Soy formulas and the effects of isoflavones on the thyroid

In November 1998 the New Zealand Ministry of Health (MOH) issued an update on its position on soy formulas.[1] The position paper was a response to questions raised about the safety of soy formulas. These concerns focused chiefly on the high levels of exposure to phytoestrogens for soy-formula-fed infants. The concerns are not new, having first been raised more than a decade ago by phytoestrogen researcher Kenneth Setchell. He compared the phytoestrogen exposure in soy formulas with the occurrence of clover disease in sheep, which was an infertility syndrome that led to permanent histological changes in the uterus and ovaries.[2] Setchell subsequently quantified the levels of phytoestrogens in soy formulas.[3]

Others have also expressed concerns regarding the potential developmental toxicity of phytoestrogens. In 1993 Daniel Sheehan, who is Director of the United States Food and Drug Administration's National Centre for Toxicological Research Estrogen Base Program, in presenting the case for expanded phytoestrogen research noted that the potential risks to infants from phytoestrogens should not be ignored.[4]

A risk assessment, in which daily levels of exposure to phytoestrogens in infants fed soy formulas were calculated,[5] led to calls for stricter control of soy formula sales.[6] This call was based on the fact that infants fed soy formulas were exposed to higher relative levels of phytoestrogens than those found to disrupt the menstrual cycle of adult women[7] and that the same compounds were known inhibitors of 17-β-hyroxysteroid oxidoreductase *in vitro*.[8] It was argued that there was, therefore, potential for the modification of key imprinting events affecting the development of many physical, physiological and behavioural characteristics in the neonate.

Internationally, there has been increasing concern regarding the potential for adverse effects in infants fed soy formulas. In July 1996, the UK Department of Health warned that phytoestrogens found in soy formulas could affect the health of infants. In issuing advice to health professionals the Chief Medical Officer said soy formulas should only be given to babies on the advice of a health professional.[9] That same year the UK Government's Food Advisory Committee asked manufacturers to investigate the removal of phytoestrogens from soy formulas.

In 1998 the United States Environmental Protection Agency's Endocrine Disruptors Screening and Testing Advisory Committee examined priorities for research into human exposures to endocrine disruptors. The phytoestrogen content of soy formulas was established as one of six topics requiring priority research.[10] In 1998 the Australian College of Paediatrics stated that the use of soy formulas might not be without side-effects as the long-term effects of contaminants, such as phytoestrogens, were unknown.[11]

The New Zealand MOH position statement discusses the appropriate use of soy formulas in paediatric practice and the risks posed by phytoestrogens. In particular it emphasises the potential for soy formulas to cause thyroid disorders in infants. On this issue MOH have recommended that:

- Clinicians who are treating children with a soy-based infant formula for medical conditions should be aware of the potential interaction between soy infant formula and thyroid function and consider assessment of thyroid function if satisfactory growth and development is not achieved or maintained.
- Clinicians treating infants with hypothyroidism should closely monitor thyroxine replacement in infants fed with soy-based infant formula or consuming high levels of soy-containing infant foods, as some of these infants may require a higher than usual dose of thyroxine to maintain a euthyroid state.

The MOH is correct in its assessment of the risks of thyroid harm in infant fed soy formulas. This paper seeks to define these issues more clearly and also to detail the risks to others who are exposed to high levels of soy phytoestrogens.

The goitrogenic effect of soy

Scientific reports of the goitrogenic effect of soy were first reported in the 1930s when it was found that goitre could be produced in rats fed soybeans[12] and in chickens fed a ration containing 25 per cent soy meal.[13] Further investigation of the goitrogenic effect of soy was limited until 1976 when it was found that rats fed soy developed malignant hyperplastic goitre if iodine was deficient. However, the goitrogenic factors were not identified at that time.[14]

As soy became part of the western diet, reports of thyroid disorders emerged. Several papers from the late 1950s and early 1960s reported cases in which infants fed soy formulas developed goitre.[15-18] Manufacturers subsequently increased the levels of iodine and reports of goitre in soy-formula-fed infants ceased. However, it has been shown that the thyroxine requirements of hypothyroid infants fed soy formulas are higher than in those not consuming soy,[19-20] indicating that the increased levels of iodine may not have entirely eliminated the earlier problems.

Recently it has been shown that soy can have profound effects on thyroid function in adults. A study by Japanese researchers concluded that intake of soy by healthy adults could cause enlargement of the thyroid and suppress thyroid function.[21] That study, from the Ishizuki Thyroid Clinic, recorded the effects of feeding 30 g of soybeans per day on thyroid function. During the course of the investigation iodine intake (via seaweed) was reported as normal in all subjects. The investigators observed a significant increase in thyroid-stimulating hormone (TSH) levels in a group of 20 adults fed for one month (group 1) and in a group of 17 adults fed for three months (group 2). In two individuals, TSH levels increased from approximately 1 mU/mL to 7 mU/mL. Mean thyroxine levels were lower in both groups fed soy compared with a control group, although the difference was not significant. However, a significant increase in free thyroxine was observed in the group 2 subjects after they ceased the regime of soy consumption.

The changes to thyroid hormone levels were of clinical significance. Diffuse goitre and hypothyroidism appeared in three of the group 1 subjects and eight of the group 2 subjects. Group 2 subjects also had symptoms associated with hypothyroidism: constipation in 53% of subjects, fatigue in 53% of subjects and lethargy in 41%.

The goitre in the 11 subjects was a diffuse goitre, with degrees I and II enlargement. One subject in group 1 developed subacute thyroiditis. Goitre size was reduced in nine of the 11 subjects after cessation of soy but goitre still persisted in two individuals. These two subjects received thyroxine treatment and their goitres reduced in size after two to six months. Hence, a moderate amount of soy was found to have a marked goitrogenic effect on adult humans even though iodine was sufficient.

Isoflavones: the goitrogenic agents in soy

Many plants contain compounds that possess goitrogenic activity.[22] Among the best known are flavonoids, which are polyhydroxyphenolic compounds, based on the compound 2-phenyl-4H-1-benzopyran-4-one, or flavone. It is well known that flavonoids possess potent and diverse anti-thyroid properties.[23] The goitrogenic activity of flavonoids is commonly understood in terms of their ability to inhibit thyroid peroxidase

(TPO), the enzyme that catalyses the oxidation and organification of thyroidal iodine, through competitive inhibition. However, flavonoids also inhibit the peripheral metabolism of thyroid hormones and affect serum thyroid hormone binding.[24]

Perhaps the most extensively studied goitrogenic flavonoids are those found in Pearl millet and Fonio millet. These grains contain significant quantities of glycosides of apigenin and luteolin. Iodine deficiency coupled with the consumption of large quantities of these flavonoids has resulted in endemic goitre in the Sudan[25] and the Republic of Guinea.[26]

Isoflavonoids, which are based on 3-phenyl-4H-1-benzopyran-4-one, or isoflavone, are structurally related to the flavonoids and also possess goitrogenic activity. Soybeans are rich sources of isoflavonoids, the best known of which are genistein (5,7-dihydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one) and daidzein (7-hydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one). These isoflavones are frequently referred to as phytoestrogens since at dietary levels they exert oestrogenic effects in diverse animal species.[27]

The goitrogenic effect of soy has recently been attributed to the presence of genistein and daidzein, which have been found to possess potent anti-thyroid activity.[28] In fact in terms of its ability to inhibit TPO, genistein is more potent than either apigenin and luteolin or either of the well known anti-thyroid drugs, methimazole and 6-propylthiouracil (Table 1).

Table 1. Concentrations of various compounds producing 50% inhibition of thyroid peroxidase.

Compound	IC_{50} (μM)
Apigenin	3.4[29]
Luteolin	13.2[29]
Genistein	3.2[28]
Daidzein	7.6[28]
Methimazole	4.2[25]
6-propylthiouracil	7.2[25]

Isoflavones: levels of dietary exposure

In their study of the relationship between millet consumption and endemic goitre in the Sudan, Gaitan et al found that 100 g of Pearl millet contained approximately 102 mg of the glucosylflavonoids glucosylvitexin, vitexin and glucosylorientin. In the gut these glucosylflavonoids are readily hydrolysed; in this manner 100 g of Pearl millet might release up to 35 mg of apigenin and 14 mg of luteolin. A 70-kg adult consuming 500 g of Pearl millet could have an intake of 2.5 mg/kg-body weight of apigenin and 1.0 mg /kg-body weight of luteolin per day. Gaitan et al estimate that this degree of exposure is equivalent to a 1 to 5 mg dose of methimazole per day.[25]

In vivo, Pearl millet flavonoids can exert goitrogenic effects even in the presence of high iodine intake.[24] Given the degree of intake of potent goitrogens, it is not surprising that goitre is endemic in Sudanese for whom Pearl millet is a staple food and iodine intake is low.

Is it also possible that consumers of soy might suffer similar effects due to isoflavonoids even when iodine intake is sufficient? The groups most at risk are infants fed soy formulas, high soy users and those taking isoflavone supplements. Soy consumption and the use of isoflavone supplements have increased in recent years in response to the promotion of the theory that isoflavones may be protective against a variety of hormone-dependent diseases, such as breast and prostate cancer. But since these same isoflavones are goitrogenic, it is important to determine the level of soy consumption, or the dose of soy isoflavones, that might be required to affect the thyroid function of humans.

The observations of Ishizuki et al[21] indicate significant, goitrogenic effects in subjects fed 30 g soybeans per day. Based on the concentrations of isoflavones found in Japanese soybeans,[30] 30 g of soybeans could contribute up to 23 mg total genistein and 10 mg of total daidzein. For a 70-kg adult this would equate to an intake of 0.33 mg/kg body weight of genistein and 0.14 mg/kg body weight of daidzein per day. This amount of isoflavone consumption is three to four times higher than the amount commonly consumed in Japan, which is 0.08 to 0.13 mg/kg body weight of total genistein per day for a 70-kg adult.[31]

For infants fed soy-formulas, the exposure to isoflavones is greater than in any other population group. Infants less than six months of age, who are solely fed soy formula, have an intake of up to 5.4 mg/kg body weight of genistein and 2.3 mg/kg body weight basis of daidzein per day.[32] Hence, soy-formula-fed infants are exposed to more than twice the equivalent amount of goitrogenic compounds consumed in the endemic goitre regions of Sudan and approximately 16 times more than that of subjects in the Ishizuki study.

The concentrations of isoflavones found in products available in New Zealand,[33] indicate that a diet of 500 g of soy milk plus 50 g textured vegetable protein (TVP) per day would result in the consumption of up to 135 mg total genistein and 80 mg total daidzein. For a 70 kg-adult this equates to an intake of 1.9 mg/kg body weight of genistein and 1.1 mg/kg body weight of daidzein per day. This degree of exposure to anti-thyroid agents is broadly similar to that found in regions of Sudan where goitre is endemic and more than five times that of subjects in the Ishizuki Thyroid Clinic investigation.

Users of isoflavone supplements may consume up to 40 mg of genistein per day. For a 70 kg adult this is equivalent to 0.57 mg/kg, body weight basis of genistein per day, which is about 1.7 times more than that found to have goitrogenic effects.

Clearly there is potential for certain individuals to consume levels of isoflavones in the range that could have goitrogenic effects. Most at risk appear to be infants fed soy formulas, followed by high soy users and those using isoflavone supplements.

Isoflavones: the risks to consumers

For soy-formula-fed infants the risks to thyroid health due to exposure to isoflavones are significant. Thyroid hormones regulate growth, development and differentiation and, therefore, are essential in the physiology of humans.[34] Alteration in thyroid hormone levels or responsivity to thyroid hormone during the neonatal period may lead to disorders of the central nervous system and abnormal psychomotor development.[35]

High plasma concentrations of isoflavones are found in infants fed soy formulas. This is a consequence of regular feeding throughout the day, the ready absorption of isoflavones by the infant gut and the reduced body clearance of these compounds. Moreover, infants fed soy formulas from birth may experience such exposure for durations of 12 months or longer.

It has been suggested that although the plasma concentrations of total isoflavones in infants fed soy formulas are within the range required to inhibit TPO, the levels of free (active) isoflavones in plasma are very low.[1] This comment is based on preliminary data[36] which found no detectable free isoflavones in the plasma of infants (although plasma concentrations of total isoflavones were similar to those reported previously) and appears to suggest that isoflavone conjugates do not possess goitrogenic activity. However, the textbook view that conjugation leads to harmless metabolites that are readily excreted is not valid. In fact, there is considerable variability in xenobiotic conjugation and conjugates with enhanced biological activity and toxicity may be produced.[37] Besides, the work of Ishizuki et al[21] appears to confirm the *in vitro* activity of isoflavones even though adults readily conjugate these compounds *in vivo*.

Hence, long-term feeding of soy formulas may result in persistent inhibition of TPO and continually elevated TSH

levels. MOH has recognised this potential and it is entirely appropriate for them to suggest that thyroid problems due to soy formulas may be 'under-recognised'. Given that the clinical symptoms of hypothyroidism can be subtle due to the maintenance of normal thyroid hormone status, MOH advice that infants fed soy formulas should undergo tests to monitor thyroid hormone status is also warranted.

The lack of recognition of potential thyroid problems attributed to soy formulas may be due to difficulties in establishing a cause and effect relationship and even experienced soy researcher's may be ignorant of the connection between isoflavones and goitre. Hence, claims that soy formula feeding has occurred for many decades with no reports of adverse effects due to isoflavones[38] fail to account for the reported cases of goitre that have occurred in infants fed iodine sufficient soy formulas. It is also worthwhile noting that there is evidence that soy-formula-fed infants may have a greater incidence of anti-thyroid antibodies than breast-fed infants[39] and of an association between feeding soy formulas and the development of autoimmune thyroid disease in later childhood.[40]

Monitoring the thyroid status of high-soy consumers and users of isoflavone supplements may also be warranted. The goitrogenic effect of soy is consistent with the mechanism by which isoflavones inhibit TPO *in vitro*. Subjects fed 30 g soybeans per day experienced elevated levels of TSH although thyroxine levels were about normal. This defines subclinical hypothyroidism, a state in which a reduction in thyroid hormone secretion is compensated for by increased TSH production in order to maintain a clinically euthyroid status.

Subclinical hypothyroidism is a common condition that may eventually evolve toward overt hypothyroidism especially in persons with anti-thyroid antibodies. It is a condition of increasing importance and its prevalence appears to be growing such that studies aimed at defining its evolution are warranted. Dietary factors may well play a major role in the development of this condition since high goitrogen intake can increase TSH secretion.[41]

High-soy consumers and users of isoflavone supplements might, therefore, exhibit classic hypothyroid symptoms without recognising a dietary connection. Unfortunately there are few data as to what constitutes an appropriate level of soy intake, although it appears that some western consumers may now be eating far greater amounts of soy than that taken as part of a traditional Asian diet. The potential for 'mega-dosing' on isoflavone supplements has been raised before[32] but advertising of over-the-counter isoflavone products commonly claims benefits without any indication of risk to thyroid function.

Enhanced secretion of TSH is also associated with an increased incidence of thyroid cancer and those consumers who use large amounts of soy sporadically may face particular risk. Here, exposure to high levels of isoflavones might increase TSH secretion until, in the absence of soy, plasma isoflavone levels diminish and normal thyroid activity is restored; therefore in high-soy consumers a sporadic pattern of use could result in cycling between elevated and normal levels of TSH secretion.

Stimulating the thyroid in such a manner is the classic method for inducing thyroid tumours in laboratory animals.

Conclusion

MOH has found that infants with a history of thyroid dysfunction should avoid soy formulas and soy milks. Additionally, there is potential for isoflavone exposure to cause chronic thyroid damage in all infants fed soy formulas. The fact that infants fed soy formulas are subject to the highest isoflavone exposure of any population group has led Daniel Sheehan to warn that infants fed soy formulas have been placed at risk in a "large, uncontrolled, and basically unmonitored human infant experiment".[42] This level of exposure is unnecessary and the risk of harm could be avoided if manufacturers removed isoflavones from soy formulas. In the interim, it is appropriate for medical practitioners to monitor the thyroid status of infants fed soy formulas.

There is also evidence that adult exposure to isoflavones in high-soy users and users of isoflavone supplements may have adverse effects on the thyroid health. Therefore a more cautionary approach to the use of soy and isoflavone supplements is warranted.

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