Research Assessment Exercise 2020
Impact Case Study

University: *City University of Hong Kong*

Unit of Assessment (UoA): *01 - Biological Sciences (incl. environmental biology, biotechnology, agriculture & food science, veterinary studies)*

Title of case study: *The Glowing Medaka Test*

1. Summary of the impact

Estrogenic Endocrine Disrupting Chemicals (EDDCs) are a global public health concern. A cheap and fast test for EDDCs, developed at City University of Hong Kong, continues to impact customer safety and animal welfare locally, regionally and internationally. Based on transgenic fish embryos the *Glowing Medaka Test* has identified previously unknown toxicities in consumer products ranging from cosmetics to baby nutrition. Today, the test is used by international corporations, government agencies and NGOs to detect EDDC toxicity and test results are being made available to customers on publicly accessible platforms.

2. Underpinning research

The research underpinning the impact of the *Glowing Medaka Test* was performed chiefly by the research group of Professor Shuk Han Cheng at the Department of Biomedical Sciences at City University of Hong Kong. In 2006, her group reported that they had cloned the liver-specific gene *ojChH* from the marine Medaka *Oryzias javanicus* [1]. Furthermore, they demonstrated that the gene's transcription is exquisitely sensitive to environmental levels of Estradiol, the most effective natural Estrogen. This result offered a first hint at the possibility of using liver-specific gene transcription as a biomarker for the exposure to estrogenic compounds. The results were published in the Journal *Aquatic Toxicology*.

In 2008, Prof Cheng's group identified the homologous gene *omChgH* in the brackish Medaka *Oryzias melastigma* [2]. In this study, the researchers focused on Estradiol-dependent gene expression in embryos. In their publication, they demonstrated that the expression of *omChH* starts to be highly sensitive to environmental estrogenic chemicals at embryonal stage 34, corresponding to an age of roughly five days. This suggested that the expression liver-specific genes could be used at an early developmental stages to test for the presence of compounds with *estrogenic activity*. The results appeared in the *Journal Exotoxicology and Environmental Safety.* The same methodology has also been used to demonstrate estrogenic endocrine disrupting activities of the flexible plastics phthalates [3].

The first author of that paper was Xueping Chen, one of Professor Cheng' s PhD students. In 2010, after completing her PhD in Environmental Toxicology, she went on to co-found the startup [redacted] with Dr [redacted], also a Bachelor degree graduate of City University. The same year, Professor Cheng and Dr [redacted] were granted the patents for labelling the transcription of choriogenin genes of type H with fluorescent reporter proteins in the Medaka species *Oryzias melastigma* and *Oryzias melastigma by the USA and EU patent offices in 2013, 2015 and 2018 respectively.*

3. References to the research

[1] Yu, R. M. K., Wong, M. M. L., Kong, R. Y. C., Wu, R. S. S, & *Cheng, S. H. (2006). Induction of hepatic choriogenin mRNA expression in male marine medaka: a highly sensitive biomarker for environmental estrogens. Aquatic Toxicology, 77, 348-358.

[2] Chen, X., Li V. W. T., Yu, R. M. K., & *Cheng, S. H. (2008). Choriogenin mRNA as a sensitive molecular biomarker for estrogenic chemicals in developing brackish medaka (Oryzias melastigma). Ecotoxicology and Environmental Safety, 71(1), 200-208.

[3] *Chen, X., Xu, S., Tan T., Lee S.T., Cheng S.H., Lee F.W.F., Xu S.J.L., Ho K.C. (2014) International Journal of Environmental Research and Public Health, 11(3), 3156-3168.

4. Details of the impact

The Problem of EDDCs

Endocrine Disrupting Chemicals (EDCs) mimic the activity of endogenous hormones. Exposure to EDCs can have harmful effects on growth, reproduction, metabolism, immunity and behaviour, often with life-long consequences [A]. A 2016 study in *The Lancet Diabetes & Endocrinology* reported that in the US alone the estimated cost of disease and dysfunction due to EDC exposure amounted to $340 billion or 2 percent of the GDP. [B] The US Environmental Protection Agency (EPA) considers an estimated 87,000 chemicals used in customer products today to require "endocrine disruptor screening and testing." [C]

Estrogenic Endocrine Disrupting Chemicals (EEDCs) are a major class of EDCs. According to a 2009 study in the Journal *Environmental Health Perspectives*, almost all commercially available plastic products "leached chemicals [with] reliably detectable estrogenic activity." [D] For instance, Bisphenol A (BPA) is commonly found in Polycarbonate plastics, epoxy resins (lining soup and metal cans) or thermal paper receipts. Furthermore Ethinyl Estradiol, can be detected at low levels in municipal water worldwide. And Genistein (GEN) is regularly identified in soy based food, soy infant formula and dietary supplements. [A]

The Glowing Medaka Test

Research carried at out the laboratory of Prof Shuk Han Cheng of City University of Hong Kong has led to the development of a fast and low-cost test for EDDCs in customer products. The researchers identified and cloned liver-specific genes from Medaka fish that respond to these chemicals. When exposed to EDDCs the genes respond by ramping up their transcription levels. The researchers observed this genetic signal in Medaka embryos as young as five days. As the fish embryos are naturally translucent, coupling of the gene signal to fluorescent reporters rendered toxic effects of EDDCs visible to the naked eye.

Impact on consumer safety

Having licensed the transgenic medaka technology from City University in 2010, the two City University Alumni founded the startup [redacted] Ltd. This biotechnology company now offers the *Glowing Medaka Test* as part of their testing platform. During the RAE 2020 assessment period, the test has generated a major impact on consumer safety and animal welfare, regionally, nationally in and globally. Today, it is used by several multinational cosmetics and food groups, such as [redacted] and [redacted], and by NGOs to ensure product safety and to inform customer choice. For instance, the *World Green Organisation,* a Hong Kong based NGO, set up Hong Kong's first *Whitelist for Pregnancy Supplements and Baby Products*. At wgo.org.hk customers can browse that list to find products that have passed a rigorous line of testing. Ingredient analysis is performed by ALS and TÜV Rheinland, two world-renowned providers of product safety tests. The *Biological Stage* testing

is performed by [redacted] using the Glowing Medaka Test.

Finally, in 2017, [redacted] launched a consumer product safety platform called *Test-It* that presents the results of [redacted]'s own test series in a user friendly manner. [E] Here customers find test results for over 400 products including cooking oils, BB creams, instant coffee, sunscreen, ice cream, lip balm, liquid milk products and lipstick. In 2018 the website had more than 1 million registered users and more than 10 million unique page visits for each safety list.

Impact on animal welfare
Acute toxicity testing relies on clinical signs and symptoms in animals after exposure to environmental toxins. [F] Concerns about animal welfare have prompted regulatory bodies worldwide to push for alternatives for animal testing. For instance, the OECD, in the latest draft of their *Guideline For The Testing Of Chemicals* states that "treating fish with a test chemical until they die [has] significant animal welfare implications." Therefore, all other means of assessing acute toxicity in fish" should be considered. Specifically "fish embryos, which are regarded as non-animals in some countries" are stated as a viable alternative. [G] Thus, the Glowing Medaka Test, by virtue of using fish embryos instead of adult animals, has a significant impact on animal welfare in the context of EDDC testing.

International Recognition and Public Awareness
The *Glowing Medaka Test* has sparked considerable international media coverage, bringing attention to the issue of EEDCs in consumer products. Articles reporting on the technology have featured in highly respected publications such as the *New Scientist* [H], *Forbes Magazine [H], The Financial Times* [H] and *Scientific American* [H]. Furthermore the test won The Grand Prix of the 43rd International Exhibition of Inventions of Geneva in 2015 [H]. [redacted] was selected as one of six most successful high-tech companies in the last decade by HK government [I]. Finally, the Glowing Medaka technology was featured as the only pioneering innovation from Hong Kong at The World Economic Forum. [J]

5. Sources to corroborate the impact

[A] Frye et al. J Neuroendocrinol. 2012 Jan; 24(1): 144–159.

[B] Attina et al. Lancet Diabetes Endocrinol. 2016 Dec; 4(12):996-1003

[C] U.S. Environmental Protection Agency Endocrine Disruptor Screening Program: Universe of Chemicals and General Validation Principles 2012

[D] Yang et al. Environ Health Perspect. 2011 Jul 1; 119(7): 989–996.

[E] Public health

Offical website of *Test-It*, a comsumer product safety platform launched by the [redacted]
https://www.fishqc.com/en/

'White List' of baby personal care products produced by WHO
http://wgo.org.hk/whitelist/en/whitelist.php

[F] European Union Reference Laboratory for alternatives to animal testing
https://eurl-ecvam.jrc.ec.europa.eu/validation-regulatory-acceptance/systemic-toxicity/acute-toxicity

[G] OECD Guideline for testing of chemicals
http://www.oecd.org/chemicalsafety/testing/Draft%20Update%20TG%20203_July%202018-for%20public%20comments.pdf

[H] Media Coverage and Awards

New Scientist
https://www.newscientist.com/article/mg21028164-400-fluorescent-fish-glows-to-show-feminising-chemicals-up/

Forbes
https://www.forbes.com/sites/rahilbhagat/2016/05/19/could-these-genetically-modified-fish-make-food-safer-for-everybody/#21cd755a1558

The Financial Times
Original link: https://www.ft.com/content/309d667a-7428-11e5-bdb1-e6e4767162cc
Full version can be found on Test-it website: https://www.fishqc.com/en/information-62

Scientific American
https://www.scientificamerican.com/article/transgenic-tadpole-glows-to-reveal-chemical-contamination/

Bloomberg
https://www.bloomberg.com/press-releases/2017-05-23/vitargent-introduces-world-s-first-product-safety-information-platform-applying-proprietary-testing-2-0-biological-testing

PWCHK
https://www.pwchk.com/en/press-room/press-releases/pr-290618.html

Grand Prix and Gold Medal of the 43rd International Exhibition of Inventions of Geneva
https://www.fishqc.com/en/information-59
http://www.vitargent.com/portfolio/grand-prix-of-the-43rd-international-exhibition-of-invention-of-geneva/#prettyPhoto[gallery]/0/

[I] Article on the HKSAR website
https://www.ceo.gov.hk/archive/2017/eng/blog/blog20150419.html

[J] [redacted] on the World Enonomic Forum
https://www.weforum.org/people/[redacted]