Institution: Ulster University

Unit of Assessment: Allied Health Professions, Dentistry, Nursing and Pharmacy (3)

Title of case study: ICS-3 Informing global policymakers on the safe consumption of fish by pregnant women and children and thereby influencing health professionals and industry for the benefit of maternal and child health

Period when the underpinning research was undertaken: 2000 – 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:
Professor JJ Strain	Professor of Human Nutrition	1981-present
Dr Emeir McSorley (née Duffy)	Senior Lecturer in Human Nutrition	2002-present
Dr Maria Mulhern (née Barnes)	Lecturer in Food Science	2006-present
Dr Alison Yeates (née McAfee)	Research Fellow	2010-present

Period when the claimed impact occurred: 2014 - 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Our underpinning research investigating the safe consumption of fish (in terms of methylmercury exposure) is used globally by:

Impact 1 Policymakers in setting current dietary recommendations for fish consumption during pregnancy worldwide to improve maternal and child health. Examples include the Food and Drug Administration (FDA), the Dietary Guidelines Advisory Committee (DGAC), the European Food Safety Authority (EFSA) and Food Standards Australia and New Zealand (FSANZ). Additionally, the Food Safety Authority of Ireland (FSAI) used our data to set dietary guidelines for children.

Impact 2 Health professionals who use these guidelines when advising pregnant women and the food industry in the promotion of products.

2. Underpinning research

Methylmercury and the Seychelles Child Development Study

Methylmercury (MeHg) is a neurotoxicant which is naturally present in all fish and to which the foetal brain is particularly susceptible. The Seychelles Child Development Study (SCDS), in which Ulster is involved, has investigated the public health risk of MeHg exposure from fish consumption during pregnancy in the high fish-eating population of the Republic of Seychelles for over 30 years. Since 2000, work at Ulster by Strain, McSorley, Yeates and Mulhern, undertaken in collaboration with the University of Rochester, New York, the Department of Health, Republic of Seychelles and the Karolinska Institute, Sweden, has provided results published in world-leading nutrition and toxicology journals which have influenced policymakers worldwide.

The need for the research

For decades, government advisories have cautioned pregnant women to restrict their fish consumption based on limited epidemiological evidence, which was not globally generalisable. Many communities worldwide depend on fish as their primary source of protein and other essential nutrients required for optimal health. Limiting maternal fish intake, therefore, has

potentially serious negative consequences to maternal health and the development of children. The SCDS is the largest prospective longitudinal study specifically designed to investigate the impact of low-level prenatal MeHg exposure from fish consumption on child neurodevelopment.

The SCDS cohorts and Ulster's involvement

The SCDS consists of four longitudinal mother-child cohorts and Ulster is involved in all four. Ulster led in the design of the first Nutrition Cohort (NC1; n=300, recruited 2001) and the second Nutrition Cohort (NC2; n=1522, recruited 2008-2011). The NC1, and subsequently the larger NC2, were set up to see if nutrition could explain the unexpected positive associations between MeHg and neurodevelopment observed in the earlier cohort (Main; n=779, recruited 1989-1990).

Methylmercury exposure and child development

Our research underpins global policies in place today on the safe consumption of fish in pregnancy. In particular, the SCDS has shown that the relationship between MeHg exposure from fish consumption and child neurodevelopment is more complex than initially thought. We have demonstrated that the benefits of the n-3 polyunsaturated fatty acids (PUFA) present in fish outweigh any adverse neurotoxic effects of prenatal MeHg exposure on child neurodevelopment (**R1-R5**). Our NC1 cohort is one of the first epidemiological studies (**R1**) to report a critical role of maternal nutrition in the relationship between prenatal MeHg exposure and child neurodevelopment.

Our partner paper, reporting on NC1 findings, expands on the beneficial role of prenatal n-3 PUFA in child development and is one of the most important sources of outstanding quality research underpinning current global policy in pregnancy (**R2**). Our research (**R3**) continues to provide evidence of improved outcomes in adolescence (Main cohort) with increasing prenatal MeHg exposure and the beneficial role of nutrients in fish consumed during pregnancy. Further research in our NC1 cohort (**R4**) provided novel data to corroborate previous findings from the SCDS and, significantly, showed that the benefits of maternal PUFA extend to five years of age in their children. Another paper (**R5**) reported no evidence of any adverse association of prenatal exposure to MeHg in young adults from the Main cohort.

The larger NC2 study confirmed findings from the NC1 cohort that n-3 PUFA in fish are beneficial for child development and identified that the balance of maternal n-6 and n-3 PUFA status is important in modifying the potential neurotoxic effects of MeHg (**R6**). Our recent publications (not cited here) suggest genetics have an important role in MeHg body burden and nutritional status: that is, polymorphisms in genes responsible for MeHg transport and excretion and for PUFA metabolism respectively, affected maternal hair MeHg and blood PUFA concentrations in all cohorts.

3. References to the research

The following outputs are published in leading peer-reviewed journals and are reviewed by internationally based editorial boards.

R1: Davidson PW, **Strain JJ**, Myers GJ, Thurston SW, Bonham MP, Shamlaye CF, Stokes-Riner A, Wallace JM, Robson PJ, **Duffy EM**, Georger LA, Sloane-Reeves J, Cernichiari E, Canfield RL, Cox C, Huang LS, Janciuras J and Clarkson TW (2008). Neurodevelopmental effects of maternal nutritional status and exposure to methylmercury from eating fish during pregnancy. *Neurotoxicology*, 29(5):767-775. DOI: 10.1016/j.neuro.2008.06.001.

R2: **Strain JJ**, Davidson PW, Bonham MP**, Duffy EM,** Stokes-Riner A, Thurston SW, Wallace JM, Robson PJ, Shamlaye CF, Georger LA, Sloane-Reeves J, Cernichiari E, Canfield RL, Cox C, Huang LS, Janciuras J, Myers GJ and Clarkson TW (2008). Associations of maternal long-chain polyunsaturated fatty acids, methylmercury, and infant development in the Seychelles Child Development Nutrition Study. *Neurotoxicology*, 29(5):776-82. DOI: 10.1016/j.neuro.2008.06.002.

R3: Davidson PW, Cory-Slechta DA, Thurston SW, Huang L-S, Shamlaye CF, Gunzler D, Watson G, van Wijngaarden E, Zareba G, Klein JD, Clarkson TW, **Strain JJ** and Myers GJ (2011). Fish consumption and prenatal methylmercury exposure: Cognitive and behavioral

outcomes in the main cohort at 17 years from the Seychelles Child Development Study. NeuroToxicology, 32, 711-717. DOI: 10.1016/j.neuro.2011.08.003
R4: **Strain JJ,** Davidson PW, Thurston SW, Harrington D, **Mulhern MS, McAfee AJ,** van Wijngaarden E, Shamlaye CF, Henderson J, Watson GE, Zareba G, Cory-Slechta DA, Lynch M, Wallace JM, **McSorley EM,** Bonham MP, Stokes-Riner A, Sloane-Reeves J, Janciuras J, Wong R, Clarkson TW and Myers GJ (2012). Maternal PUFA status but not prenatal methylmercury exposure is associated with children's language functions at age five years in the Seychelles. Journal of Nutrition, 142(11):1943-9. DOI: 10.3945/jn.112.163493.
R5: Van Wijngaarden E, Thurston SW, Myers GJ, **Strain JJ,** Weiss B, Zarcone T, Watson GE, Zareba G, **McSorley EM, Mulhern MS, Yeates AJ,** Henderson J and Gedeon J (2013). Prenatal methylmercury exposure in relation to neurodevelopment and behavior at 19 years of age in the Seychelles Child Development Study. Neurotoxicology and Teratology, 39, 19-25. DOI: 10.1016/j.ntt.2013.06.003.
R6: **Strain JJ, Yeates AJ,** van Wijngaarden E, Thurston SW, **Mulhern MS, McSorley EM,** Watson GE, Love TM, Smith TH, Yost K, Harrington D, Shamlaye CF, Henderson J, Myers GJ and Davidson PW (2015). Prenatal exposure to methylmercury from fish consumption and polyunsaturated fatty acids: associations with child development at 20 mo of age in an observational study in the Republic of Seychelles. *American Journal of Clinical Nutrition*, 101(3):530-7. DOI: 10.3945/ajcn.114.100503.

Key research grants:

- Strain JJ, McSorley EM, Mulhern MS and Yeates AJ. *Factors modifying the toxicity of methylmercury in a fish-eating population* (in collaboration with the University of Rochester, NY). Funded by the National Institute of Health (NIH), 2015-2020; GBP768,785.
- Yeates AJ, McSorley EM, Mulhern MS and Strain JJ. *Genetic susceptibility to developmental neurotoxicity of methylmercury in fish - MercuryGen II* (in collaboration with Karolinska Institute, Sweden and the University of Rochester, NY) Funded by the Swedish Research Council, 2017-2020; GBP20,478.
- Strain JJ, Yeates AJ, Mulhern MS, Allsopp P, Crowe W and McSorley EM. *MeHg exposure and autoimmunity in the Seychelles Child Development Study Main Cohort* (in collaboration with the University of Rochester, NY). Funded by the National Institute of Health (NIH), Environmental Health Sciences Center, 2017-2018; GBP15,121.
- Yeates AJ, Strain JJ, Mulhern MS and McSorley EM. *Genetic Modifiers of Hg toxicity – MercuryGen I* (in collaboration with Karolinska Institute, Sweden and the University of Rochester, NY) Funded by the Swedish Research Council, 2014-2016; GBP26,516.
- Strain JJ, McSorley EM, Mulhern MS and Yeates AJ. *Factors modifying the neurotoxicity of methylmercury* (in collaboration with the University of Rochester, NY). Funded by the NIH, 2013-2015; GBP4,044.
- Strain JJ, Wallace JMW and Duffy EM. *Methylmercury effects on adolescent development.* Funded by US National Institute of Environmental Health Sciences, NIH; 2011-2015; GBP53,514.
- Strain JJ, Chang, CK, Wallace JMW and Duffy EM. *Toxicity of methylmercury in a fish-eating population.* Funded by US National Institute of Environmental Health Sciences; 2010-2014; GBP711,785.
- Strain JJ, Wallace JMW, Robson PJ, Rowland I and Livingstone, MBE. *Factors modifying the toxicity of methylmercury in a fish-eating population.* Funded by US National Institute of Environmental Health Sciences, NIH; 2001-2012; GBP472,000.
- Strain, JJ, Bonham MP, Wallace JMW, Duffy EM, Rowland I and Livingstone MBE. *Public health impact of low-level mixed element exposure in susceptible population strata (PHIME).* Funded by grant from the EC through its Sixth Framework Programme for RTD; 2006-2011; GBP517,740.

4. Details of the impact

Impact 1: Setting dietary recommendations by policymakers for safe fish consumption during pregnancy and in childhood:

- Experts and global leaders in health have used the research undertaken in the SCDS to revise guidelines on fish intake during pregnancy. The SCDS remains the only series of longitudinal studies to address the risk of fish consumption in pregnancy with respect to MeHg and is the most informative for policymakers.
- The United States FDA in 2014 modelled the benefits to foetal neurodevelopment of PUFA and the possible harm to foetal neurodevelopment from MeHg for various fish (the "net effects" models [**C1**]). These models showed that the benefits to foetal neurodevelopment from fish consumption during pregnancy exceed the possible adverse effects from MeHg until the mother consumes uncommonly large quantities of fish. Data from the SCDS were germane in reaching this conclusion and a total of 6 references to our work, including **R1-R3, R5,** are cited in the document [**C1**]**.**
- The Panel on Dietetic Products, Nutrition and Allergies (NDA) of the European Food Safety Authority (EFSA) in 2014 published a Scientific Opinion on the health benefits of seafood consumption in relation to health risks associated with exposure to MeHg [**C2**]. Data from studies undertaken in the SCDS (**R1, R2, R4**) were central to these changes and conclusions. This Opinion was a landmark with respect to revising global recommendations for maternal advice on fish consumption during pregnancy and recognised the evidence from the SCDS that n-3 PUFA in fish may counteract potential negative effects from MeHg exposure. The Opinion considered that beneficial nutrients in fish may account for the positive outcomes in the SCDS study compared with the adverse outcomes in previous research undertaken in mother-child cohorts elsewhere.
- The Environmental Working Group (EWG) in America in 2014 utilised information from the SCDS (**R2**) to inform the American members of the Codex Panel about the safe consumption of fish during pregnancy [**C3**].
- Arising from our underpinning research, maternal advice has been revised by policymakers in several countries, including the Food Standards Australia and New Zealand (FANZS), to reflect better the direct benefits and risks of fish eaten during pregnancy [**C4, updated Dec 2020**].
- In the updated 2015-2020 Dietary Guidelines for Americans [**C5**], it was appreciated that a variety of seafood in recommended amounts outweighs the health risks associated with MeHg. In 2019, the most recent version of the advice given to pregnant women on fish consumption from the Environmental Protection Agency (EPA) and the US FDA [**C6**], promotes the science-based recommendations of the 2015-2020 Dietary Guidelines for Americans.
- Most recently, the Scientific Report of the 2020 Dietary Guidelines Advisory Committee (DGAC) in the US used data from the SCDS (**R1**) in its review which concluded that there was moderate evidence to indicate that seafood intake during pregnancy is positively associated with measures of cognitive development in young children. Using this information, the DGAC has been updating Dietary Guidelines for Americans 2020-2025 and the most recent update has used data (**R1**) from the SCDS [**C7**].
- In addition to setting dietary recommendations for fish consumption during pregnancy, our data (including **R4, R6**) were used in 2020 by the Food Safety Authority of Ireland (FSAI) in setting food-based dietary guidelines for n-3 PUFA for 1- to 5-year-olds in Ireland [**C8**].

Impact 2: Use of dietary recommendations globally by health professionals to improve maternal and child health and by the food industry to promote its products.

- Globally, the dietary recommendations developed with input from the SCDS (including **R1-R5**) have been cited on various websites, including the American College of Obstetricians and Gynecologists [**C9**]. This website is utilised not only by clinicians and health professionals when giving updated policy influenced advice to pregnant women, but is also directly accessed by the public for up-to-date evidence-based advice on a healthy pregnancy.
- In response to the revised dietary recommendations the food industry, and in particular the marine food industry, is now (from 2017) using these guidelines in promotional

literature [**C10**]. Our underpinning research, therefore, has economic benefits, in that industry is promoting fish consumption in line with addressing global nutritional needs.

- Furthermore, revisions to dietary guidelines automatically impact the entire food industry in that every product with a claim relating to fish consumption (on pack or elsewhere), will comply with the most recent guidelines set by the authorities in the relevant region; this in turn impacts public health globally. Such guidelines promoted by food manufacturers e.g., the State of Alaska and the Alaska Seafood Industry [**C10**], reach a wide audience and give benefit to consumers who receive and act upon the evidence-based information.

5. Sources to corroborate the impact

C1: United States Food and Drug Administration; Quantitative Assessment of the Net Effects on Fetal Neurodevelopment from Eating Commercial Fish (As Measured by IQ and also by Early Age Verbal Development in Children) | FDA (May/June 2014).

C2: EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014. Scientific Opinion on health benefits of seafood (fish and shellfish) consumption in relation to health risks associated with exposure to methylmercury. EFSA Journal 2014;12(7):3761, 80 pp. doi:10.2903/j.efsa.2014.3761.

C3: Environmental Working Group (EWG) America, Consumer guide to seafood.

C4: Food Standards Australia and New Zealand (FSANZ), Advice on fish consumption.

C5: U.S. Department of Health and Human Services and U.S. Department of Agriculture. *2015–2020 Dietary Guidelines for Americans*. 8th Edition. December 2015 (page 24: reference to FDA and EPA dietary guidance for safe consumption of fish during pregnancy).

C6: FDA, Advice about eating fish. EPA-FDA, Advice about eating fish and shellfish (July 2019).

C7: Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC. Part D. Chapter 2: Food, Beverage, and Nutrient Consumption During Pregnancy (reference 175).

C8: FSAI, Scientific recommendations for food-based dietary guidelines for 1 to 5 year-olds in Ireland (page 130, 177).

C9: For example: ACOG, Update on seafood consumption during pregnancy.

C10: For example: Pure Alaska Omega webpage: The Science of Pure Alaska Omega; and, Alaska Seafood webpage: Alaska Seafood health & nutrition (A public-private partnership between the State of Alaska and the Alaska seafood industry).