Short- and long-term effects of a dentifrice containing dual zinc plus arginine on intra-oral halitosis: improvements in breath quality. *Journal of Clinical and Experimental Dentistry.* 29, pp. A46-54 https://uwe-repository.worktribe.com/output/5464239

**Evidence of the quality of the underpinning research**

**G1** Saad, S. *Funding for Odour judge assessment Continuous Professional Development (CPD) programmes*, GABA International, 2010 – 2013, £56,000; MEDA Manufacturing GmBH, 2013, £13,700.
**G2** Greenman, J. *Breath Trail*, Healthcare Brands International, 2009, £27,500**.**
**G3** Saad, S. *In vitro perfusion biofilm model to study the anti-malodour effects of oral formulation*, Johnson & Johnson Consumer & Personal Products Worldwide, 2012, £28,777.
**G4** Greenman, J. *In vitro modelling of tongue microbial biofilms and their response to treatments*, EPSRC, 2013, £95,148.

**G5** Saad, S. *In vitro study on the Effects of Agent Formulations on Oral Malodour Parameters and Tongue Microbes Compared with Control*, Helperby Therapeutics Group Limited, 2015, £47,840.
**G6** Saad, S. *Diabetic foot and breath analysis*, Avon Primary Care Research Collaborative (now NHS Bristol), 2017, £25,406
**G7** Greenman, J. *In vitro perfusion biofilm models for testing toothpaste formulations: Comparison of two unknown toothpaste test compounds (A and B) with placebo*, GABA International, 2009, £52,364; Saad, S. *Clinical Study on the Breath Freshening Effects of Oral Formulations*, GABA International, 2011, £44,690.
**G8** Saad, S. *Development of in vitro biofilm model to study effects of mechanical, chemical and photodynamic devices against oral malodour*, Phillips Research Laboratories, 2012 – 2014, £167,100; Saad, S. *Cumulative reduction of oral malodour by a sonic tongue brush with active fluid flow deliver*, Phillips Research Laboratories, 2013 – 2015, £130,500.
**G9** Saad, S. *Study of tongue microbiology and oral malodour*, Colgate-Palmolive, 2011, £35,000; Saad, S. *The effects of oral formulations on oral malodour parameters, saliva and tongue microbiology*, Colgate-Palmolive, 2014, £126,430; Saad, S. *The effects of Zn-containing toothpaste on oral malodour and on oral microbiology*, Colgate-Palmolive, 2015, £171,900; Saad, S. *Effects of a SnF2-containing toothpaste on oral malodour*, Colgate-Palmolive, 2018, £110,262; Saad, S. *Oral microflora in patients with Type 2 diabetes and their response to oral formulations targeting periodontal complications*, Colgate-Palmolive and UWE, 2019 – 2023, £66,569.
**G10** Saad, S. *Validation of the use of artificial nose (NeOse) for discriminating microbial infections and conditions producing VOCs in humans and animals Phase I,* Cemag Care, Aryballe Technologies and Colgate-Palmolive, 2016 – 2018, £30,211; Saad, S. *Effect of zinc-containing toothpaste on oral malodour measured by Neose and SIFT-MS*, Cemag Care, Aryballe Technologies and Colgate-Palmolive, 2020 – 2021, £189,676; Saad, S. *Detection of volatiles associated with diabetic foot and gum diseases in diabetics*, Cemag Care, Aryballe Technologies and Colgate-Palmolive, 2018 – 2022, £40,000.

## 4. Details of the impact

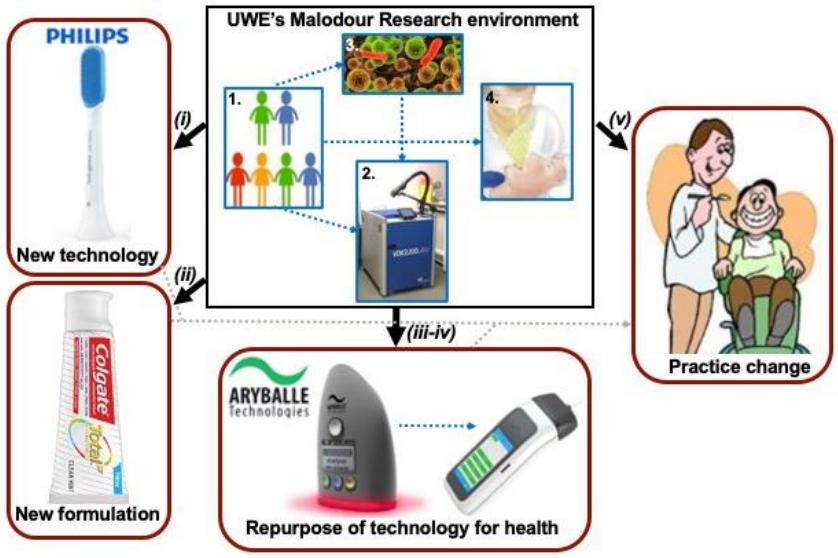


Figure 1: Summary of the research and its impact. UWE's Malodour Research environment (see Section 2) includes: 1. Clinical Trial capability; 2. VOC detection using gold standard SIFT-MS; 3. flat-bed *in vitro* biofilm model and 4. qualified organoleptic breath assessment. (i-v) Impacts resulted from the research (details are provided below).

### (i) Development and launch of a novel oral care technology

In collaboration with Philips Research Laboratories, Saad developed superior halitosis products (**R5**, **G8**). A Senior Scientist at Phillips stated that Saad's research showed *'a direct*

*relationship between bacterial numbers and strength of odour',* critical in determining *'to what extent tongue bacteria count had to be reduced in order to achieve sustained clean breath'* (**S1**). Philips invested in feasibility studies, prototype development and clinical studies with UWE, allowing Philips '*to further iterate the technology*' and to devise various technologies including *'customised bristles under sonic motion to remove bacteria from deep within the tongue structure'* (**S1**). The assistance from UWE meant that '*TongueCare+ was developed and launched in record 3 years from initial idea to market launch*' (**S1**). '*TongueCare+ was initially launched in 2016 in Europe and USA before global rollout* [and at the time] … *first year sales were projected to exceed 25M Euros*'. '*TongueCare+ is currently retailed by major global retailers such as Amazon, Walmart and Boots*' (**S1**). Further impacts were '*the creation of a new sub-category of breath odour for Philips Oral Health Care'* and *enabling 'new marketing strategies and technology functions'* (**S1**).

**(ii) Development of a reformulated oral care product with new evidence-based claims**

Colgate-Palmolive reformulated their best-selling toothpaste, Colgate Total®, which '*represents approximately $1bn of annual revenue for the company'* (**S2**, **S3**). This included replacing the active ingredient triclosan (where regulatory scrutiny risked business and reputation) with Dual Zinc plus Arginine (**S3**) as antimicrobial and odour-neutralising agents (**R6**, **G9**). Saad's research provided the *'evidence-based claims for the product'* (**S2**). Additionally, for such an established product, Saad's research allowed Colgate-Palmolive to make new claims namely '*the Dual Zinc plus Arginine dentrifice in Colgate-Total® can provide short-term (twelve hours) and long-term (one month) improvements in breath quality from a single use'* (**R6**, **S2**). UWE's Malodour Research environment (figure 1) allowed Colgate-Palmolive '*to capture and analyse new dimensions in oral malodour*' such as previously uncharacterised volatile compounds. The reformulated toothpaste was *'re-launched in January 2019'* (**S2**, **S3**).

**(iii) Repurposing an existing device for the healthcare market resulting in time and cost savings**

Saad tested a prototype electronic nose NeOse™ Pro invented by the technology company Aryballe and funded by CEMAG Care. NeOse™ Pro, the bio-optic smell sensor, was targeted at detecting environmental fumes, such as smoke. Saad's research showed that the core technology in NeOse™ Pro conformed to both the SIFT-MS and the organoleptic score providing *'a sound underpinning validation of the NeOse™ Pro in the field of halitosis'* (**S4**). '*Saad made recommendations to improve the early prototypes … to reliably test VOC compounds'* and *'directed the development of key accessories'* (**S5**). The core technology was given a new casing including a newly developed mouthpiece for collecting VOCs. Consequently, Aryballe filed a patent application in France with Saad as a named inventor in 2020 (**S6**). The Chief Scientific Officer of CEMAG stated that Saad's work demonstrated *'the first published use for the technology in the field of healthcare*' that can be used '*to measure the full spectrum of compounds in halitosis'* (**S4**). Saad's work quickly resulted in proof-of-concept data and '*led to a saving of around one year in the pipeline of this technology*' (**S4**). Subsequently, Saad and Varadi set up new collaborations between Colgate-Palmolive and CEMAG-Aryballe (**G9**, **G10**) providing credibility and validation for the device (**S5**) and *'accelerating the route to market in this field'* with consequent cost savings (**S5**).

**(iv) Improving patient diagnosis, classification and treatment**

Saad's research (**R1**, **R5**, **R6**, **G1**) underpinned UWE's 'Odour Judge Assessment' continuous professional development (CPD) programme. Twelve participants (dentists, physicians, hygienists, microbiologists, maxillofacial surgeons) attended each of the six

programmes (2004-2013) from the USA, Netherlands, France, Italy, Germany, Sweden, Norway, Iceland, Poland, Hungary and UK. A participant periodontologist and Associate Professor at the Dental Faculty of Strasbourg, is now '*able to differentiate [between] the different gases*' leading to discrimination '*between physical … and psychiatric conditions*' and *'coming to a definitive diagnosis'* in a halitosis clinic providing a service for patients across France (**S7**). Another participant, dentist and Associate Professor of Medical Technologies at the University of Cagliari, stated that he can now '*assess oral malodour prior to dental implantation*' to prevent implant failure (**S8**). He now offers in his referral clinic a service for patients with *'delusional halitosis'* with appropriate interventions (**S8**). Additionally, he included a new topic on '*microflora of the tongue and oral malodour*' in the dental curriculum at his University (**S8**). One dentist involved in Saad's clinical trials, used Saad's research to recommend interventions and oral care products to patients that were '*successful in alleviating malodour'* and *'educating patients about tongue cleaning has made a huge difference'* in his practice and has been shared with six partner clinics in London (**S9**). He also highlighted that the knowledge he gained from Saad's research is '*improving the quality of life for our patients'* (**S9**).

**5. Sources to corroborate the impact**

**S1** Supporting impact data from a Senior Scientist at Philips Research Laboratory
**S2** Supporting impact data from a Senior Scientist at Colgate-Palmolive
**S3** https://investor.colgatepalmolive.com/static-files/8856158d-04ae-4770-a979-dbdf4db2559b; page 18 of the report
**S4** Supporting impact data from the Chief Scientific Officer, CEMAG Care
**S5** Supporting impact data from the Project Engineer, Aryballe
**S6** Patent application documentation (TR: ICG090391 - dispositif de prélèvement document), reference FR2006978
**S7** Supporting evidence from Associate Professor, Department of Periodontology, Dental Faculty, Strasbourg, France
**S8** Supporting evidence from Associate Professor of Medical Technologies, University of Cagliari, Italy
**S9** Supporting impact data from dentist, Open Dental Care, London