COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Third arm results from FSA-funded research study T05029 - the effect of soy phytoestrogen supplementation on thyroid status and cardiovascular risk markers in patients with subclinical hypothyroidism: a randomized double blind crossover study

Reserved business

Background

1. Phytoestrogens are chemicals naturally produced by some edible plants, notably soy. They are present, to varying extents, in the UK diet. In the body, they can mimic or block the action of human oestrogens, although they are much less potent. Their main mode of action is binding to the oestrogen receptor (ER) and interfering with the natural hormonal responses in humans and animals. They may also induce effects not mediated by ERs, for example on thyroid hormones.

2. The thyroid gland is responsible for the production of hormones involved in regulating metabolism, bodyweight and oxygen requirements, as well as normal growth and development during childhood. It has been shown that soy phytoestrogens affect thyroid function in both animals and in human studies; however these changes reported have been considered too small in magnitude to be physiologically important in subjects with normal thyroid function. The effect of phytoestrogens upon patients whose thyroid function is already compromised may be clinically important. A swelling in the thyroid gland called a goitre can result if the normal functions of the thyroid gland are disturbed. Usually this is as a result of an iodine deficiency. A high consumption of goitrogen-rich foods (for example soybean) can lead to a goitre forming.

3. Hypothyroidism is a condition that occurs when the thyroid gland is underactive. When the thyroid gland is functioning normally, it is in a euthyroid state. The thyroid gland is responsible for producing the hormone thyroxine (T_4), which is converted to the more active hormone triiodothyronine (T_3), primarily in the liver; these hormones regulate metabolism. Hypothyroidism can result in a large number of varied symptoms; common symptoms of an underactive thyroid include fatigue, weakness, an intolerance to the cold,

weight gain, lifeless hair, dry skin, aches or muscle pain, constipation, fluid retention, mental sluggishness and depression.

4. Subclinical hypothyroidism occurs when thyroid stimulating hormone (TSH) levels are elevated in order to drive the failing thyroid to produce its hormones, resulting in normal T_4 and T_3 levels. When the thyroid gland is unable to produce T_4 in response to the TSH and the T_4 and T_3 levels drop then this is termed primary hypothyroidism due to the failing thyroid gland. The prevalence estimates range from 3–8%, increasing with age; incidence is more common in women than in men.

5. It has been hypothesised that phytoestrogens may interact with the thyroid gland by a number of potential mechanisms and this can interfere with normal function. It has been demonstrated that some phytoestrogens, notably genistein and daidzein, are structurally similar to the hormones T_3 and T_4, therefore have the potential to be active in the thyroid. Some phytoestrogens have the potential to inhibit thyroperoxidase (TPO), the enzyme responsible for synthesising T_3 and T_4. Thyroid binding globulin (TBG) is a plasma protein involved in the inactivation and transport of T_3 and T_4. It has been hypothesised that phytoestrogens could potentially increase TBG concentrations, resulting in the lowering of T_4 and the subsequent over production of TSH to account for this deficit.

6. Due to the potential interaction between phytoestrogens and the thyroid gland, it is possible that the thyroid function of hypothyroid individuals consuming high levels of phytoestrogen- or goitrogen-rich foods and supplements may be adversely affected.

Conclusions of the COT Report on Phytoestrogens and Health (2003)[1]

7. Following a review of the available literature, the COT identified individuals with hypothyroidism as a subgroup of the population of potential concern. The COT Report concluded that consumption of phytoestrogen supplements, or a soy-rich diet, may provide sufficient concentrations of phytoestrogens to interfere with T4 replacement therapy. Although no adverse effects in hypothyroid children or adults had been reported in the published literature, the Report recognised that research had not addressed this issue specifically. In view of the increasing availability of phytoestrogen-rich food and supplements in the UK, the Report recommended that research be conducted to monitor the plasma T4 levels of children and adults with hypothyroidism who consume large quantities of dietary phytoestrogens.

[1] http://cot.food.gov.uk/cotreports/cotwgreports/phytoestrogensandhealthcot

FSA-funded study

8. T05029 was a double-blind controlled crossover trial, investigating the effect of soy isoflavones on thyroid hormones in subjects with compensated hypothyroidism. The aim of the study was to determine whether soy in the diet may be clinically important in patients with compensated thyroid function.

9. The study was undertaken in three independent arms and the results will be disseminated as such. Each arm was a cross-over, double-blind, controlled clinical trial involving 60 patients with compensated hypothyroidism. In all the three arms there were two month phase one (active or control), followed by a two month wash out period, that is followed by a phase two crossover for a further two month period (active or control).

Arm 1:

10. During this arm sachets containing 30g isolated soy (isoflavone free) protein powder (Solcon F) incorporating 16mg of isoflavones (representative of vegetarian diet) or 30g the isolated soy (isoflavone free) with 2mg of isoflavones (representative of Western diet) were administered daily for 2 months, followed by a two month wash out period which was then followed by a phase two of alternative supplementation crossover for a further two month period.

Arm 2:

11. Using the same protocol as Arm 1 30g isolated soy (isoflavone free) protein (Solcon F) with 60mg of isoflavones (equivalent dose to ingestion of phytoestrogen supplements) or 30g the isolated soy (isoflavone free) protein alone as control were administered daily for 2 months, followed by a two month wash out period which was then followed by a phase two crossover of alternative supplementation for a further two month period.

Arm 3:

12. Using the same protocol as Arm 1, 30g of isolated soy (isoflavone free) protein (Solcon F) alone, or 30g casein protein alone (as control) are being administered daily for 2 months, followed by a two month wash out period which is then followed by a phase two crossover of alternative supplementation for a further two month period. This arm, which is ongoing, will help clarify whether effects associated with the consumption of soy are particularly due to a protein effect of soy protein or a general protein effect.

13. At meetings in February and March 2011 the Committee was presented with pre-publication results from the first and second arms of the FSA-funded study (T05029). Minutes of these discussions are at Annex A.

The first arm was published in the Journal of Clinical Endocrinology and Metabolism[2]

14. The Committee's opinion is now sought on the data from the third arm of the study (presented in Annex B), a cross-over of 30g of isolated soy (isoflavone free) protein (Solcon F) alone, or 30g casein protein alone (as control) as well as the study overall.

15. Members are reminded that at the last meeting they discussed the results of two randomised, double-blind, parallel studies to examine the effects of soy protein and isoflavones on bone turnover markers in women within 2 years after the onset of menopause and men with type II diabetes and subclinical hypogonadism. There were consistent small observed changes in thyroid hormone levels, which remained within the normal range, following consumption of soy protein and isoflavones in both these populations. Members considered these effects were unlikely to have a major impact in the general population. However, health risks in certain population subgroups, such as elderly, were possible.

16. The secretariat undertook a literature search to ascertain whether any other relevant data had been published since the first arm of the study. Only two potentially relevant publications were identified; a paper detailing case reports of two patients with congenital hypothyroidism who continued to manifest clinical hypothyroidism while receiving recommended doses of hormone and ingesting soy products (formula and milk) (Fruzza *et al*., 2012) and a review of the impact of flavonoids on thyroid function (Gonçalves *et al*., 2011). These papers are attached at annex C. This review concludes that flavonoids as a group demonstrate antithyroid effects, through affecting biosynthesis, metabolism and transport of thyroid hormones in vivo and in vitro.

Questions on which the views of the Committee are sought

17. Members are invited to provide comments on any aspect of the draft paper. Members may wish to comment in particular on the following:

i. Whether the results from arm 3 support the contention that the results in arms 1 and 2 were due to the isoflavone content

ii. Do Members consider that, although within the normal range, the consistent observed changes in thyroid hormone levels following soy protein containing phytoestrogens in women within 2 years after the

[2] http://press.endocrine.org/doi/abs/10.1210/jc.2010-2255?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed

onset of menopause and men with type II diabetes and subclinical hypogonadism should be considered supporting evidence for assessing the potential risks of soy ingestion in hypothyroidism

iii. Whether the conclusions reached by the Committee in 2011, that the first and second arms of the study did not provide a sufficiently strong basis for issuing advice on phytoestrogen consumption to patients with compensated hypothyroidism remain valid

iv. What further work would be needed to give answer on risk to sub-clinically hypothyroid individuals from consumption of soy?

v. Do Members consider that the effects shown by isoflavones on thyroid function are more likely related to flavonoid compounds in general and whether this might merit further consideration in the future

vi. Do Members have recommendations for further research that would help to reduce the uncertainties

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Minutes of previous COT discussions

Minutes of the meeting held on 1 February 2011 relating to arm 1 are available at:
http://cot.food.gov.uk/cotmtgs/cotmeets/cotmeet2011/cotmeet1feb2011/cotmins1feb2011

Minutes of the meeting held on 22 March 2011 relating to arm 2 are still reserved pending publication.

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Note: This is a draft pre-publication version of the paper and bibliographic details will be provided once the paper is published

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Unawareness of the Effects of Soy Intake on the Management of Congenital Hypothyroidism. Fruzza AG, Demeterco-Berggren C and Jones KL. Pediatrics 2012; 130: e699-702

Impact of flavonoids on thyroid function. de Souza Dos Santos MC, Gonçalves CF, Vaisman M, Ferreira AC, de Carvalho DP. Food Chem Toxicol. 2011 49:2495-502. doi: 10.1016/j.fct.2011.06.074. Epub 2011 Jul 2. Review

For copyright reasons the papers in this Annex aew not included in the published version on the COT website. The bibliographic details of the annexed material are listed above. The documents are in the public domain and individuals can obtain them by application to appropriate sources.

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