**Institution:** University of Ulster

**Unit of Assessment:** 3B Allied Health Professions, Dentistry, Nursing and Pharmacy – Biomedical Sciences

**Title of case study:** Folate (folic acid), health policy and the consumer

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

For over 20 years, conclusive evidence has existed that folic acid in early pregnancy prevents spina bifida and related birth defects (collectively known as neural tube defects; NTD), leading to folic acid recommendations for women of reproductive age worldwide. However, translating these recommendations into practice remains a significant challenge. This case study is focussed on identifying and addressing the challenges in implementing current folic acid policy into practice in healthy populations, and in parallel investigating newer roles for folate in preventing disease. Our international outputs to date have provided a scientific foundation for developing evidence-based, sometimes controversial, policy in this area and its translation to consumers.

**2. Underpinning research** (indicative maximum 500 words)

Our research findings have addressed a number of practical limitations in relation to the goal of preventing NTD in populations worldwide through improved folate status. Our published papers over the years have identified that:

- the bioavailability of folates naturally occurring in foods is poor compared to that of the synthetic vitamin form, folic acid, which greatly limits the ability to achieve optimal folate status (*Cuskelly et al 1996,* our landmark paper in *the Lancet);*
- folic acid-fortified foods can help greatly in meeting the challenge of achieving optimal folate status because, unlike natural food folate sources, they provide a highly bioavailable form of the vitamin (*Cuskelly et al 1999; Hoey et al 2007);*
- poor compliance by women of reproductive age with folic acid supplementation policy is another major obstacle in achieving a reduction in NTD; we estimated that only 1 in 5 women commence folic acid before conception as globally recommended under current policy *(McNulty 2011*).

Our published work and other research outputs have also done much to inform scientists and policymakers on the risk-benefit debate surrounding food fortification with folic acid, an urgent topic in the UK and Europe. In particular, mandatory folic acid-fortification (as introduced in North America and elsewhere) is controversial, because, although there are proven beneficial effects in preventing NTD, there are also certain concerns about potential adverse effects on health. Our recent paper (*Tighe et al 2011*) showed that the dose of folic acid required for beneficial effects was much lower than previously believed, and that exposing the population to higher levels was neither necessary nor desirable. This paper not only triggered an accompanying editorial at the time of its publication but was also selected for inclusion in the American Society of Nutrition's compilation of papers (*The Best of Clinical Nutrition 2012)* selected by the experts for their impact in addressing 'evidence-based issues of our day in food, diet and health'.

Public health policy in this area recognises that, apart from preventing NTD, there are potential benefits of optimal folate in protecting against chronic diseases of ageing. Our underpinning research (supported by grants from the UK Food Standards Agency and European Commission) has contributed much to the evidence-base to support these newer roles for folate throughout the lifecycle, such as protecting against the development of heart disease, stroke and certain cancers, and maintaining cognitive function and bone health (*Scott & McNulty 2008*). We have also highlighted the important roles (and interactions) of vitamins B2, B6 and B12 in maintaining normal folate metabolism. For example, our findings published in *the Lancet*, established that once folate status is optimised, a much greater dependency on the status of vitamin B12 emerges in order to sustain methylation reactions (*Quinlivan et al 2002*). More recently, our research findings have begun to address the influence on disease risk of common genetic variations and their interactions with folate and related B-vitamins; this work has led to a novel discovery in relation to B-vitamins and blood pressure, as fully described in the accompanying case study (BMSRI No2).

Key Researchers at Ulster:

*PhD students*: Geraldine Cuskelly (1994-1997); Michelle McKinley (1996-1999); Derek McKillop (1998-2001); Paula Tighe (2000-2004); Maeve Kerr (2002-2006); Breige McNulty (2004-2007); Nadine Askin (2004-2008).

*Current key staff*: Helene McNulty (Professor; 1992-); Kristina Pentieva (Senior Lecturer; 1998-); Mary Ward (Senior Lecturer; 1999-); JJ Strain (Professor, 1987-); Leane Hoey (Lecturer; 2003-).
*External academic collaborators at Trinity College Dublin (1992-present):* John M Scott (Professor); Anne Molloy (Associate Professor).

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

McNulty, B., Pentieva, K., Marshall, B., Ward, M., Molloy, A.M., Scott, J. M., McNulty, H. (2011) Women's compliance with current folic acid recommendations and achievement of optimal vitamin status for preventing neural tube defects. *Human Reproduction*, 26, 1530-1536.
Times Cited: 14 SJR: 2.066 SNIP: 1.979 Impact Factor: 4.670

Tighe, P., Ward, M., McNulty, H., Finnegan, O., Dunne, A., Strain, J. J., Molloy, A. M., Duffy, M., Pentieva, K., Scott, J. M. (2011). A dose-finding trial of the effect of long-term folic acid: implications for food fortification policy. *American Journal of Clinical Nutrition*, 93, 11-18.
Times Cited: 15 SJR: 2.816 SNIP: 2.404 Impact Factor: 6.669

McNulty, H., Scott, J. M. (2008). Intake and status of folate and related B-vitamins: considerations and challenges in achieving optimal status. *British Journal of Nutrition,* 99 (suppl): S48-S54.
DOI: 10.1017/S0007114508006855
Times Cited: 39 SJR: 1.052 SNIP: 1.176 Impact Factor: 3.013

Hoey, L., McNulty, H., Askin, N., Dunne, A., Ward, M., Pentieva, K., Strain, J. J., Molloy, A. M., Flynn, C., Scott, J. M. (2007). Effect of a voluntary food fortification policy on folate, related B-vitamin status and homocysteine in healthy adults. *American Journal of Clinical Nutrition,* 86: 1405-13.
Times Cited: 28 SJR: 2.816 SNIP: 2.404 Impact Factor: 6.669

Quinlivan, E. P., McPartlin, J., McNulty, H., Ward, M., Strain, J. J., Weir, D. G., Scott, J. M. (2002). Importance of both folic acid and vitamin B-12 in reduction of risk of vascular disease. *Lancet*, 359: 227-228.
DOI: 10.1016/S0140-6736(02)07439-1
Times Cited: 117 SJR: 5.917 SNIP: 6.197 Impact Factor: 38.278

Cuskelly, G. J., McNulty, H., Scott, J. M. (1999). Fortification with low amounts of folic acid makes a significant difference in folate status in young women: implications for the prevention of neural tube defects. *American Journal of Clinical Nutrition*, 70: 234-239.
Times Cited: 39 SJR: 2.816 SNIP: 2.404 Impact Factor: 6.669

Cuskelly, G. J., McNulty, H., Scott, J. M. (1996). Effect of increasing dietary folate on red-cell folate: implications for prevention of neural tube defects. *Lancet,* 347: 657-59.
DOI: 10.1016/S0140-6736(96)91205-2
Times Cited: 225 SJR: 5.917 SNIP: 6.197 Impact Factor: 38.278

***Key Research Grants (1998-2013):***

Strain, J. J., McNulty, H., Ward, M. National Nutritional Phenotype Database ('JINGO'). Funded by The Irish Department of Agriculture, Food & the Marine and Health Research Board through the Food Institutional Research Measure (FIRM) initiative; 2008-2013; £631k.

McNulty, H., Livingstone, M. B. E., Pentieva, K., Strain, J. J. EURRECA: Harmonising nutrient recommendations across Europe with special focus on vulnerable groups and consumer understanding. Funded by C.E.C. – Framework 6 food quality and safety NOE; 2007-2012; £320.5k.

McNulty, H., Strain, J. J., Ward, M., Wallace, J. Irish Universities Nutrition Alliance Project: Building additional and sustainable research capacity in nutrition and bone health. Funded by the Northern Ireland Department for Employment & Learning (DEL) through Cross Border R&D Funding

Programme: 'Strengthening the All-Island Research Base'; 2008-2011; £1.24m.

McNulty, H., Pentieva, K. Development of nutritionally enhanced milk by natural means: better opportunities for Ireland's Dairy Sector. Funded by Invest Northern Ireland – Proof of concept; 2004-2006; £150k.

McNulty, H., Pentieva, K., Ward, M., Strain, J. J. Influence of gender, age and genotype on the known suboptimal status of folate, vitamin B-12, vitamin B-6 and riboflavin. Funded by The Food Standards Agency; 2003-2005; £432.6k.

McNulty, H., Strain, J. J. The Bioavailability of folic acid and natural folates: studies using the functional marker plasma homocysteine. Funded by Ministry of Agriculture Fisheries & Food and The Food Standards Agency; 1998-2002; £681k.

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

Two specific areas of international food and health policy have been influenced by our underpinning research:

- Dietary Folate Recommendations: In revising dietary recommendations for folate in the United States in 1998, a new direction was adopted, i.e. that of expressing the recommended levels as *dietary folate equivalents* (DFE). The DFE recognised for the first time the much lower bioavailability of natural food folates compared to the synthetic vitamin folic acid and the decision to adopt it was influenced considerably by the findings of our landmark paper (*Cuskelly et al 1996*). Over the years, this paper has continued to have major impacts on informing dietary folate recommendations worldwide (e.g. US 2001, Institute of Medicine's (IOM) Dietary Reference Intakes; Australia 2006, National Health and Medical Research Council's Nutrient Reference Values; 2006, Food Standards Australia New Zealand (FSANZ); UK 2006, Scientific Advisory Committee (SACN) **[1-4]**.

- Food Fortification Policies: A policy of mandatory folic acid-fortification of cereal grains was implemented in 1998 by the US government with the aim of reducing pregnancies affected by NTD. This strategy was deemed necessary because alternative policies for NTD protection which recommended increasing folate intake from natural food sources had been reported by us to be ineffective, together with the widespread problem of poor compliance by women with periconceptional folic acid supplementation. In more recent years, our research papers have continued to inform health services and regulatory authorities on the beneficial effects of voluntary food fortification with B-vitamins. Evidence provided by *Hoey et al 2007* was integrated into the Health Council of the Netherland's 2008 advisory report **[5]** and also featured in the Food Safety Authority of Ireland's (FSAI) 2008 report to the Department of Health and Children **[6]**.

Global impact for populations and the consumer: The achievement of optimal folate status to prevent NTD is a global concern and a driver of food policy worldwide. Through our published work and other dissemination activities, we have contributed substantially to the scientific evidence-base thus influencing the necessary players internationally who have incorporated our research insights into major reports, including those of US Center for Disease Control and Prevention (CDC) and similar bodies internationally **[7]**. Other impacts have included contributions to international meetings involving scientists, government ministries, and non-governmental bodies, such as meetings of the Flour Fortification Initiative (FFI), an international partnership of organisations, which is striving to encourage folic acid fortification of grain foods on a mandatory basis worldwide to reduce NTD. Professor McNulty has contributed (as invited speaker and chair) to international meetings of FFI and other significant partners e.g. Bucharest Romania, October 2008 and Ankara Turkey June 2012; FFI conferences jointly hosted with UNICEF **[8]**. Evidence of the success of such initiatives is that, as of July 2013, as many as 74 countries worldwide have passed regulations for mandatory fortification of staple foods with folic acid. (http://www.ffinetwork.org/global_progress/index.php).

In addition, links with industry are proving highly relevant in translating folic acid issues to the consumer. For example, the Kellogg Company has incorporated our research findings at a 2009

meeting of the Associate Parliamentary Food and Health Forum (FHF) **[9]**, a forum for the exchange of views and information on food policy in the UK Parliament. Our general portfolio of media interest and citations includes features on various websites associated with the food industry and the provision of scientifically based nutrition information to health professionals and consumers **[10, 11]**.

In summary, our underpinning research in relation to folic acid has had important impacts, not only on the development of food and health policy, but also in translating this policy to the consumer.

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


1) Institute of Medicine (U.S.). Standing Committee on the Scientific Evaluation of Dietary Reference Intakes., et al. (1998). Dietary reference intakes for thiamin, riboflavin, niacin, vitamin $B_6$, folate, vitamin $B_{12}$, pantothenic acid, biotin, and choline. Washington, D.C., National Academy Press.
*Available at*: http://www.ncbi.nlm.nih.gov/books/NBK114310/ [Accessed August 2012].
2) Australian National Health and Medical Research Council (2006). Nutrient Reference Values for Australia and New Zealand.
*Available at*: http://www.nhmrc.gov.au/guidelines/publications/n35-n36-n37 [Accessed August 2012].
3) Food Standards Australia New Zealand (2006) Draft Assessment Report: Consideration of mandatory fortification with folic acid. *Available at*: http://www.foodstandards.gov.au/foodstandards/proposals/proposalp295considerationofmandatoryfortificationwithfolicacid/p295finalassessmentr3568.cfm [Accessed August 2012].
4) Scientific Advisory Committee on Nutrition (2006) Folate and Disease Prevention. TSO, London. *Available at*: http://www.sacn.gov.uk/pdfs/folate_and_disease_prevention_report.pdf [Accessed August 2012].
5) Health Council of the Netherlands. (2008). Advisory Report to the Minister of Health, Welfare and Sport: Towards an optimal use of folic acid. The Hague. *Available at*: http://www.gezondheidsraad.nl/sites/default/files/200802E_0.pdf [Accessed August 2012].
6) Food Safety Authority of Ireland. (2008). Report of the Implementation Group on Folic Acid Food Fortification to the Department of Health and Children. FSAI, Dublin. Available at: www.fsai.ie/WorkArea/DownloadAsset.aspx?id=7602 [Accessed August 2012].
7) The Centers for Disease Control and Prevention (CDC; U.S). (2009). Preventing Neural Tube Birth Defects: A Prevention Model and Resource Guide. Our paper was 1 of just 9 references in a 158 page report. *Available at*: http://www.cdc.gov/ncbddd/orders/pdfs/09_202063-A_Nash_Neural%20Tube%20BD%20Guide%20FINAL508.pdf [Accessed August 2012].
8) Invited Speaker (Prof Helene McNulty) at international joint meetings of FFI with UNICEF:
- Bucharest Romania, October 2008: at the European Regional Flour Fortification Consultation on Micronutrients jointly with the European Food Safety Authority (EFSA)
- Ankara Turkey, June 2012 Addressing Micronutrient deficiencies through flour fortification in the CEE/CIS region. *Available at*: http://www.ffinetwork.org/about/calendar/2012/TurkeyWorkshops.html

9) Kellogg Company (19 May 2009) Food fortification – a valuable option in a "junk" food society. *Presentation by Dr Jenny Walton at Associate Parliamentary Food & Health Forum Available at*: http://www.fhf.org.uk/meetings/2009-05-19_walton.pdf
*10)* Neale T (28 December 2010). Low-Dose Folic Acid Cuts Homocysteine Levels. *MedPage TodayAvailable at:* http://www.medpagetoday.com/PrimaryCare/DietNutrition/24091 [Accessed August 2012].
11) NUTRI-FACTS (15 January 2013). Expert Opinion Detail: Nutrition throughout life: Folic acid. Available at: http://www.nutri-facts.org/eng/expert-opinion/detail/backPid/54/article/nutrition-throughout-life-folic-acid/ [Accessed August 2012].