SOYA INFANT FORMULA:

THE HEALTH CONCERNS

AND ADDENDUM

A FOOD COMMISSION BRIEFING PAPER

Written by Dr Mike Fitzpatrick and Sue Dibb

OCTOBER 1998

For information contact:

Dr Mike Fitzpatrick
PO Box 33-849
Takapuna
New Zealand
Tel: 0064 9 486 8068
Fax: 0064 9 486 8072
e-mail: mfitzpatrick@kma.co.nz
foodcomm@compuserve.com

Sue Dibb
The Food Commission
94 White Lion Street
London N1 9PF, UK
Tel: 0044 171 837 2250
Fax: 0044 171 837 1141
e-mail:

BACKGROUND

In July 1996 the UK Department of Health warned that phytoestrogens found in soya infant formulas could affect the health of infants. Issuing advice to health professionals, the Chief Medical Officer, Sir Kenneth Calman, said soya formula should only be given to babies on the advice of a health professional. He stressed that breast-feeding is the best way to protect babies from allergies and advised that alternatives to soya are available on prescription for those babies with allergies who cannot be breastfed.

Soy-based infant formulas and the majority of soy products contain a class of naturally occurring compounds known as phytoestrogens that exhibit biological activity in humans and other mammals. As the name suggests, phytoestrogens are able to mimic some of the actions of the female hormone oestrogen, however phytoestrogens also elicit a wide range of other endocrine system effects. There are concerns that the type of phytoestrogens found in soy (isoflavones) have significant potential for reproductive and developmental toxicity if fed to infants. In 1996 the UK government's Food Advisory Committee asked companies to investigate the removal of soy isoflavones from soy-based infant formulas but, despite evidence that this is possible (see below) companies have not yet done so.

THE HEALTH CONCERNS

- The potential for biological effects in infants due to the soy isoflavones has been clearly identified and includes changes in the function of sex glands, the central nervous system, the thyroid, and behavioural patterns (1-6).

- Exposure of infants fed soy-based formulas to isoflavones is high, greater than 1000 times that found for infants fed on breast-milk or cow's-milk based formula (7-9).

- Isoflavones are readily absorbed by infants (7) and the levels of isoflavones in the blood plasma of infants fed soy-based formulas are comparable to levels that exert significant estrogenic effects in experimental animals (10).

- Like many endocrine disruptors, the soy isoflavones cause thyroid dysfunction in humans. Several papers from the1960s reported that infants fed soy-based formulas developed goitre although the goitrogenic factors were not identified at that time (11-15). More recent reports have identified the actual and potential toxicity of soy to the thyroid (16-19) and the active factor in soy has been identified as the isoflavones. *In vitro* these compounds inhibit thyroid peroxidase catalysed reactions at concentrations that are comparable to those found in the plasma of human infants (20). Malignant goitre has occurred in experimental animals fed soy (21) and there is potential for soy isoflavones to cause thyroid cancer in humans.

- Other biological effects of isoflavones on infants have been reported (22-23).

- Biological effects in human adults have also been reported. In one UK feeding study involving premenopausal women, 60g of soy protein per day for one month disrupted the menstrual cycle and the effects of isoflavones continued for three months even after cessation of the soy diet (24). These effects were at dose per body-weight levels at least one order of magnitude lower than levels that soy-based formula-fed infants are exposed to. For infants, high levels of exposure, coupled with frequent and regular feeding throughout the day, results in soy-based formula fed infants having much higher plasma levels of isoflavones than any other population group. Therefore, infants fed soy-based formulas are exposed to significantly higher doses of isoflavones for much longer durations compared with the premenopausal women affected by soy consumption in the feeding trials. Indeed, infants that are fed soy-based formulas from birth may experience these high exposures for up to 12 months, or longer, including through the critical periods of postnatal sexual differentiation.

- The effects of isoflavones on adult women to date are changes to the sex steroid hormone status and nipple fluid secretion (24-25). In premenopausal women there is a clear potential for the soy isoflavones to modify fertility.

- Although the study was not conclusive, consumption of soy-based formulas was identified as a significant positive association in an increased occurrence of premature thelarche in Puerto Rico (26).

- *In vitro* the soy isoflavones are potent inhibitors of 17-β-hydroxysteroid oxidoreductase (27-28) and, therefore, can modulate the synthesis and metabolism of oestradiol and other steroid hormones (29).

- The reproductive and developmental toxicity of isoflavones has been demonstrated in several species of animals (30-34).

- It was the toxicity of dietary levels of isoflavones to animals that first raised the awareness of the scientific community to the fact that soy isoflavones were endocrine disruptors (35). Reproductive effects, infertility, thyroid disease or liver disease due to dietary intake of isoflavones had been observed for several animals including cheetah (34), quail (32), mice (33), rats (21), sturgeon (36) and sheep (37).

REMOVING ISOFLAVONES FROM INFANT FORMULA

Soya formula companies were asked by the UK government's Food Advisory Committee in 1996 to investigate the possibility of reducing phytoestrogen levels in their products. Standard processing does little to reduce the relative levels of isoflavones in soy-based infant formulas (38-39). However, isoflavones can readily be removed by ethanolic extraction and this has been demonstrated in numerous papers that detail methods for the analysis of

isoflavones in soy products (38-40). Also, isoflavone-free soy protein is available such as Arcon F, a soy-protein product produced by the Archer Daniels Midland Company, used as a control in feeding trials (24). Abbott-Ross Laboratories (manufacturers of the soya-based formula, Isomil) have developed a low phytoestrogen formula and has reported on a successful trial of the product (41).

Despite good evidence that it is possible to remove phytoestrogens on a commercial basis, manufacturers of soya infant formulas have not acted to do. In the UK their trade association, the Infant and Dietetic Foods Association (IDFA), has told the Food Commission that processing to remove the phytoestrogens would affect protein quality (42) - a statement which appears to be at odds with the above evidence.

It is well established that infants are especially sensitive to endocrine disruptors and, hence, that they are a high-risk group in terms of exposure. Therefore, any exposure of infants to endocrine disruptors, including phytoestrogens, should be kept to a minimum. Currently, however, infants fed soya formulas are subject to the highest exposure of any population group; a situation which has led Dr Daniel Sheehan, the head of Reproductive and Developmental Research at the US Food and Drug Administration's National Centre for Toxicological Research (NCTR), to note that infants fed soy-based formulas have been placed at risk in a 'large, uncontrolled, and basically unmonitored human infant experiment'(43).

The risks associated with phytoestrogen exposure in infants are well established and concerns were first raised more than a decade ago (44). Subsequently, harmful effects of phytoestrogens in infants fed soya formulas have been identified: in particular it is apparent that infants fed soya formulas are at real risk of chronic thyroid damage, indeed those infants with a history of thyroid dysfunction should avoid soya formulas and soya milks. It may be some time before other identified risks are fully quantified, but all risk could be avoided because the technology to greatly reduce the phytoestrogen content of soya formulas is already available to manufacturers.

The Food Commission believes it is irresponsible for manufacturers of soya formulas to continue to place infants at unnecessary risk of exposure to phytoestrogens and we have requested the immediate removal of phytoestrogens from soya infant formulas.

ADDENDUM: APRIL 1999

What about the traditional use of use soy in infant feeding?

Soy was not used in infant feeding in Asia. Writing in the 1930's, Dr RA Guy of the Department of Public Health of the Peiping Union Medical College found it 'pertinent to note that we have never found soybean milk naturally used by Peiping women to feed their children. This beverage is not made in the home in Peiping, but is sold by street vendors, as a hot, very weak solution of soybean protein and is usually drunk by old people in place of tea. The milk, as reinforced for the feeding of young infants, is rather tedious and difficult to prepare. As dispensed recently by the various health stations, it is in demand, but is just as artificial in this community as cow's milk' (45).

In a later publication, Guy reported on the use of soybean milk as a food for infants. The whole purpose of this report was to comment on the possible use of soy milk to address the problem of feeding those infants without sufficient maternal milk in a country were cow's milk was not native. He again noted that although a weak soy milk or 'tou fu chiang' was 'sold hot in Peking by street vendors and was taken by old people in place of tea', that 'contrary to Western notions' it was not usual to feed soy milk to infants (46).

Can soy cause thyroid disorders in humans?

Soy has been shown to have an affect on thyroid function in humans. A study by Japanese researchers concluded that intake of a moderate amount of soy by healthy adults could cause enlargement of the thyroid and suppress thyroid function (17)

These researchers studied the effects of feeding 30 g per day of pickled soybeans 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 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 dramatically, from approximately 1μU/mL to 6.5 to 7.5 μU/mL. There was no significant change in inorganic iodide, T_3 or T_4 in either group but a significant increase in FT_3 and FT_4 group 2 subjects following cessation of soy intake.

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% of subjects).

The goitre in the 11 subjects was a diffuse goitre with degrees I and II enlargement. One subject in group 1 developed sub-acute thyroiditis. Goitre size was reduced in nine of those subjects with goitre one month after cessation

of soy but goitre persisted in two subjects. These two subjects required up to 6 months T_4 treatment before their goitres reduced in size.

The combination of a moderately elevated TSH with a normal free T_4 defines sub-clinical hypothyroidism, an increasingly common condition that eventually may evolve towards overt hypothyroidism especially in persons with anti-thyroid antibodies. Subclinical hypothyroidism is defined as an asymptomatic state in which the reduction in thyroid hormone secretion is compensated for by an increased TSH production to maintain a clinically euthyroid status.

This condition is of increasing importance and its prevalence appears to be increasing. Dietary factors may well play a major role in the development of this condition. High goitrogen intake can increase TSH secretion and enhanced secretion of TSH is also associated with an increased risk of thyroid cancer. It is worthwhile noting that in the United States the incidence of thyroid disorders in those aged under 45 years has approximately doubled since 1985.

Soy and breast cancer

Those consuming soy or isoflavone supplements with the expectation that this will reduce the risk of contracting certain cancers should think twice. While consumers and health experts are being bombarded with advertising from the industry that extols the anti-cancer properties of soy isoflavones, many cancer researchers are saying just the opposite; that the consumption of soy isoflavones may increase the risk of cancer.

For example, postmenopausal women consuming soy isoflavones as a 'natural HRT' may place themselves at greater risk of breast cancer. In 1996 Dr Nicholas Petrakis, University of California, San Francisco, reported that 'Prolonged consumption of soy protein isolate has a stimulatory effect on the premenopausal female breast, characterised by increased secretion of breast fluid, the appearance of hyperplastic epithelial cells and elevated levels of estradiol. These findings are suggestive of an estrogenic stimulus from the isoflavones genistein and daidzein contained in soy protein isolate' (25).

Dr Craig Dees of Oak Ridge National Laboratory has found that soy isoflavones cause breast cancer cells to grow. He reported that 'low concentrations of genistein may stimulate MC-7 cells to enter the cell cycle' (47). Dees concluded that ' women should not consume particular foods (eg. soy-derived products) to prevent breast cancer'.

In support of a cautionary approach to consuming soy to prevent breast cancer is Dr William Helferich of the University of Illinois. He has recently stated that 'there is potential for dietary genistein to stimulate the growth of estrogen-dependent tumors in humans with low circulating endogenous estrogen levels, such as those found in postmenopausal women' (48).

How much soy is safe to eat?

The observations from the Ishizuki Thyroid Clinic study indicate significant, goitrogenic effects in subjects fed 30 g soybeans per day. Based on the concentrations of isoflavones found in Japanese soybeans (38), 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 approximately three times higher than the amount typically consumed in Japan, which is 0.08 to 0.13 mg/kg-body weight of total genistein per day for a 70 kg adult (49).

For infants fed soy-formulas, the exposure to isoflavones is greater than in any other population group. Infants less than 6 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 (7). Hence, soy formula fed infants are exposed to approximately 16 times greater levels of isoflavones than the subjects in the Ishizuki study.

The concentrations of isoflavones found in products available in New Zealand (33) indicate that a diet of 500g of soy milk plus 200g tofu 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 isoflavones is more than five times that of subjects in the investigation by Ishizuki et al.

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.

Therefore, soy formula fed infants, high soy consumers and users of isoflavone supplements might exhibit classic hypothyroid symptoms without recognising a dietary connection. Unfortunately there is little data as 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.

Soy users should be cautious about consuming more than 30 mg soy isoflavones per day. Thyroid disorders (see above for discussion on the active dose in the Ishizuki Thyroid Clinic study) and other biological effects have been observed at dose around this level.

As an approximate guide 30 mg of soy isoflavones can be found in:

Soybeans and soyflours:	9 - 20g (0.3 - 0.7oz).
Soy mince:	12g (0.4oz).
Tofu:	50 - 110g (1.8 - 3.9oz).
Soy milks:	150 - 240g (5.3 - 8.5oz).
Miso:	35 - 45g (1.2 - 1.6oz).
Soybean sprouts:	80g (2.8oz).

Why isn't this information readily available?

People deserve the right to know about what they are eating and what they are feeding their children. So why are government agencies so reluctant to share information with the public?

Dr Mike Fitzpatrick met with California DHS staff in June 1998 to express his concerns about soy, and particularly soy formulas. He received a written response from DHS toxicologist Dr Susan Loscutoff. Loscutoff stated:

"I agree that high levels of dietary exposures to isoflavones in infants fed soy-based formulas is cause for concern".

"I do not agree that parents have a right to know that soy-based formulas contain isoflavones and the kinds of toxicities isoflavones might demonstrate in infants, since parents would not know how to interpret the information."

This kind of response it quite typical of agencies fearing a severe backlash from the soy lobby should they alert the public to the potential health concerns of soy isoflavones.

What can I do?

Share this information with your health professionals and friends.

Write to your State Health Department demanding information on the risks associated with the consumption of soy isoflavones, especially by infants, and the safety of isoflavone supplements/OTC-drugs.
Write to potentially sympathetic politicians (e.g. Senator Barbara Boxer or Senator Fred Lautenberg), and express your concern about the presence of isoflavones in soy formulas. Ask for clarification regarding the safety of soy formulas and soy isoflavone supplements/OTC drugs.

Be prepared for a 'no evidence of harm' response. The facts, however, tell a different story.

REFERENCES

1 Clarkson TB et al. Estrogenic soybean isoflavones and chronic disease. Risks and benefits. Trends Endocrinol Metab 6: 11-16 (1995).
2 Chapin et al. Endocrine modulation of reproduction. Fund Appl Tox 29: 1-17 (1996).
3 Santi R et al. Phytoestrogens: potential endocrine disruptors in males. Tox Ind Health 14: 223-237 (1998).
4 Sheehan DM. Herbal medicines, phytoestrogens and toxicity: risk: benefit considerations. PSEBM 217:379-385 (1998).
5 Tönz O and Zimmerli B. Phytoöstrogene in säuglingsnahrung auf sojaproteinbasis. Paediatrica 8: 14-15 (1997).
6 Theo Colborn, Dianne Dumanoski and John Peterson Myers. Our Stolen Future, Little Brown and Company, London, 1996.
7 Setchell KDR et al. Exposure of infants to phytoestrogens from soy-based infant formula. Lancet 350: 23-27 (1997).
8 Murphy PA et al. Isoflavones in Soy-Based Infant Formulas. J Agric Food Chem 45: 4635-4638 (1997).
9 Irvine CHG et al. Phytoestrogens in soy-based infant foods: concentrations, daily intake, and possible biological effects. PSEBM 217:247-253 (1998).
10 Santell RC et al. Dietary genistein exerts estrogenic effects upon the uterus, mammary gland and the hypothalamic/pituitary axis in rats. J. Nutr 127: 263-269 (1997).
11 Van Wyk et al., The effects of a soybean product on thyroid function in humans. Pediatrics 24: 752-760 (1959)
12 Hydovitz JD. Occurrence of goiter in an infants on a soy diet. New Eng J Med 262: 351-353 (1960).
13 Shepard TH. Soybean goiter. New Eng J Med 262: 1099-1103 (1960).
14 Ripp JA. Soybean induced goiter. Am J Dis Child 102: 136-139 (1961).
15 Pinchera A et al. Thyroid refractoriness in an athyreotic cretin fed soybean formula. New Eng J Med 273: 83-87 (1965).
16 Fort P et al. Breast and soy-formula feeding feedings in early infancy and the prevalence of autoimmune thyroid disease in children. J Am Coll Nutr 9: 164-167 (1990).
17 Ishizuki Y et al. The effects on the thyroid gland of soybeans administered experimentally in healthy subjects. Nippon Naibunpi gakkai Zasshi 67: 622-629 (1991).
18 Chorazy PA et al. Persistent hypothyroidism in an infant receiving a soy formula: case report and review of the literature. Pediatrics 148-150 (1995).
19 Jabbar MA et al. Abnormal thyroid function tests in infants with congenital hypothyroidism: the influence of soy-based formula. J Am Coll Nutr 16: 280-282 (1997).
20 Divi RL et al. Anti-thyroid isoflavones from the soybean. Biochem Pharmacol 54: 1087-1096 (1997).
21 Kimura S et al. Development of malignant goiter by defatted soybean with iodine-free diet in rats. Gann 67: 763-765 (1976).
22 Fort et al. Breast feeding and insulin-dependent diabetes mellitus in children. J Am Coll Nutr 5: 439-441 (1986).

23 Cruz et al. Effects of infant nutrition on cholesterol synthesis rates. Ped Res 35: 135-140 (1994).
24 Cassidy A et al. Biological effects of a diet of soy protein rich in isoflavones on the menstrual cycle of premenopausal women. Am J Clin Nutr 60: 333-340 (1994).
25 Petrakis NL at al. Stimulatory influence of soy protein isolate on breast secretion in pre- and postmenopausal women. Cancer Epid Bio Prev 5: 785-794 (1996).
26 Freni-Titulaer et al. Premature thelarche in Puerto Rico. AJDC 140: 1263-1267 (1986).
27 Keung W-M. Dietary estrogenic isoflavones are potent inhibitors of β-hydroxysteroid dehydrogenase of *P.Testosteronii*. Biochem Biophys Res Comm 215: 1137-1144 (1995).
28 Makela SI et al., Estrogen specific 17β-hydroxysteroid oxidoreductase type I (E.C.1.1.1.62) as a possible target for the action of phytoestrogens. PSEBM 208: 51-59 (1995).
29 Phytoestrogens: potential endocrine disruptors in males. Santti R, Makela S, Strauss L, Korkman J, Kostian ML, Toxicol Ind Health 14:1-2 223-37 (1998).
30 Carter AW et al. Effect of genistin on reproduction of the mouse. J Nutr 55: 639 (1955).
31 Matrone G et al. Effect of genistin on growth and development of the male mouse. J Nutr 59: 235 (1956).
32 Leopald AS. Phytoestrogens: Adverse effects on reproduction in California Quail. Science 191: 98-100 (1976).
33 Drane HM et al. Oestrogenic activity of soya-bean products. Fd Cosmet Technol 18: 425-427 (1980).
34 Setchell KDR et al. Dietary estrogens - a probable cause of infertility and liver disease in captive cheetahs. Gastroenterology 93: 225-233 (1987).
35 Pope GS and Wright HG. Oestrogenic isoflavones in red clover and subterranean clover. Chem Ind 1019-1020 (1954).
36 Pelissero C et al. Estrogenic effect of dietary soy bean meal on vitellogenesis in cultured Siberian Sturgeon *Acipenser baeri*. Gen Comp End 83: 447-457 (1991).
37 Braden et al. The oestrogenic activity and metabolism of certain isoflavones in sheep. Aust J Agr Res 18:335-348 (1967).
38 Wang H and Murphy PA. Isoflavone content in commercial soybean foods. J Agric Food Chem 42: 1666-1673 (1994).
39 Barnes S et al. Isoflavones and their conjugates in soy foods: Extraction conditions and analysis by hplc-mass spectrometry. J Agric Food Chem 42: 2466-2474 (1994).
40 Franke AA et al. Quantitation of phytoestrogens in legumes by HPLC. J Agric Food Chem 42: 1905-1913 (1994).
41 Tolerance of soy formulas with reduced phytate/phytoestrogens fed to healthy term children, Janus L Ostrum, Ross Products Division, poster presentation at the Second International Symposium on the Role of Soy in Preventing and Treating Chronic Disease, Brussels, September 16-19, 1996.

42 Phytoestrogens in Soya Infant Formula, Infant and Dietetic Foods Association, letter to the Food Commission, 24 September 1998.
43 Sheehan DM. Isoflavone content of breast milk and soy formulas: benefits and risks (letter). Clin Chem 43:850 (1997).
44 Setchell, KDR. Naturally occurring non-steroidal estrogens of dietary origin. In 'Estrogens in the Environment' J McLachlan (Ed), Elsevier, New York, 1985.
45 Guy RA. The diets of nursing mothers and young children in Peiping. Chinese Med J. 50:434-442 (1936).
46 Guy RA and Yeh KS. Soybean milk as a food for young infants. Chinese Med J. 54:1-30 (1938).
47 Dees C et al. Dietary estrogens stimulate human breast cells to enter the cell cycle. Environ Health Perspect 105 (Suppl 3): 633-636 (1997).
48 Hsieh C-Y et al. Estrogenic effects of genistein on the growth of estrogen receptor-positive human breast cancer (MCF-7) cells in vitro and in vivo. Cancer Res 58:3833-3838 (1998).
49. Fukutake M et al. Quantification of genistein and genistein in soybeans and soybean products. Food Chem Toxicol 1997; 34: 457-461.