

Institution: University of East Anglia
Unit of Assessment: 6 - Agriculture, Veterinary and Food Science
Title of case study: <p style="text-align: center;">Risk assessment and health claims for soy and human health</p>
<p>1. Summary of the impact</p> <p>Our impact has been to protect the public by informing and influencing both the international policy debate on health claims associated with soy consumption, and the relevant regulatory risk assessment authorities.</p> <p>Our research formed a key component of dossiers that resulted in the rejection of health claims by the European Food Safety Authority (EFSA, the EU agency responsible for the scientific substantiation of health claims) relating to soy isoflavones and a number of health endpoints including bone health, heart health and menopausal symptoms. Earlier work had underpinned decisions on comparable health claims in the US and UK.</p> <p>Our soy isoflavone research also provided key scientific data on the absorption of isoflavones by the body (and dependence on age and food source) to the UK Government Committee on Toxicity (COT) policy review on the toxicity of chemicals with a specific focus on soy infant formula. This expands on COT advice in 2003, which used earlier Cassidy research and helped to inform the UK government's (Food Standards Agency) research programme on phytoestrogens /isoflavones.</p>
<p>2. Underpinning research</p> <p>Our underpinning research is based on a body of work building the evidence-base for the role of plant bioactive compounds called isoflavones (which are almost exclusively present in soy based foods/supplements) on human health and disease risk.</p> <p>Professor Cassidy has an extensive track record of research in this area from the 1990s and has continued this work at UEA since joining in 2004. Her research has contributed significantly to the literature on the risk:benefit profile of isoflavone foods/supplements, providing evidence to inform both health claim submissions and policy.</p> <p><u>Evaluation of health claims for EFSA on soy isoflavones and bone health:</u> We conducted a 1 year multicentre randomised controlled trial which investigated the effects of isoflavone-enriched foods on bone mineral density, bone metabolism, and hormonal status in postmenopausal women (research reference 1). This robust long-term trial observed no effect of isoflavone consumption on validated measures of osteoporosis risk, and provided strong supportive evidence for the EFSA opinion to conclude that consumption of soy isoflavones were not effective in preventing bone loss. The EFSA opinion was further informed by our research conducted as part of a pan-EU network of excellence called Phytohealth (research reference 2) which examined optimal dose, food source and duration of use of isoflavones for a range of health outcomes including bone health. Our research (research reference 2) was also considered in the EFSA panel decisions to reject other soy health claims (corroborating source C) with the panel concluding that the evidence for a cause and effect relationship was not established between soy isoflavone consumption and a range of health endpoints including vasomotor symptoms and cardiovascular risk factors.</p> <p><u>Risk assessment of isoflavones:</u> There has been substantial debate on the risks:benefits of soy isoflavones for specific consumer groups, including infants fed soy infant formula, and postmenopausal women. For postmenopausal women there has been significant focus on potential risks in relation to hormonal effects, breast cancer risk and thyroid function. Hormonal effects have been investigated in numerous studies, but findings have been equivocal and the risks:benefit is a contentious issue. Our research on how isoflavones are absorbed and handled by the body (bioavailability) reported on the importance of the dietary form of the food and showed that isoflavones are more rapidly absorbed from soy milk than from solid soy foods (research reference 3). Using our original clinical trial data (investigating how these compounds are metabolised by the body and their health effects) together with our expertise in systematic reviewing methodologies, our research has provided considerable clarity in areas where medical</p>

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and public concern had been expressed. We also showed that given the totality of evidence the effects on hormonal status are modest and unlikely to be deleterious to health (research reference 4) and do not alter breast density (a biomarker of breast cancer risk in either pre- or post-menopausal women) (research reference 5). Furthermore we have shown that the source of soy is critical for potential cardiovascular benefits: soy protein isolate in food, but not in isolated isoflavone supplements, improved blood pressure and cholesterol levels (research reference 6).

Lead UEA researchers:

- **A Cassidy**, Professor of Nutrition (UEA since 2004), played a leading role in all the studies. Professor Cassidy published the first paper showing the biological effects of soy isoflavones in humans in 1994. Since then, she has conducted numerous investigations on bioavailability and health effects of isoflavones, and led systematic reviews, backed by high quality research grants.
- **L Hooper**, Senior Lecturer (UEA since 2005), National Institute for Health Research Career Development Fellow and member of the World Health Organisation Nutrition Guidance Expert Advisory Group, provided expertise in systematic reviews/meta-analyses.

3. References to the research

(UEA authors in bold) {citation count from Scopus on 21/11/13}

1. Long-term consumption of isoflavone-enriched foods does not affect bone mineral density, bone metabolism, or hormonal status in early postmenopausal women: a randomized, double-blind, placebo controlled study
Brink E, Coxam V, Robins S, Wahala K, **Cassidy A**, Branca F; PHYTOS Investigators
Am J Clin Nutrition **2008** 87:761-70 {64}
<http://ajcn.nutrition.org/content/87/3/761>
2. Critical review of health effects of soyabean phyto-oestrogens in post-menopausal women
Cassidy A, Albertazzi P, Lise Nielsen I, Hall W, Williamson G, Tetens I, Atkins S, Cross H, Manios Y, Wolk A, Steiner C, Branca F
Proc Nutr Soc. **2006** 65:76-92 {135}
doi: 10.1079/PNS2005476
3. Factors affecting the bioavailability of soy isoflavones in humans after ingestion of physiologically relevant levels from different soy foods
Cassidy A, Brown JE, Hawdon A, Faughnan MS, King LJ, Millward J, Zimmer-Nechemias L, Wolfe B, Setchell KD
J Nutr. **2006** 136:45-51 {91}
<http://jn.nutrition.org/content/136/1/45>
4. Effects of soy protein and isoflavones on circulating hormone concentrations in pre- and post-menopausal women: a systematic review and meta-analysis
Hooper L, Ryder JJ, Kurzer MS, Lampe JW, Messina MJ, Phipps WR, **Cassidy A**
Hum Reprod Update. **2009** 15:423-40 {54}
doi: 10.1093/humupd/dmp010
5. Effects of isoflavones on breast density in pre- and post-menopausal women: a systematic review and meta-analysis of randomized controlled trials
Hooper L, Madhavan G, Tice JA, **Leinster SJ**, **Cassidy A**
Hum Reprod Update. **2010** 16:745-60 {32}
doi: 10.1093/humupd/dmq011
6. Flavonoids, flavonoid-rich foods, and cardiovascular risk: a meta-analysis of randomized controlled trials
Hooper L, Kroon PA, Rimm EB, Cohn JS, **Harvey I**, Le Cornu K, Ryder J, Hall WL, **Cassidy A**
Am J Clin Nutrition **2008** 88:38-50 {324}
<http://ajcn.nutrition.org/content/88/1/38>

Key funding for the research:

- MAFF/FSA – (Cassidy PI) Absorption, distribution, metabolism & excretion of isoflavones in

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vivo (1998–2001) £181K

- MAFF/FSA (Cassidy PI) Absorption & metabolism of dietary phytoestrogens in humans – effect of age, gender, food matrix & chemical composition (1999–2002) £388K
- EU Phytohealth network of Excellence (2003–2006) £555K
- Diabetes UK (Cassidy PI) Reducing cardiovascular risk with dietary flavonoids in postmenopausal women with type 2 diabetes (2007–2011) £223K
- Soy Nutrition Institute, USA (Soy Industry body) Effects of soy and isoflavones on hormonal status in women: a systematic review (2008) £38K
- BBSRC Dietary Flavonoids, Fish oils and cardiovascular Health (Joint PI Minihane, BBSRC (IFR/UEA Institute Strategic Programme grant) (Sept 2012- Aug 2017) £2.2 million

4. Details of the impact

Evaluation and substantiation of health claims for EFSA on soy isoflavones and health:

Health claims made in relation to food products require authorisation under EU law before they can be used in the labelling and marketing of products in the EU. EFSA are the EU agency who are responsible for verifying the scientific substantiation of any health claims. These health claims are a core marketing strategy that the global food industry employ to increase sales of premium products with claimed enhanced functionality. For the consumer, the demonstration of evidence-based health claims can protect them from purchasing foods with misleading information on potential benefits. To substantiate or refute the significant number of claims made by the food industry, EFSA (the EU agency that provides independent scientific advice and communication on existing and emerging risks associated with the food chain) committees comprehensively review all clinical trials and associated research following a submission by the food industry to produce a panel consensus document (EFSA scientific opinion). Our research has been used to underpin a number of EFSA scientific opinions on health claims for isoflavones present in soy foods.

In 2009, the EFSA Panel on Dietetic Products, Nutrition and Allergies relied on some of our research (research reference 1-2) to develop a scientific opinion that cause and effect relationships have not been established between the consumption of soy isoflavones and the maintenance of bone mineral density in postmenopausal women. Specifically, a distinct contribution of our work (research reference 2) was to draw attention to the 'lack of evidence of a clear dose-response relationship between dietary intake of soy isoflavones and the claimed effect, and the different results obtained depending on the source and nature of the isoflavones used' (pp.6-7, corroborating source A). This health claim was reviewed by EFSA in 2012, and our EU funded work (research reference 1) was used to further inform the opinion that consumption of soy isoflavones does not show an effect on bone mineral density (pp. 8&12, corroborating source B). As a result, the health claim was rejected by EFSA, and food companies (and others) are not permitted to promote food containing soy isoflavones for bone health in Europe. Our research (research reference 2) was also key to the rejection of other soy health claims (corroborating source C) with the panel concluding that the evidence for a cause and effect relationship was not established between soy isoflavone consumption and a range of other health endpoints including vasomotor symptoms and cardiovascular risk factors. Professor Cassidy's earlier work on soy foods, specifically soy protein, was used to underpin decisions on health claims relating to heart health in the USA (Food & Drink Administration, 1999) and the UK Joint Health Claims Initiative (JHCI) (2002).

Risk assessment 'Hazard characterisation of isoflavones' - Refinement of regulation EC

1924/2006: Professor Cassidy, through her research outputs and committee involvement has significantly informed the policy debate surrounding the potential risks:benefits of consuming soy isoflavones. Some controversy surrounds the consumption of soy, given its oestrogenic potential and the potential for high levels of exposure in certain population groups through supplement use and soy infant formula. Our research has influenced the consensus statements of international government agencies including EFSA, the American Heart Association (AHA) Advisory group and the UK Government Committee on Toxicity (COT), who have examined the potential hazards associated with consumption of soy isoflavones.

In the UK, COT's policy review of the toxicity of chemicals in the diet was informed by Cassidy's soy isoflavones based research. The recent 2012 initial report focusses on the infant diet in

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support of a review by the UK Government Scientific Advisory Committee on Nutrition on infant feeding. In particular, the report uses UEA research (research reference 3) to provide scientific evidence on the absorption of isoflavones by the body, depending on age and the food source (pp.6-7, corroborating source G). This expands on COT advice in 2003 (corroborating source F), which used earlier Cassidy research, and partly defined the UK government's subsequent research programme on phytoestrogens/isoflavones. Professor Cassidy's earlier work on soy also informed an American Heart Association advisory for health professionals on the risks:benefits from soy intake (2006, corroborating source H).

In summary, our impact has been to protect the public by providing balanced scientific evidence for health claims, and to raise awareness of the potential risk:benefit profile of consuming soy foods with a specific focus on isoflavones.

5. Sources to corroborate the impact

Health claims on soy:

A. Scientific Opinion on the substantiation of health claims related to soy isoflavones and maintenance of bone mineral density (ID 1655) pursuant to Article 13(1) of Regulation (EC) No 1924/2006

EFSA J **2009** 7:1270 doi:[10.2903/j.efsa.2009.1270](https://doi.org/10.2903/j.efsa.2009.1270)

Reference to UEA research: pp.5-7 (Cassidy *et al.*, 2006)

B. Scientific Opinion on the substantiation of health claims related to soy isoflavones and maintenance of bone mineral density (ID 1655) and reduction of vasomotor symptoms associated with menopause (ID 1654, 1704, 2140, 3093, 3154, 3590) (further assessment) pursuant to Article 13(1) of Regulation (EC) No 1924/2006

EFSA J **2012** 10:2847 doi:[10.2903/j.efsa.2012.2847](https://doi.org/10.2903/j.efsa.2012.2847)

References to UEA research: pp.6,7 & 14-16 (Cassidy *et al.*, 2006); pp.8,12,15,16 (Brink *et al.*, 2008)

C. Scientific Opinion on the substantiation of health claims related to soy isoflavones and protection of DNA, proteins and lipids from oxidative damage (ID 1286, 4245), maintenance of normal blood LDL cholesterol concentrations (ID 1135, 1704a, 3093a), reduction of vasomotor symptoms associated with menopause (ID 1654, 1704b, 2140, 3093b, 3154, 3590), maintenance of normal skin tonicity (ID 1704a), contribution to normal hair growth (ID 1704a, 4254), "cardiovascular health" (ID 3587), treatment of prostate cancer (ID 3588) and "upper respiratory tract" (ID 3589) pursuant to Article 13(1) of Regulation (EC) No 1924/2006

EFSA Journal **2011** 9:2264 doi:[10.2903/j.efsa.2011.2264](https://doi.org/10.2903/j.efsa.2011.2264)

References to UEA research: pp.7 (Cassidy *et al.*, 2006)

D. Food Labeling: Health Claims; Soy Protein and Coronary Heart Disease - Final rule
US Food and Drug Administration (FDA), 1999

<http://www.gpo.gov/fdsys/pkg/FR-1999-10-26/pdf/99-27693.pdf>

E. Approved generic health claim for soya protein and blood cholesterol by the UK Joint Health Claims Initiative (JHCI) **2002**

Copy held on file at UEA

Risk assessment of soy isoflavones:

F. Committee on Toxicity report **2003** – Phytoestrogens and Health

<http://www.food.gov.uk/multimedia/pdfs/phytoreport0503>

G. Committee on Toxicity report **2012** – review of potential risks from high levels of soy phytoestrogens in infant diet

<http://cot.food.gov.uk/pdfs/tox201239.pdf>

References to UEA research: p.6-7 (Cassidy *et al.* 2006)

H. Soy protein, isoflavones, and cardiovascular health: An American Heart Association Science Advisory for Professionals from the Nutrition Committee.

Sacks FM, Lichtenstein A, Van Horn L, Harris W, Kris-Etherton P, Winston M

Circulation **2006** 113:1034-44 doi: [10.1161/CIRCULATIONAHA.106.171052](https://doi.org/10.1161/CIRCULATIONAHA.106.171052)