Institution: University of Dundee
Unit of Assessment: UoA4 Psychology, Psychiatry and Neuroscience
Title of case study: The role of long-chain polyunsaturated fatty acids in the health and development of children

1. Summary of the impact

This research provided the first evidence that long-chain polyunsaturated fatty acids (LCPUFAs) added to infant formula improve the development of specific cognitive abilities. Manufacturers of infant formula have included the research in their submissions to regulatory authorities to justify inclusion of LCPUFAs in infant formula. The research is also included in information and advice on infant feeding provided by manufacturers for the general public. Between 2008 and 2013, the research has been cited by national and international organisations in connection with recommendations for dietary intakes of LCPUFAs and policy on infant nutrition. Formulas enriched with LCPUFA are now available in most countries, and the formula-fed infants worldwide receive the benefits of LCPUFAs.

2. Underpinning research

The LCPUFAs docosahexaenoic acid (DHA) and arachidonic acid (ARA) are important for normal brain development. In the 1980s it was understood that breast-fed infants received adequate amounts of DHA and ARA, but at that time these LCPUFAs were not added to infant formula because it was thought that bottle-fed infants could produce DHA and ARA by converting other fats. However, in the late 1980s research demonstrated that infants were unable to produce sufficient LCPUFAs to meet the needs of the developing brain and it became imperative to determine whether it was necessary to add them to formula.

The initial study, a randomised controlled trial of normal infants whose mothers had elected bottle feeding, was carried out solely at Dundee by Dr **Willatts** (Senior Lecturer, School of Psychology, University of Dundee) and Professor Forsyth (Consultant Paediatrician and Medical Director, NHS Tayside Single Delivery Unit). Infants received formula either containing no LCPUFAs or with added DHA and ARA for the first four months of life. Their cognitive ability was assessed at nine and ten months of age using tests of problem solving developed by **Willatts**. At both ages, the LCPUFA group had significantly better problem solving ability than the standard formula group [i,ii].

These assessments have since been used by other researchers who also found improved problem solving in infants fed LCPUFA-supplemented formula. In 2000 **Willatts** and Forsyth [iii] published one of the first reviews of evidence showing that LCPUFAs affect the development of infant cognition; in 2008 they and others published a more extensive review which has since been cited by expert authorities in recommendations and policy statements concerning infant nutrition [iv].

This work was funded by the formula manufacturer Milupa GmbH & Co KG. A follow-up of the children in Dundee and in three of these centres was undertaken by **Willatts** and Forsyth in 1997-2000 [v]. Measures were taken of IQ, problem solving and blood pressure at six years of age. It was known that children who were breast fed have lower blood pressure than children who were bottle fed and this follow up provided an opportunity to test the hypothesis that LCPUFAs in breast milk contribute to reduced blood pressure. There were two main findings. Although overall problem solving ability was the same in the two groups, children who received LCPUFAs were 20 per cent faster at solving problems [vi]. This result showed that LCPUFAs in infancy had a long term effect on problem solving efficiency at six years. Additionally, children who received LCPUFAs in their formula had lower blood pressure than children who received formula with no LCPUFAs. This was the first direct evidence that LCPUFAs in infant milk affect blood pressure in later childhood [v]. Blood pressure is known to track from childhood into adult life and deviations from normal blood pressure during childhood are amplified in later life. This result is therefore relevant to public health strategies aimed at improving the long-term health of the population.

3. References to the research

i. **Willatts** P, Forsyth JS, DiModugno MK, Varma S and Colvin M (1998). Effect of long-chain polyunsaturated fatty acids in infant formula on problem solving at 10 months of age. *Lancet* **352**, 688-691 (DOI:10.1016/S0140-6736(97)11374-5).

ii. **Willatts** P, Forsyth JS, DiModugno MK, Varma S and Colvin M (1998). Influence of Long-Chain Polyunsaturated Fatty Acids on Infant Cognitive Function. *Lipids* **33**, 973-980 (DOI: 10.1007/s11745-998-0294-7).

iii. **Willatts** P and Forsyth JS (2000). The role of long-chain polyunsaturated fatty acids in infant cognitive development. *Prostaglandins, Leukotrienes and Essential Fatty Acids* **63**, 95-100 (DOI: 10.1054/plef.2000.0198).

iv. Koletzko B, Lien E, Agostoni C, Bohles H, Campoy C, Cetin I, Decsi T, Dudenhausen JW, Dupont C, Forsyth JS, Hoesli I, Holzgreve W, Lapillonne A, Putet G, Secher NJ, Symonds M, Szajewska H, **Willatts** P and Uauy R (2008). The roles of long-chain polyunsaturated fatty acids in pregnancy, lactation and infancy: review of current knowledge and consensus recommendations. *J. Perinatal Medicine* **36**, 5-14 (DOI: 10.1515/JPM.2008.001).

v. Forsyth JS, **Willatts** P, Agostoni C, Bissenden J, Casaer P and Boehm G (2003). Long chain polyunsaturated fatty acid supplementation in infant formula and blood pressure in later childhood: follow up of a randomised controlled trial. *Brit. Med. J.* **326**, 953-955 (DOI: http://dx.doi.org/10.1136/bmj.326.7396.953).

vi. **Willatts** P, Forsyth JS, Agostoni C, Casaer P, Riva E and Boehm G (2013) Effects of long-chain polyunsaturated fatty acid supplementation in infant formula on cognitive function in later childhood. *Am. J. Clin. Nutr.* **98**, 536S-542S (DOI: 10.3945/ajcn.112.038612).

Funding

- **Willatts** P in conjunction with J.S. Forsyth (Child Health) The relation of maternal fatty acid status in pregnancy to behaviour problems in later childhood; Martek Biosciences (01/08/05 – 31/03/06) £24,056.
- **Willatts** P in conjunction with J.S. Forsyth (Child Health) and P. Ross (Molecular & Cellular Pathology): A randomised controlled study of LC-PUFA supplementation from 6 to 18 months of age; Wyeth Nutritionals (01/01/02 – 31/12/05) £688,132.
- **Willatts** P in conjunction with J.S. Forsyth (Child Health) and G. Mires (Obstetrics & Gynaecology): Investigation into maternal and infant LCP status; Nutricia Ltd (01/6/99 - 31/05/00) £52,522.
- **Willatts** P in conjunction with J.S. Forsyth (Child Health): A randomised study of the relation of LCPUFA in infant formula to cognitive and executive function in 5-year-old children; Milupa GmbH & Co KG (01/11/97 - 30/11/00) £174,431.
- **Willatts** P in conjunction with J.S. Forsyth (Child Health) & G. Mires (Obstetrics & Gynaecology): A study of the relation of maternal and infant long-chain polyunsaturated fatty acid status to infant cognitive function; Chief Scientist Office, Scotland (01/6/97 - 31/7/99) £136,764.
- **Willatts** P in conjunction with J.S. Forsyth (Child Health): A randomised study of the effects of long-chain polyunsaturated fatty acids in infant formula on 3-year-old cognitive behaviour and attention; Milupa Ltd (01/2/96 - 1/1/98) £48,908.
- **Willatts** P in conjunction with J.S. Forsyth (Child Health): The relation between LCP enriched formula and infant cognitive development; Milupa Ltd (01/6/93 - 3/07/95) £64,857.

4. Details of the impact

Our research has informed worldwide dietary advice and therefore the health and development of children. It has been cited by national and international organisations in connection with

recommendations for dietary intake of LCPUFAs and policies on infant nutrition which influence the dietary advice given by governments to the public. Additionally, infant formula manufacturers are guided by recommendations from expert bodies when considering the amount of LCPUFAs to add to formula and cite the research in advice given to the public about infant feeding.

- In 2013, The World Health Organisation (WHO) published a systematic review of the long-term benefits of breastfeeding [1], citing Forsyth *et al.* (2003) [v]. The WHO plays a leading role in advising governments and national health organisations on policy concerning breastfeeding.
- In 2012, the U.S. National Heart, Lung, and Blood Institute of the Department of Health and Human Services published new guidelines for cardiovascular health and risk reduction in children [2]. The report cited Koletzko *et al* (2008) and Forsyth *et al.* (2003) [iv,v].
- In 2011, the French Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (Anses) published updated recommendations for dietary intake of fatty acids [3], citing Koletzko *et al.* (2008) [iv].
- In 2011, the Food Safety Authority of Ireland published Scientific Recommendations for a National Infant Feeding Policy (2nd edition) [4], citing Koletzko *et al*. (2008) [iv].
- In 2009 the U.S. Food and Drug Administration published a summary of published research on the beneficial effects of fish consumption and omega-3 fatty acids on neurodevelopmental health [5], citing **Willatts** *et al.* (1998a, 1998b) [i,ii] and **Willatts** and Forsyth (2000) [iii].
- In 2009, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) published a statement on breast feeding [6] citing Forsyth *et al.* (2003) [v].
- In 2008, the International Society for the Study of Fatty Acids and Lipids published a statement on dietary fats in infant nutrition [7] which cited the article by Koletzko *et al.* (2008).

The European Food Safety Authority (EFSA) publishes opinions of the evidence portfolios surrounding claims for the health benefits of foods which are submitted by the food industry in European member states. These opinions form the basis of food law passed by the European Commission, and are relevant to the health of the population in Europe. The research by **Willatts** and Forsyth contributed to several recent opinions (2009-2012) [8] published by EFSA concerning the health benefits of LCPUFAs.

Willatts has been actively involved in communicating the findings of this research to the general public and health care professionals. He has given numerous radio, television and press interviews, as well as presentations to health care professionals at workshops and symposia. Infant formula manufacturers have highlighted the research in the information and advice on infant feeding they provide to the general public and healthcare professionals. Examples include Mead Johnson Nutrition [9], Wyeth Nutrition [10], Danone (Aptamil) [11], DSM [12] and Nutricia [13].

Willatts has been an invited speaker at numerous national and international meetings on LCPUFAs and children's development which were sponsored by industry and other organisations to inform health-care professionals, industry and the public:

- Lecture at the Middle East Pediatric Update in Budapest, May 2013, for invited health-care professionals, sponsored by Danone.
- Lectures in Hanoi and Ho Chi Minh City, February 2012, to 500 and 800 invited health-care professionals, sponsored by Mead Johnson Nutrition.
- Lecture for Mead Johnson Nutrition Staff on methods employed in infant nutrition studies, September 2011, Colombo, Sri Lanka.
- British Science Festival, Bradford, September 2011. An invited presentation in a symposium organised by the British Nutrition Foundation (attended by general public).
- International Life Sciences Institute: Southeast Asia Region. Symposium on Nutrition and Cognition – Towards Research and Application for Different Life Stages, Kuala Lumpur, October 19-21 2010 (attended by health-care professionals and industry).

- Lecture in Moscow, September 2010 for invited health-care professionals, sponsored by Mead Johnson Nutrition.
- Lecture for Mead Johnson Nutrition staff on methods employed in infant nutrition studies, April 2010, Hong Kong.

5. Sources to corroborate the impact

1. Horta BL and Victora CG (2013). Long-term effects of breastfeeding. World Health Organization. ISBN 978 92 4 150530 7; available at: www.who.int/iris/bitstream/10665/79198/1/9789241505307_eng.pdf.
2. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (2012) Full Report. U.S. National Heart, Lung, and Blood Institute of the Department of Health and Human Services; available at: http://www.nhlbi.nih.gov/guidelines/cvd_ped/peds_guidelines_full.pdf.
3. Actualisation des Apports Nutritionnels Conseillés pour les acides gras (2011), Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail; available at: http://www.anses.fr/Documents/NUT2006sa0359Ra.pdf.
4. Food Safety Authority of Ireland (2011) Scientific Recommendations for a National Infant Feeding Policy, 2nd Edition. ISBN 1-904465-78-1; available at:

   www.fsai.ie/scientificrecommendationsforanationalinfantfeedingpolicy.html
5. US Food and Drug Administration (2009) Summary of Published Research on the Beneficial Effects of Fish Consumption and Omega-3 Fatty Acids for Certain Neurodevelopmental and Cardiovascular Endpoints: Section B – Neurodevelopmental; available at:

   http://www.fda.gov/Food/FoodborneIllnessContaminants/ChemicalContaminants/ucm153054.htm
6. Agostoni C, Braegger C, Decsi T, Kolacek S, Koletzko B, Michaelsen KF, Mihatsch W, Moreno LA, Puntis J, Shamir R, Szajewska H, Turck D, van Goudoever J. ESPGHAN Committee on Nutrition (2009) Breast-feeding: A Commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* **49**,112–125 (DOI: 10.1097/MPG.0b013e31819f1e05).
7. Gibson R, Makrides M, Koletzko B, Brenna T and Craig-Schmidt M (2008) ISSFAL Statement on Dietary Fats in Infant Nutrition (May 2008); available at: http://www.issfal.org/statements/pufa-recommendations/statement-2.
8. EFSA Panel on Dietetic Products, Nutrition and Allergies (2009) Scientific Opinion: DHA and ARA and brain development; Scientific substantiation of a health claim related to docosahexaenoic acid (DHA) and arachidonic acid (ARA) and brain development pursuant to Article14 of Regulation (EC) No 1924/2006 *The EFSA Journal* **1000**, 1-13; available at: http://www.efsa.europa.eu/en/scdocs/doc/1000.pdf.
9. http://www.meadjohnsonasia.com.my/expert-information/icare/scientific-studies-on-dha-and-ara.aspx; http://www.mjn.com/newsletterimages/v5s3pp.html; http://www.prnewswire.com/news-releases/new-enfamil-lipiltm-the-first-and-only-infant-formula-to-contain-additional-nutrients-important-to-babies-mental-and-visual-development-75397202.html
10. https://www.wyethnutritionacademy.org/Wyeth-Nutrition/resources-hcps/nutrition-for-toddlers/dha-and-aa/information
11. http://www.aptamilhcp.ie/products/43-products/from-6-months/108-aptamil-follow-on-milk-aptamil-follow-on-milk?prd=1
12. http://www.dsm.com/content/dam/dsm/foodandbeverages/en_US/documents/53331-mediakit-spread-infantdev-%282%29.pdf
13. http://www.nutricia.ie/articles/infatrini_the_completepackage_for_faltering_growth