MINISTRY OF HEALTH

MANATŪ HAUORA

Soy-based Infant Formula

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Soy-based Infant Formula

In October 1995 an article in *Prescriber Update* reviewed the current literature for soy-based infant formula. The Ministry of Health has recently developed a pamphlet for parents which addresses some of the concerns about soy-based infant formula, in particular, the presence of the phyto-estrogen group of compounds, some members of which are known as isoflavones. This article provides an update for health professionals on recent research and makes a number of recommendations regarding the appropriate use of soy-based infant formula in paediatric practice. The reader is advised to review the 1995 *Prescriber Update* article (Tuohy 1995) for a more in-depth coverage of the background (available from the Ministry of Health Web site http://www.moh.govt nz).

Since 1995 there have been a number of publications in peer-reviewed journals which address the issue of phyto-estrogens and soy-based infant formula. Setchell et al (1997) studied seven infants fed soy-based infant formula. They showed that infants are able to absorb significant levels of isoflavones, reaching blood levels that are higher than those which have been shown to have physiological effects on the menstrual cycle of adult women (Cassidy et al 1994). Metabolites of phyto-estrogens are also pharmacologically active, with one particular metabolite of daidzein (equol) being significantly more oestrogenic than its parent compound (Kelly et al 1995; Sathyamoorthy and Wang 1997). This metabolite was found to be present at similar levels in the urine of infants fed cow's-milk-based or soy-based infant formula (Venkataraman et al 1993; Setchell et al 1997). A recent study of the acute oestrogen activity of genistein and daidzein using an in-vivo mammalian assay (Milligan et al 1998) indicated that daidzein had minimal oestrogenic activity and that of genistein was around 1/1000th to 1/10,000th that of naturally occurring oestrogens.

A recent publication commissioned by the Ministry of Health from Crop and Food Research (Taylor and Burlingame 1998) examined the phyto-estrogen levels in foods likely to be consumed by New Zealand infants.

They confirmed the high levels of phyto-estrogens in soy-based infant formula and some weaning foods.

There have been no human studies that have shown abnormalities in infant growth or subsequent reproductive development attributable to the phyto-estrogens in soy-based infant formula. However until the last decade little research has been directed into this issue. There have been a number of articles and reviews published over the last 40 years regarding the effect of phyto-estrogens on the function of the thyroid gland in infancy. Taylor and Burlingame (1998) identified a small number of case reports (comprising 12 individuals), documenting thyroid abnormalities which were clinically associated with ingestion of soy-based infant formula (Hydovitz 1959; Van Wyk et al 1959; Shepard et al 1960; Pinchera et al 1965). There has been one case report of thyroid abnormalities associated with soy-based infant formula since iodine supplementation was introduced in 1959 (Labib et al 1989).

Another paper suggesting an association between soy-based infant formula and autoimmune thyroid disease (ATD) was published in 1990 (Fort et al 1990). This paper retrospectively reviewed cases of Hashimoto's thyroiditis and Graves' disease in children and compared them with siblings and non-related controls. The authors found an increased rate of thyroid disease in subjects who had been fed soy-based infant formula as infants. However a cause and effect relationship was not established, and there was no information presented on the reason for commencing soy-based infant formula in these infants.

A recent report (Divi et al 1997) suggests that phyto-estrogens (genistein and daidzein) in soy-based infant formula are capable of inhibiting the action of an enzyme involved in iodination of thyroxine (thyroid peroxidase, TPO) through competitive inhibition (ie, by acting as an alternative substrate). The presence of additional iodide in the reaction completely abolished the inactivation of TPO. The study this report was based on has not been replicated in vivo, although studies in adults have indicated small decreases in circulating thyroid hormone levels (Van Wyk et al 1959) or elevated levels of thyroid stimulating hormone (TSH) which were nevertheless within the normal range (Ishizuki et al 1991). These findings could be accounted for by (phyto)-estrogen mediated increases

in thyroid binding globulin (TBG), which by providing a higher level of binding capacity will transiently reduce free thyroxine levels. This in turn stimulates TSH which will restore the free thyroxine levels to normal and total thyroxine will reach a new elevated homeostasis. Divi et al's report did not address the issue of uptake of phyto-estrogens into the cells of the thyroid gland, and commented that the free aglycone (ie, the unconjugated form of the isoflavone) was the most potent inhibitor in the experimental system. The levels of total isoflavones in the plasma of infants fed soy-based infant formula are within the range required to partially inhibit TPO, but levels of free aglycone in plasma are not known but are undoubtedly very low.

Huggett et al (1997) found no free aglycone in the plasma of four infants after four weeks of continuous feeding on soy-based infant formula, despite high levels of total plasma isoflavones, which corresponded to the levels described by Setchell et al (1997). In adult women only 3 percent of circulating oestradiol is free, with the remainder protein bound (Ganong 1981). Even at the upper limits of total isoflavone concentrations in plasma, and assuming a maximum of 5 percent free aglycone, the levels would be around the lower limit of inhibition for TPO.

There have been few recent case reports of semi-refractory hypothyroidism and persistently elevated TSH in infants with hypothyroidism who were being fed soy-based infant formula (Chorazy et al 1995; Jabbar et al 1997). The infant's requirement for additional thyroxine (above expected replacement levels) disappeared once the soy-based infant formula was ceased. The mechanism was postulated to be faecal wastage of oral thyroxine replacement, however inhibition of TPO could have a similar effect.

Consideration of these case reports and Divi's in-vitro study (1997) suggest that the isoflavone component of soy-based infant formula may have the capacity to affect the thyroid function in infants, either through acting as a mild goitrogen or through promoting malabsorbtion of ingested thyroxine in cases where thyroid replacement is required. However the research has not yet clearly established that the levels of free phyto-estrogen in infants' plasma are sufficient to significantly inhibit TPO, and the clinical significance of phyto-estrogen consumption in the presence of adequate

iodine intake remains unclear. Considering the large number of infants fed on soy-based infant formula, the paucity of case reports suggests that if there is a problem, it is either very infrequent or under-recognised.

Over the last three years there have been a number of publications or position statements from regulatory or professional bodies with regard to soy infant formula. The Chief Medical Officer in the United Kingdom published guidelines for health professionals and parents which suggested that the use of soy infant formula should be restricted to specific indications particularly those relating to nutritional problems in infants, such as cow's milk, or protein intolerance (Calman 1996). The Swiss Federal Commission on Food has published a similar position statement (Tonz and Zimmerli 1997; Zimmerli and Schlatter 1997) to paediatricians only (not a public statement). Recently the Australian College of Paediatrics (ACP) has revised its soy protein formula position statement (ACP 1998) along similar lines. The recommendations of the ACP are:

1. The indiscriminate use of soy formulae for vague symptoms and signs not proven to be due to cow's milk protein intolerance is to be avoided. Casual treatment in this manner is undesirable because it leads to over-diagnosis of food intolerance with potential long-term effects on child health and behaviour.
2. Soy formulae should not be used routinely as prophylaxis in infants thought to be at risk for the development of allergy. Soy protein is a potential allergen in its own right. The diagnosis of gastrointestinal Cow's Milk Protein Intolerance (CMPI) should not be made without careful evaluation by an expert in the field. When proven, it should be treated with formulae containing protein hydrolysates.
3. Conditions in infancy for which soy formula may be appropriately prescribed are galactosaemia and lactose intolerance.
4. The use of soy formula may not be without side-effects. There is some evidence that soy formula may impair immunity and the long-term effects of contaminants of soy (e.g. aluminium and phytoestrogens) are unknown.

The Ministry of Health supports the first three points of the position statement of the Australian College of Paediatrics. The ACP suggestion that immune suppression may be related to soy-based infant formula

(Zoppi et al 1983) is based on differences in the immune responses to vaccination between children fed breast milk and a range of infant formula. However the clinical significance of these changes in immune response is arguable. Phyto-estrogens are not proven to be a cause of impaired immunity in children. Although in-vitro studies have suggested that the isoflavone genistein has some immuno-suppressant activity (Atluru and Atluru 1991), the plasma levels which produce immunosuppression in vitro are unlikely to be attained by infants fed on soy-based infant formula.

The Ministry of Health's recommendations regarding the use of soy-based infant formula are:

- Soy formula should only be used under the direction of a health professional for specific medical indications, such as proven cow's milk protein intolerance or allergy, or lactose intolerance, in the absence of soy protein intolerance or allergy. Health professionals undertaking dietary treatment of these conditions should first consider the use of alternative non soy-based infant formula which are available in New Zealand.
- Soy-based infant formula is indicated for galactosaemia as a first-line treatment.
- 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.
- 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.
- Further research is required to determine whether there may be any other clinically significant interactions between phyto-estrogens in soy-based infant formula and endocrine function in infants.

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