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

WORKING GROUP ON PHYTOESTROGENS

Submission from Mr Richard James (received 07/08/00)

Background

1. In conjunction with Dr Mike Fitzpatrick (see submission PEG/2001/3), Mr James runs the Soy Online Service website in New Zealand. He is concerned about the toxicity of soya products. The website aims to raise awareness on the potential adverse health effects of ingesting soya & soya-based products. Mr James's interest in this area stems from the observation that parrots he was breeding developed health problems, which he associated with the soya-based diet the parrots were fed. Mr & Mrs James also fed their children soya-infant formulae & have associated the subsequent health problems their children experience with the use of soya formulae.

Submission

2. In a letter (also sent by email 04/08/2000) to the Working Group, Mr James argues that soya-based infant formulae is toxic & has not undergone the necessary testing procedures. The submission contains a number of complete & incomplete articles identified from a search conducted of United States Government files & scientific articles, which he cites to support his argument.

3. Mr James recommends that full safety studies are required on soy protein & until these are conducted, consumers should be provided with warnings regarding its toxicity. He also asks the Working Group to consider the health risks from protease inhibitors & phytic acid in soya. Mr James suggests the levels of isoflavones consumed in some human diets are:

- Reproductively toxic: as ingestion of soya can alter the length of the menstrual cycle and suppress the FSH & LH mid-cycle surge in pre-menopausal women (Cassidy *et al*, 1994). This paper was presented in the beneficial effects paper (PEG/2000/16). Members considered at the April 2000 meeting that the quantity of soya used in this study, equivalent to an intake of 45mg isoflavones/d, did result in physiological effects & this level of intake could be regarded as a high dose.
- Chronically toxic: as isoflavones can inhibit thyroid peroxidase (Divi et al 1997). This paper was considered by Dr Hindmarsh in the 'Position statement on soya-based foods and the thyroid gland' presented at the January 2001 meeting.
- Teratogenic: A pre-publication draft of the supporting reference, 'A maternal vegetarian diet in pregnancy is associated with hypospadias.' (North *et al*, 2000) was discussed by the COT in 1999. They concluded that there was

insufficient evidence to support the conclusion that phytoestrogens in a vegetarian diet had a deleterious effect on the male reproductive tract.

- Subacutely toxic: The supporting reference, a study of dementia among elderly Japanese-American (Ross *et al*, 1997), does not make any associations between dementia & diet.
- Mutagenic: A study has demonstrated that genistein, but not daidzein, can induce DNA strand breaks in cultured Chinese hamster V79 cells (Kulling *et al*, 1997). The authors postulate that this is due to inhibition of topoisomerase II. Although the study was not presented to the Working Group in the adverse effects paper (PEG/2000/22), studies of topoisomerase inhibition by genistein were included.
- Carcinogenic A study (Dees *et al*, 1997) shows genistein increases cyclin dependent kinase 2 (Cdk2) activity, cyclin D1 synthesis & stimulates hyperphosphorylation of retinoblastoma in MCF-7 cells. The authors suggest this activity is responsible for the proliferative effect of genistein observed in *in vitro* cell culture. In addition, isoflavones bind to estrogen receptors from breast cancer cells (Martin *et al*, 1978).

EVALUATION OF THE HEALTH ASPECTS OF SOY PROTEIN ISOLATES AS FOOD INGREDIENTS

4. Mr James has also included a paper prepared for the US Bureau of Foods of the Food and Drug Administration (1979) evaluating the safety of soya protein isolates used as food ingredients. The paper notes that soya protein isolates used as substances, which may migrate from packaging into foods, as food ingredients & as food binders or extenders are generally recognised as safe (GRAS). The composition & processing of soya protein isolate is reviewed. Estimates of consumer exposure to soya protein isolates in 1970 are given: (150mg/d for adults, 22.6 (50 percentile) & 27.2g/d (90 percentile) for infants fed soya formulae.

5. The paper reviews biological & toxicological studies of soya protein isolate. Studies of gastric pH and gastric emptying, protein quality, nitrogen balance and mineral metabolism found that fortification of soya protein isolate with methionine increased the nutritional quality. However, when soya protein isolates were supplied as the sole or major source of protein to animals the utilisation of fat-soluble vitamins and minerals was impaired. Soy protein isolate was not observed to produce toxicity in acute, multi-generation or teratogenicity studies. However, renal cytomegalic lesions in the pars recta of the proximal tubule were demonstrated in rats fed diets containing 20-30% alkali-treated soy protein isolates as the sole source of protein. Removal of the protein from the diet appeared to reverse the changes and cytomegaly was reduced or did not occur in rats fed alkali-treated rats supplemented with an untreated soya protein. It was suggested that the cytomegaly was caused by protein bound lysoalanine in an amino acid deficient/imbalanced diet.

6. The paper concludes that well-processed soy protein isolate adequately supplemented with methionine, minerals and vitamins either added to the isolate or as provided by other dietary components is not hazardous to health. In addition, whilst specifications for food grade soy

protein isolates should be established there is no evidence that soy protein isolates are hazardous at the then current (1970) or future levels. The document does not consider isoflavones in soya & has not been considered by the Working Group

SOYABEANS AND RELATED PRODUCTS AN INVESTIGATION INTO THEIR TOXIC EFFECTS

7. Also included in the submission is an unpublished study (in part) prepared for Mr James by Dr Mike Fitzpatrick (1994). Dr Fitzpatrick suggests that the ability of a compound to interact with the estrogen receptor determines its estrogenic activity. High chronic doses of estrogens are carcinogenic & can adversely effects the developing foetus (i.e DES). He cites a number of old publications which have not been included in the adverse effects paper (PEG/2000/22) (Martin *et al*, 1978; Verdeal *et al*, 1980; Mori, 1979; Kincl *et al*, 1967; Weisburger *et al*, 1966). Dr Fitzpatrick comments that little is known about the metabolism of isoflavones & suggests that without a full understanding of how these compounds are metabolised, it is difficult to predict how estrogenic they are.

8. The paper highlights the study by Cassidy *et al* (1994) outlined above & suggests that isoflavones possess the same capability as oral contraceptives to prevent ovulation. These physiological effects are also relevant to infants fed soya formulae (Setchell *et al*, 1984 & 1994). Two studies where phytoestrogens have produced adverse effects in mice are identified (Matrone *et al*, 1956; Leopald *et al*, 1976). Although these old studies have not been presented to the Working Group a number of more recent studies have been considered. A number of other studies of adverse effects on other species are highlighted (Carter *et al*, 1955; Braden, 1967 & Bennetts, 1946). These are all uncontrolled feeding studies in wildlife and have not been considered by the Working Group.

9. The estrogen binding affinities of phytoestrogens relative to synthetic estrogens & levels of phytoestrogens in soya products are reviewed. An intake of isoflavones from soya infant formulae 3-5-fold greater than the quantity of isoflavones found to elicit estrogenic activity in women is estimated. These figures are used to derive a daily estrogen intake from soya infant formulae of 8-12 contraceptive pills.

10. The paper suggests that whilst the incidence of some disease is reported to be lower in Oriental populations with a high soya consumption increased soya consumption (Whitten et al, 1992) this may be because 'traditional' methods of preparation reduce the isoflavone content (Murphy, 1982).

11. The paper concludes that long-term effects of continued exposure to these compounds in infants, adults and animals remains unknown and as such they should be viewed as serious toxic dietary factors. Dr Fitzpatrick recommends that isoflavones should be extracted from all products intended

for infants and that the public should be informed about the potential side effects associated with consumption of these compounds.

12. Many of the references cited do not directly relate to the effects of soya phytoestrogens but relate to the nutritional quality and allergenicity of soya and soya-based foodstuffs, the biological effects of estrogen or synthetic estrogens as well as analytical methods.

Conclusions

13. On the basis of the evidence he has provided, Mr James concludes that in 1959 when soya protein entered the food chain, scientists knew that they were not removing all the natural toxins. In addition, as there is no evidence that soya protein was subject to pre-market approval procedures in the US Mr James concludes that it cannot be considered a legal ingredient of foodstuffs. For this reason it cannot comply with the CODEX guidelines G4/89 for vegetable protein products (VPP) (also included in the submission), which outline the uses & establish the safety and nutritional quality of VPP. He could find no evidence of a risk assessment having been performed for any natural toxins in the finished product and he suggests that the only uses for which soy protein has been granted GRAS status are as a binder and sealant for cardboard packaging.