

## SOY-BASED INFANT FORMULAS

In October 1995 an article in *Prescriber Update* reviewed the current literature with regard to soy-based infant formulas. The Ministry of Health has recently developed a pamphlet for parents which addresses some of the concerns about soy infant formulas, in particular, the presence of the phytoestrogen group of compounds. The reader is advised to review the original *Prescriber Update* article for a more in-depth coverage of the background

Since 1995 there have been a number of publications in peer reviewed journals which address the issue of phytoestrogens and soy infant formula. *Setchell (1997)* showed that infants are able to absorb significant levels of isoflavones, reaching blood levels which are higher than those which have been shown to have physiological effects on the menstrual cycle of adult women (*Cassidy 1994*). There is no new information which has confirmed the bioactivity of phytoestrogen conjugates in infants and children. (*Huggett 1997*). Metabolites of phytoestrogens are also pharmacologically active, with one particular metabolite of Daidzein (Equol) being significantly more estrogenic than its parent compound (*Kelly 1995*). This metabolite was found to be present at similar levels in the urine of infants fed cows milk based or soy based infant formula (*Venkataraman 1993*), or higher in infants fed cows milk based formula than either soy or human milk (*Setchell 1997*). A recent study of the acute estrogen activity of Genistein and Daidzein (using an in-vivo mammalian assay) indicated that Daidzein had minimal estrogen activity and that of Genistein was around 1/1000<sup>th</sup> to 1/10,000<sup>th</sup> that of naturally occurring estrogens. Neither Daidzein or Genistein were shown to have oestrogen blocking effects. (Milligan SR 1998)

A recent publication commissioned by the Ministry of Health from Crop and Food Research (Taylor GJ, Burlingame BA, 1998) examined the phytoestrogen levels within foods likely to be consumed by New Zealand infants. They confirmed the high levels of phytoestrogens in soy infant formulae and some weaning foods.

Apart from an investigation of an outbreak of premature thelarche (breast development) in Puerto Rico in the period 1978-81 which found a statistically significant but

unexplained positive association between soy formula (OR 2.7 (1.1 - 6.8)), maternal ovarian cysts (OR 6.8 (1.4 - 33.0)), chicken consumption (OR 4.9 (1.1 - 21.9)) and premature thelarche, (Lambertina et al 1986) there have been no human studies which have shown abnormalities and growth or reproductive development unequivocally attributable to soy infant formula.

There have however been a number of articles and reviews published over the last forty years regarding the effect of phytoestrogens on the function of thyroid gland in infancy. The literature has been well reviewed by *Taylor and Burlingame (1998)*. They identified a small number of case reports (comprising 12 individuals) which have documented thyroid abnormalities which were clearly associated with ingestion of soy infant formulae. (*Hydovitz, 1959, van Wyk 1959, Shepard 1960, Pinchera et al 1965*). Another paper suggesting an association between soy infant formula and autoimmune thyroid disease (ATD), was published in 1990 by *Fort and associates*. This paper retrospectively reviewed cases of ATD (Hashimoto's thyroiditis and Graves disease) in children and compared them to siblings and non-related controls. The authors found an increased rate of thyroid disease in subjects who had been fed soy infant formula as infants. However a cause and effect relationship was not established in this paper. A significant flaw was that the parent respondents were not asked the reason for commencing soy formula. It is possible, and plausible to consider that children who suffer gastrointestinal problems as infants could become predisposed to ATD and may be more likely to be fed soy as part of the treatment for the gastrointestinal disease. There has been one case report of thyroid abnormalities associated with soy infant formula since iodine supplementation was introduced in 1959 (*Labib et al 1989*).

A recent report from *Divi et al 1997* suggests that phytoestrogens (genistein and daidzein) in soy infant formula are capable of competitively inhibiting the action of thyroid peroxidase (TPO) through competitive inhibition. (i.e. by acting as an alternative substrate). The presence of additional iodide to the reaction completely abolished the inactivation of TPO. This study 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 slightly elevated levels of Thyroid stimulating Hormone (TSH) which were nevertheless within the normal range. (*Ishizuki et al 1991*) This acute decrease in

thyroxine levels and consequential elevation TSH could be accounted for by estrogen mediated increases in Thyroid Binding Globulin (TBG), which by providing a higher level of binding capacity will transiently reduce free thyroxine levels, and stimulate TSH. The situation is self limiting, as reduced tissue metabolism of thyroxine, and the elevated TSH soon restore the free thyroxine levels to normal (and total thyroxine will reach a new elevated homeostasis). The paper by Divi did not address the issue of uptake of phytoestrogens into the cells of the thyroid gland, and commented that the free aglycone was the most potent inhibitor in the experimental system. The  $IC_{50}$  (The level at which 50% inhibition of TPO occurs) was similar to the levels of plasma phytoestrogens reported in by *Setchell et al* 1997. (Around 1 - 2.5 micromols/l). However Setchell measured total phytoestrogens after dissociation of the compounds from protein and hydrolysis. The amount of phytoestrogen in the infant's plasma which is pharmacologically active (free aglycones and to a lesser extent conjugated phytoestrogens) was not reported and is significantly less than the levels of free aglycones measured, due to specific and non-specific protein binding of phytoestrogens. In adult women only 3% of circulating estradiol is free, with the remainder protein bound. (*Ganong 1981*). Even at the upper limits of phytoestrogen in plasma, and assuming a maximum of 5% free aglycone, the levels would be around the lower limit of inhibition for TPO.

There have been a few recent case reports of semi-refractory hypothyroidism and persistently elevated TSH in infants with hypothyroidism who were being fed soy infant formula. (*Chorazy PA 1995, Jabbar MA 1997*) The infant's requirement for additional thyroxine (above expected replacement levels) disappeared once the soy formula was ceased. The mechanism was postulated to be decreased absorption of thyroid replacement by the affected infants, however inhibition of TPO could have the same effect.

Consideration of these case reports and *Divi's* in-vitro study suggests that the isoflavone component of soy formula has the capacity to affect the thyroid function in infants. However the research has not yet clearly established that the levels of free phytoestrogen in infant's plasma are sufficient to significantly inhibit TPO.

For infants in whom the iodine intake is low or borderline or the thyroid function is compromised there is potential for clinical concern. Until further information is available

regarding bioavailability of phytoestrogens in the infant thyroid, it would be prudent to avoid the use of soy infant formula in children with hypothyroidism. Clinicians who are treating children with a soy based infant formula for allergic, gastrointestinal or metabolic conditions should monitor growth and development and biochemical thyroid function in these children.

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, protein intolerance. (*CMO 1996*) The Swiss Federal Commission on Food has published a similar position statement (*Tonz O. and Zimmerlei B. 1997*) and *Zimmerli B, Schlatter J, 1997*), to Paediatricians only (not a public statement). Recently the Australian College of Paediatrics 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 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. However we believe that the evidence with respect of immune suppression related to soy (Zoppi 1988) clearly relates to the known effects of protein under-nutrition and the consequent immune suppression associated with this condition since a poor immune response to immunisation was also seen in the infants fed low protein cows milk. Thus it is not clear as stated by the ACP that phytoestrogens are the cause of the reduced response to immunisation seen in the children in the study who were fed the non-commercial soy formula.

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

- Soy formula should only be used under the direction of a health professional for specific medical indications, such as cow's milk protein intolerance, and lactose intolerance. However these conditions have viable alternative formulae available in New Zealand and these should be used preferentially.
- Soy based infant formula is indicated for galactosemia as a first line treatment.
- Infants with hypo-thyroidism should not be fed a soy infant formula or soy containing foods as a major part of their diet, unless there is no reasonable alternative.
- Clinicians who are treating children with a soy based infant formula for allergic, gastrointestinal or metabolic conditions should monitor growth and development and biochemical thyroid function in these children.
- Further research is required to determine whether any other clinically significant adverse effects on endocrine function or growth in infants can be attributable to phytoestrogens.
- There is insufficient evidence to make recommendations about the effect of phytoestrogens in soy on adult thyroid function. However there is some

epidemiological evidence that phytoestrogens in soy may confer health benefits on adults.

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