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

First draft statement on the effects of soya consumption on thyroid status.

Introduction

1. A 2003 Committee on Toxicity (COT) report on phytoestrogens and health identified individuals with hypothyroidism as a subgroup of the population of potential concern for adverse effects of phytoestrogens in soya, and made recommendations for research. During 2014 the Committee considered the results of several FSA-funded research studies on phytoestrogens including the third arm of T05029: “The effect of soya phytoestrogen supplementation on thyroid status and cardiovascular risk markers in patients with subclinical hypothyroidism: a randomized double blind crossover study”. As a result the Committee considered that it would be timely to review evidence related to potential effects of phytoestrogens on thyroid function, which had become available since the 2003 COT report on phytoestrogens and health.

2. Annex A contains the first draft COT statement summarising the new literature concerning potential risks from consumption of soya phytoestrogens on thyroid function, with particular emphasis on the risks to individuals with hypothyroidism.

Questions on which the views of the Committee are sought

3. Members are invited to comment on the structure and text of the draft statement.

Secretariat
November 2014

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

First draft statement on the effects of soya consumption on thyroid status.

Background

1. A 2003 COT report on phytoestrogens and health[1] identified individuals with hypothyroidism as a subgroup of the population of potential concern for adverse effects of phytoestrogens in soya, and made recommendations for research. The Food Standards Agency subsequently commissioned research to address these recommendations and invited the Committee to consider the results. The Committee concluded that it would be timely to review evidence related to potential effects of phytoestrogens on thyroid function, which had become available since the 2003 COT report on phytoestrogens and health. This statement summarises the results of that review and the COT conclusions. Only human studies as the most relevant have been included in the review. The criteria that were employed in the literature search are set out in Appendix 1.

Phytoestrogens

2. Phytoestrogens are chemicals of plant origin naturally produced by some edible plants, notably soya. They have been shown to influence biological processes mainly through their structural similarities to oestrogens, and their ability to bind to oestrogen receptors (ER) and interfere with the natural hormonal responses in humans and animals. The largest group of phytoestrogens are flavonoids, which can be further divided into three subclasses, coumestans, prenylated flavonoids and isoflavones (genistein, daidzein).

Thyroid gland

3. 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. The thyroid gland produces hormones thyroxine (T_4) and triiodothyronine (T_3), which are synthesised from iodine and the amino acid tyrosine. The production of T_3 and T_4 is controlled by thyroid stimulating

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

hormone (TSH), secreted from the pituitary gland and regulated by the central nervous system (CNS).

4. An inhibition of T_3 and T_4 synthesis results in an increased secretion of TSH by the pituitary gland. This can result in enlargement of the thyroid gland, known as a goitre, which can occur in hyper- and hypothyroidism. Hyperthyroidism results from over production and secretion of free thyroid T_3 and T_4. Hypothyroidism is a condition that occurs when the thyroid gland is underactive and T_4 concentration is supressed below normal range. The thyroid gland enlargement results, in this case, from the increased production of TSH, infiltration of the gland by lymphocytes (autoimmune reaction) and/or iodine deficiency.

Potential effects of phytoestrogens on thyroid function

5. Some phytoestrogens, notably genistein and daidzein, have been shown to have a similar chemical structure to thyroid hormones. It has been hypothesised that they may interact with the thyroid gland by a number of potential mechanisms which could interfere with its normal function.

6. Phytoestrogens can interact with and inhibit thyroperoxidase (TPO), an enzyme involved in the synthesis of T_3 and T_4, which would then lead to reduced concentrations of T_3 and T_4 and increased release of TSH. Genistein and daidzein, at concentrations of 1-10 µmol/L, have the potential to inhibit the activity of TPO (Divi *et al*., 1997; BfR, 2007).

7. Ebmeier and Anderson (2004) reported that genistein and daidzein can also inhibit the activity of intrathyroidal sulphotransferase enzymes involved in the inactivation and elimination of thyroid hormones.

8. Transthyretin (TTR) is one of the thyroid hormone binding proteins, and has an affinity for T_3 approximately ten times lower than for T_4 (De Groot and Jameson, 2013). In serum, TTR binds up to 20% of T_4. TTR is involved in the distribution of T_4 in the body and in preventing T_4 excretion in the kidneys. TTR is the most important thyroid hormone-binding protein in cerebral spinal fluid (CSF). In serum and CSF, genistein and related isoflavones are highly efficacious inhibitors of T_4 and T_3 binding to TTR (Kd = 40 nmol/l, equimolar to T_4 binding), thus altering the distribution of thyroid hormones in the body (Green *et al*., 2005; Radovic *et al*., 2006; BfR, 2007).

9. Phytoestrogens could also potentially interact with thyroid binding globulin (TBG), a plasma protein involved in the inactivation and transport of T_3 and T_4, increasing its concentration. This results in the lowering of T_4 levels and the subsequent over production of TSH to account for this deficit.

Previous conclusions

The COT Report on Phytoestrogens and Health (2003)

10. The report noted that animal studies showed that dietary soya and isoflavones could affect thyroid function and have a goitrogenic effect in rodents deficient in dietary iodine. Data from human studies suggested that isoflavones were unlikely to affect thyroid function in normal individuals with adequate iodine intake.

11. No data were found to indicate that maternal ingestion of phytoestrogens during pregnancy influence the development of the thyroid gland. However, the COT considered it possible that, together with low iodine intake, increased metabolic demands during pregnancy and increased need for thyroxine, maternal consumption of soya products could adversely influence the neurological development of the fetus.

12. A number of scientific publications evaluated by the Committee in 2003 noted the possibility that soya-based infant formulae might affect thyroid function in infants. Cases had been reported in the 1950s and 1960s of goitre associated with consumption of soya formulae, and of increased faecal loss of orally administered thyroxine in an athyreotic[2] hypothyroid patient when fed soya formula as compared with cows' milk formula. As a consequence, changes were made in the processing and formulation of infant formulae (supplementation with iodine and replacement of soya flour with soya protein isolate), and no further reports of goitre were published.

13. 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 soya-rich diet, may provide sufficient concentrations of phytoestrogens to interfere with T_4 replacement medication, which is given to patients with hypothyroidism. Although no adverse effects in hypothyroid children or adults were 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 on the plasma T_4 levels of children and adults with hypothyroidism who consume large quantities of dietary phytoestrogens.

Conclusions reached by organisations in other countries

14. A number of concerns were raised in a 2007 risk assessment by the German Federal Institute for Risk Assessment (BfR). The BfR reported that available toxicological studies showed that isoflavones, when consumed at high doses (for example by menopausal women), can change mammary gland tissue and impair the functioning of the thyroid gland. The BfR advised against long-term consumption of isoflavone-containing products made from soya (BfR, 2007).

15. The American Academy of Pediatrics (AAP) Committee on Nutrition concluded in its review that the evidence for adverse effects of dietary soya isoflavones on human development, reproduction or endocrine function is not conclusive (Bhatia *et al*., 2008). The National Toxicology Program (NTP) considered that health effects described in the literature were not sufficient to reach the conclusion that consumption of soya infant formula produced adverse thyroid effects. Further studies in this area were recommended (NTP, 2010).

16. Taking into account concerns that have been raised in respect to potential negative effects of soya isoflavones on sexual, reproductive and neurobehavioral development, immune function and thyroid function, the European Food Safety Authority (EFSA) considered that concentrations of isoflavones in infant formula and follow-on formula should be kept as low as is feasible (EFSA, 2014).

Food Standards Agency-funded research

17. The aim of the randomised double-blind controlled crossover study, T05029: "The effect of soya phytoestrogen supplementation on thyroid status and cardiovascular risk markers in patients with subclinical hypothyroidism", was to determine whether soya in the diet may be clinically important in patients with compensated thyroid function. The study was undertaken in three independent arms, each involving 60 patients with compensated hypothyroidism. Each arm used the same protocol where treatments (different in each arm) were administered daily for 2 months, followed by a two month wash out period, followed by the second alternative treatment in that arm for a further two month period. The treatments in each arm were:

- Arm 1: 30 g isolated soya protein powder (isoflavone free) with 16 mg of isoflavones (representative of vegetarian diet) or 30 g isolated soya (isoflavone free) with 2 mg of isoflavones (representative of Western diet);
- Arm 2: 30 g isolated soya protein (isoflavone free) with 60 mg of isoflavones (equivalent dose to ingestion of phytoestrogen supplements) or 30 g the isolated soya protein (isoflavone free) alone;
- Arm 3: 30 g of isolated soya protein (isoflavone free) alone, or 30 g casein protein alone (as control).

18. In February 2011 the Committee considered the results from the first arm of the study. The study suggested that there was a threefold increase in the risk of developing overt hypothyroidism following dietary supplementation of 16 mg soya phytoestrogens in individuals with subclinical hypothyroidism, especially in female patients (Sathyapalan *et al*., 2011). The second arm results were considered in March 2011. Although a higher dose of isoflavones was used the results of the first arm were not confirmed. Fewer patients developed overt hypothyroidism and it was suggested that the reason for that was the higher drop out rate and difference in the gender ratios in the two arms. The Committee noted although this was a possible explanation, the difference in transition to overt hypothyroidism could also have occurred by chance. The Committee concluded that the combined results of 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. However, once the third and final arm of the study had been completed, consideration would need to be given to the value of further research to resolve outstanding uncertainties. The third arm was conducted to help to clarify whether effects associated with the consumption of soya are particularly due to a soya

protein effect or a general protein effect. None of the patients in the third arm developed overt hypothyroidism during the study.

19. The results of all three arms of the T05029 study indicate that soya protein alone does not have an effect on thyroid in patients with mild thyroid dysfunction. Thus, the effects observed in the first two arms of the study appeared to have been caused by isoflavones. The Committee noted that the researchers had previously reported no effect on thyroid function from 132 mg of isoflavones alone. The study outcomes suggest a combination or matrix effect when isoflavones were administered in the presence of soya protein.

20. Thyroid function has also been evaluated in two other FSA-funded randomised double-blind controlled crossover studies investigating the effects of soya in men with type 2 diabetes (three month treatment, T01057[2]) and women during their early menopause (six month treatment, T01060[3]). These studies were also undertaken by the same researchers. There was no effect of soya protein alone (without isoflavones). However, when soya protein was administered together with 66 mg isoflavones, a significant increase in TSH and reduction in thyroxine was observed in both studies. Although within the normal range, the consistency of the changes observed in thyroid hormone levels following consumption of soya protein containing phytoestrogens, both by women within 2 years after the onset of menopause, and by men with type II diabetes and subclinical hypogonadism, supported the possibility of risks from soya ingestion in people with compensated or overt hypothyroidism.

New data

21. A summary of relevant publications emerging since the COT report was published in 2003 is provided below.

Studies of thyroid function in children

22. Conrad *et al*. retrospectively analysed the medical records of infants diagnosed with congenital hypothyroidism and seen at a hospital during their first year of life. Two groups of patients were considered: a soya diet group consuming exclusively soya infant formula, who started on levothyroxine (a synthetic derivative of T_4) treatment at a median age of 15 days (n=8), and a non-soya diet group, who started treatment at 17 days (n=70). There was no significant difference in serum levels of TSH and T_4 levels between the groups before the start of treatment with levothyroxine. There was a significant difference between the two groups in; time to TSH normalisation (four times longer in soya group), first TSH measured after treatment began (six times higher in soya group), percentage of infants with increased TSH at 4 months of age and throughout the first year of life (approximately

[2] The effect of soya protein with and without isoflavones in men with type 2 diabetes and subclinical hypogonadism – A randomized double blind parallel study. University of Hull.
[3] Soya protein with isoflavones reduce bone turnover markers in women during their early menopause – A randomised double blind placebo controlled parallel study. University of Hull.

four times higher in soya group). The authors suggested that these soya fed infants need close monitoring of free thyroxine and TSH measurements as they may need increased levothyroxine to achieve normal thyroid function tests (Conrad *et al*., 2004).

23. Fruzza *et al*. (2012) described two patients (females, 3-week-old and 5-year-old) with congenital hypothyroidism who, although on levothyroxine treatment, were persistently hypothyroid. They were both consuming soya-based formula and soya milk respectively (no details of isoflavone levels were available). When the consumption of soya-based products was discontinued and the dose of levothyroxine decreased, the thyroid function slowly normalised over the course of a few weeks. The authors made the recommendations for children requiring levothyroxine treatment to avoid the use of soya products if possible, and if there was no other alternative to monitor levels of thyroid hormones and adjust/increase dose of treatment as required (Fruzza *et al*., 2012).

24. A low iodine intake by a vegan mother was the suggested cause of hypothyroidism in her child (examined at 10 day of life). A normal plasma TSH level was achieved in the infant following thyroxine treatment (infant) and Lugol's iodine solution administration (mother) over a course of one week and one month respectively (Shaikh *et al.*, 2003). The authors were subsequently criticised by J. Borak for overlooking anti-thyroid effects of soya milk consumed by the vegan mother as one of the causative factors (Borak, 2005).

25. Consumption of soya was investigated as a risk for goitre in primary school girls in Iran. There were no significant differences in consumption of soya between girls with goitre (n=284) and girls not presenting such symptoms (n=288). Iodine loss following storage in open containers, medium socioeconomic family status, and place of residence were found to be the main risk factors (Mousavi *et al*., 2006).

26. Thyroid hormones and thyroid antibodies were measured along with serum concentrations of genistein and daidzein in iodine-replete school children (n=268; age 8-15 years) without overt thyroid diseases. A significant positive association of genistein with thyroglobulin (TG) antibodies and a negative correlation with thyroid volume was reported by the authors. Higher levels of thyroxine were found in children (n=36) who had eaten soya in the preceding 24 hours. As soya products were not part of the normal diet in participating children, it was suggested that even small differences in soya phytoestrogens consumption may have an impact on thyroid function, especially when accompanied by insufficient iodine intake (Milerova *et al*., 2006).

27. An association between exposure to endocrine disruptors, including isoflavones (genistein, daidzein and equol), and the occurrence of congenital hypothyroidism was investigated by Jung *et al*. (2013). Two groups of infants took part in this study: infants with congenital hypothyroidism (n=39) and healthy infants (n=20). Equol (a metabolite of daidzein) and daidzein showed no significant difference between the groups, whereas genistein plasma concentration was significantly higher in healthy infants (11.15 ng/mL) than in patients (6.93 ng/mL),

p=0.00026. It was suggested that genistein may contribute to the improvement of congenital hypothyroidism.

Studies of thyroid function in adults

28. The use of soya protein cocktail supplement (details unknown) in a short space of time prior to oral administration of levothyroxine by a 45-year-old woman with hypothyroidism was reported as a causal factor of poor intestinal absorption of the drug. This led to unusually high doses of levothyroxine to achieve suppressive serum levels of T_4 and TSH. Subsequent separation of the intake of levothyroxine and consumption of soya cocktail resulted in lower levothyroxine doses needed to maintain therapeutic serum thyroid hormone levels (Bell and Ovalle, 2001).

29. In a randomised double-blind, placebo-controlled clinical trial post-menopausal women not on hormone replacement therapy (age 64-83 years) received a supplement (containing 90 mg of isoflavone) (n=22) or placebo (maltodextrin) (n=16) per day, plus a multi-vitamin and mineral supplement daily for six months. TSH, T_4 and T_3 were measured at baseline and after 90 and 180 days. No statistically significant differences in thyroid hormone measurements were recorded in this healthy iodine replete group of subjects (Bruce *et al*, 2003).

30. One randomised cross-over study in healthy young men taking isoflavones (as aglycone equivalents) in soya protein isolate (SPI) at two levels (mean ± SD) (low isoflavone; 1.64 ± 0.19 mg isoflavones/day or high isoflavone; 61.7±7.4 mg isoflavones/day) for 57 days, separated by 4 week washout periods and using milk protein isolate as a control, reported that soya isoflavones did not significantly influence circulating thyroid hormones in healthy young men. Blood was collected on days 1, 29 and 57 and analysed for total and free T_3 and T_4, TSH and TBG, no significant changes were recorded in any parameters measured in blood. Urines were also collected and analysed for isoflavones and revealed a significant increase in urinary isoflavones in the high isoflavone SPI compared to the low (Dillingham *et al*, 2007).

31. Hampl *et al.* (2008) reported that short-term soya consumption had only a modest and transitory effect on thyroid parameters, stating that ‘some thyroid hormone parameters do correlate with actual isoflavone levels.’ Male (n=32) and female (n=54) university students with normally functioning thyroid consumed unprocessed boiled natural soya beans (2 g/kg bw/day; containing approximately 1.2 – 4.2 mg isoflavones/g dry weight) for 7 days. TSH, free thyroid hormones, antibodies to TPO and TG, and actual levels of genistein and daidzein were measured in serum collected at the end and one week after completing the soya consumption. Levels of both isoflavones rose at the end of soya consumption and returned to background levels one week on. No significant changes were found in the female group, while in males a transitory increase in TSH was recorded (Hampl *et al*., 2008).

32. The effect of a 3-year administration of genistein as aglucone (54 mg/day) on thyroid function was investigated in osteopenic, postmenopausal women (n=71).

Thyroid hormones (TSH, free T_3, free T_4) and thyroid-specific autoantibodies (TPO, TG and thyroid microsomal antigen [TMA]) were assessed following 3-year treatment and were shown to be in the normal range (Bitto *et al*., 2010).

33. A lack of association between soya consumption during early pregnancy and development of thyroid dysfunction or autoimmunity was suggested by Li *et al*. (2011). Based on soya intake frequency, participants were divided into three groups: frequent (three or more times a week; 18.6%; n=94); conventional (twice per month>three times a week; 62.6%; n=316); and occasional consumers (two or less times per month; 18.8%; n=95). There was no significant difference between the three groups in free T_4, TSH, and TPO antibody levels. No marked difference was found in the prevalence of overt, subclinical hyper- and hypothyroidism; however, there was a non-significant increase in the percentage of subjects with subclinical hypothyroidism among frequent consumers. Urinary daidzein and genistein levels were determined in randomly selected frequent, conventional and occasional representative subjects (about 20% of the three groups: n=20, 59 and 16 respectively) and levels of both were significantly higher in frequent consumers.

34. Effects of isoflavones on thyroid functions (free T_3 and T_4, TSH, TBG and anti-TPO antibodies) were investigated in oophorectomised women in India (<55 years of age, with baseline TSH values): isoflavone (n=17) and placebo (n=17) groups. A tablet containing 75 mg of isoflavones was administered once a day orally at bedtime with 150 ml of water for 12 weeks. Participants were advised to avoid food products containing phytoestrogens during the study period. A modest reduction in serum free T_3 levels in the isoflavone group (p=0.02) in the absence of any significant effect on other thyroid parameters was reported (Mittal *et al*., 2011).

35. Healthy postmenopausal women (n=25; man age 58 years) consumed seaweed capsules (475 µg iodine/day) for 7 weeks and powdered soya protein isolate (141.3 mg isoflavones/day) during the 7th week. No changes in serum thyroid hormone concentrations were associated with isoflavones consumption in this double-blinded crossover randomised study (Teas *et al*., 2007).

Studies on soya consumption with changes in thyroid function as a secondary outcome

36. Effects of soya consumption on thyroid function were investigated by several studies as an additional secondary outcome. Alekel *et al*. (2014) looked at effects of isoflavone treatment (80 and 120 mg/day) on endometrial thickness, circulating hormones and adverse events in postmenopausal women, over a 3 year period. There were no effects on circulating TSH concentrations in either of the treatment groups when compared to baseline levels. Lack of significant differences in levels of TSH and antibodies to TPO were also reported by Levis *et al.* (2011) in menopausal women receiving tablets containing 200 mg isoflavone/day for 2 years. Steinberg *et al.* (2011) reported slightly lower (p=0.052) free T_4 concentrations in menopausal women on isoflavone treatment for 2 years (80 mg/day, n=119; 120 mg/day, n=117) when compared to baseline. No significant changes in TSH concentrations were reported (Steinberg *et al*., 2011). No significant effect of soya foods (approximately

36 mg isoflavones/day) on thyroid hormone status in premenopausal women was reported by Zhou *et al*. (2011).

Discussion

37. Since the 2003 COT report several human studies concerning impact of soya consumption on thyroid function have been published. Children with congenital hypothyroidism, who consume soya infant formula while receiving levothyroxine treatment were found as a group, which could require a close monitoring of thyroid hormones and increased levothyroxine treatment to achieve normal thyroid parameters (Conrad *et al*., 2004). Avoidance of the use of soya products by children on levothyroxine treatment was recommended if possible (Fruzza *et al*., 2012). Insufficient iodine intake by a mother was suggested to cause hypothyroidism in her child (Shaikh *et al*., 2003). However, Shaikh *et al.* did not associate soya milk consumption as causative factors. Even small intakes of soya phytoestrogens by healthy children (iodine-replete, without thyroid disease) were shown to have an impact on thyroid function. This effect could be additionally amplified by insufficient iodine intake (Milerova *et al.,* 2006). This was also highlighted as one of the risk factors for goitre by Mousavi *et al*., 2006. Jung *et al*., (2013) suggested that genistein may contribute to improvement of congenital hypothyroidism – this observation was made based on higher level of genistein plasma concentration in healthy controls compared to hypothyroid children.

38. The use of soya protein cocktail while on levothyroxine treatment in a 45-year-old woman was reported as a causative factor for poor intestinal absorption of the drug (Bell and Ovalle, 2003). In general no significant effects on thyroid hormone measurements were reported in healthy, iodine-replete postmenopausal women (Bruce *et al*., 2003; Teas *et al*., 2007; Bitto *et al*., 2010; Levis *et al*., 2011; Zhou *et al*., 2011; Sosvorova *et al*., 2012; Alekel *et al*., 2014), women in the early stages of pregnancy (Li *et al*., 2011) and healthy men (Dillingham *et al*., 2007). In healthy male university students consuming soya beans for 7 days, a transitory increase in TSH was measured. No effects were observed in female students, and serum levels of isoflavones returned to normal after the cessation of treatment (Hampl *et al*., 2008). A modest significant reduction in serum free T_3 levels in oophorectomised women in India was reported following consumption of isoflavone supplement for 12 weeks (Mittal *et al.*, 2011), and a small nearly significant reduction in serum free T_4 in menopausal women (2 year isoflavone supplementation) by Steinberg *et al*. (2011).

39. Available studies and numerous reviews highlighted the fact that currently available evidence is in general inconclusive and further studies of long duration, recorded isoflavone dosage and addressing different soya-based foods and mixtures of isoflavones were needed. However, a potential for isoflavones to cause effects on thyroid function, especially if ingested at high levels by sensitive subgroups of iodine-deficient children or postmenopausal women, was noted. Probable interactions of isoflavones with thyroid medications were also mentioned as one of the risk factors. Close medical monitoring of such patients was recommended.

Conclusions

40. The Committee considered the evidence on soya and thyroid function which had become available since the 2003 COT report, and concluded that there was sufficient new evidence that it was timely to re-evaluate the interaction of soya-based food products containing isoflavones, and the thyroid gland.

41. This new evidence included the results of three FSA funded randomised double-blind controlled crossover studies in which thyroid function was determined. Thyroid function was measured after treatment with soya protein alone or soya protein containing 66 mg isoflavones for three months in men with type II diabetes and subclinical hypogonadism, and six months in women within 2 years after the onset of menopause. A significant increase in TSH and reduction in thyroxine was observed in both studies following consumption of soya protein containing phytoestrogens. Although within the normal range, the consistency of the changes observed in thyroid hormone levels supported the possibility of risks from soya ingestion in people with compensated or overt hypothyroidism. The third study looked at the effects following administration of casein, soya protein alone or soya protein containing 2, 16 or 66 mg isoflavone for two months in individuals with compensated hypothyroidism.

42. Some patients with compensated hypothyroidism developed overt hypothyroidism following ingestion of soya protein containing isoflavone for two months but not with soya protein alone or casein. These results are suggestive that, when combined with soya protein, the isoflavones are likely to be responsible for the thyroid effect although this had not been observed in another study with isolated isoflavones by the same researchers. However there are a number of limitations to the study which do not allow us to draw definitive conclusions from it. There was no clear dose response relationship between the isoflavones and overt hypothyroidism as there was greater incidence at 16 mg compared to 66 mg, however this may have been confounded by the study design with three separate arms (2 vs 16 mg, 0 vs 66 mg, soya vs casein) with 60 patients per arm which resulted in different patient demographics in the 16 and 66 mg groups. The number of individuals developing overt hypothyroidism was low and group sizes may not have been sufficient to detect this consistently. This may have been exacerbated by a significant drop out rate which varied between the arms. Thus the difference in transition to overt hypothyroidism could also have occurred by chance. Despite these limitations we consider that on the basis of this study, it was not possible to dismiss the 2003 conclusion that individuals with hypothyroidism were a subgroup of the population of potential concern.

43. Although there were some additional publications since 2003 the results reported were not always consistent due to differences in study design and comparators. However in general isoflavone intake appeared to decrease thyroid hormone levels to a small extent and that this was exacerbated in individuals with iodine deficiency.

44. Overall the Committee concluded that there was consistently observed evidence that thyroid hormone levels were reduced following consumption of soya in different groups of the population. The changes in thyroid hormone level were small and remained within the normal range in the general population including in men with type 2 diabetes and women during their early menopause. Some individuals with compensated hypothyroidism developed overt hypothyroidism following administration of soya protein containing isoflavones. However, it was not possible to determine a dose response relationship from the data available nor to identify other risk factors (with the exception of iodine deficiency), which might influence this progression. Therefore it would still be prudent to consider all individuals with hypothyroidism a subgroup of the population of potential concern.

45. The Committee recommends that this population should be made more aware that increased consumption of soya in their diet or as supplements might exacerbate their condition. The Committee also recommends that general practitioners and endocrinologists should be informed that this group might require more frequent checks of their thyroid hormone status.

Secretariat
November 2014

Abbreviations

AAP	American Academy of Pediatrics
BfR	German Federal Institute for Risk Assessment
CNS	central nervous system
COT	Committee on Toxicity
CSF	cerebral spinal fluid
EFSA	European Food Safety Authority
ER	oestrogen receptors
FSA	Food Standards Agency
Kd	dissociation constant
NTP	National Toxicology Programe
SD	standard deviation
SPI	soya protein isolate
T_3	triiodothyronine
T_4	thyroxine
TBG	thyroid binding globulin
TG	thyroglobulin
TMA	thyroid microsomal antigen
TPO	thyroperoxidase
TSH	thyroid stimulating hormone
TTR	transthyretin

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Appendix 1

Search strategy

Websites of international authorities/advisory bodies interrogated

- COT
- EFSA
- FSA
- IARC
- JECFA

Scientific literature search

PubMed was interrogated to identify publications published until November 2014 and relevant to effects of soya consumption on thyroid status. Specific search terms and the number of hits associated with those queries are listed below. The list below does not take into account overlap of search results between search terms. These hits have been further refined via interrogation of the abstracts and the articles themselves, excluding articles that were investigating effects of soya-based food products/isoflavones/phytoestrogens in combination with other compounds, in individuals with health problems not relevant to thyroid, in individuals with concomitant illnesses, studies in animals and in vitro studies, studies mentioned in the 2003 COT report. A reasonable number of relevant studies investigating thyroid effects in humans have been found. Therefore they have been the only ones included in this statement. The final list of articles used in this document can be found in the references section.

Specific search terms	Hits in Pubmed
Flavonoids AND hypothyroidism	27
Flavonoids AND subclinical hypothyroidism	2
Genistein/Daidzein/Glycitein AND hypothyroidism	4/2/0
Genistein/Daidzein/Glycitein AND subclinical hypothyroidism	1/0/0
Genistein/Daidzein/Glycitein AND thyroid	93/30/1
Isoflavones AND hypothyroidism	20
Isoflavones AND subclinical hypothyroidism	2
Isoflavones AND thyroid	143
Phytoestrogens AND hypothyroidism	6

Phytoestrogens AND subclinical hypothyroidism	2
Phytoestrogens AND thyroid	98
Soy/Soya AND hypothyroidism	22/22
Soy/Soya AND subclinical hypothyroidism	1/1
Soy/Soya AND thyroid	124/134
Soy/Soya protein AND hypothyroidism	7/5
Soy/Soya protein AND subclinical hypothyroidism	1/0
Soy/Soya protein AND thyroid	71/52