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

DEPARTMENT OF HEALTH

STATEMENT ON PHYTOESTROGENS

Phytoestrogens are widely distributed plant chemicals which can cause oestrogenic effects. Two of the main classes of phytoestrogens are the coumestans and the isoflavones. They are capable of binding to the oestrogen receptor but in many tests *in vivo* and *in vitro* are considerably less potent than endogenous oestrogens. Because of the differences in efficacy and in binding affinities to the oestrogen receptor and the dependence on the intrinsic oestrogenic state (ie prepubertal, premenopausal, postmenopausal) of the target tissue, either agonistic or antagonistic responses can be produced (1-5).

Phytoestrogens have been shown to cause infertility in animals, the first cases being noted in ewes which became infertile, less sexually receptive and more aggressive. The infertility syndrome, named *Clover Disease*, was subsequently discovered to be caused by high concentrations of coumestrol (a coumestan) in the clover grazed by the sheep (2, 6-8). In laboratory animals, exposure to coumestrol via dams milk has also been shown to cause effects on oestrous cycling, LH response following oestrogen and progesterone priming, and behaviour which only become apparent as the animals reach sexual maturity. Furthermore, administration of phytoestrogens to these same species can cause androgenisation of females and feminisation of males, although the effects vary according to time and duration of intake (9-14).

At present, there are only limited data on the intake of phytoestrogens in specific population groups in the UK. People consuming an Asian diet and vegetarians have high intakes of soy, a major source of isoflavones (4, 15-20). The isoflavones found in plant material are mainly bound to sugar residues and are inactive (2, 21). The active aglycones are released in the gastro-intestinal tract by gut microflora and are subsequently absorbed and metabolised (2, 22). Known differences in the microflora between people consuming a Japanese diet and those consuming a Western diet could result in differences in the effects of isoflavones in these different population groups (23). Human studies have also indicated that there is inter-individual variation in the metabolism of daidzein, one of the isoflavones found in soy. Approximately 30% of the population is able to metabolise daidzein extensively to equol, while the majority of the population produce smaller amounts of this metabolite (24). Phytoestrogen excretion has also been reported in a small study in male infants fed either human milk, cows' milk formula or soy-based formula from birth to 4 months of age (25). Total urinary isoflavonoid concentration was approximately 20 microgram per litre (μg/l) for the infants fed human milk, 100 μg/l for the infants fed cows' milk formula and 600 μg/l for the infants fed soy-based formula. Of the three isoflavones determined, only daidzein and genistein were detected, with the concentration of equol being minimal in all groups.

Consideration of phytoestrogen toxicity and subsequent risk to certain groups of the population is complex since their actions are tissue and end-point specific and depend on the developmental and maturational context in which they are assessed. The complexity is further compounded by differences in metabolism as outlined above.

In preliminary studies in premenopausal women normally consuming a Western diet, ingestion of soy protein (60g per day for one month, equivalent to 0.73 mg isoflavones/kg bw/day) has been shown to suppress mid-cycle peaks of LH and FSH and significantly increase the duration of the follicular phase (26, 27). The effects lasted for up to 3 months following the termination of soy consumption. There are reports that phytoestrogens can reduce blood cholesterol (25, 26, 28, 29), and that they may protect against osteoporosis and reduce flushing in postmenopausal women (29, 30). Epidemiological evidence from adult populations which habitually ingest high quantities of soy (eg, Chinese and Japanese) suggest that these individuals have a lower incidence of some types of cancer (4, 15, 18, 28, 29). However, it is difficult to resolve the effects and consequences of other dietary variables such as fibre, vitamins, fruit, vegetables and meat when considering the validity of this observation. The subject of dietary constituents and cancer is presently under review by a Working Group of the Committee on Medical Aspects of Food Policy (COMA).

The potential for phytoestrogens, including isoflavones, to affect adversely infants is of particular concern since it is possible that a hormonal imbalance in early life can permanently affect sexual development and fertility. Such effects have been observed in a number of animal species (2, 4, 9-14). We are not aware of any reports which suggest that populations which habitually ingest high quantities of soy (eg Chinese, Japanese) have impaired fertility or altered sexual development. Limited data indicate that the estimated intake of isoflavones by infants fed soy-based formulae is in the region of 4 mg/kg bw/day (31, 32). This is higher than the intake reported to cause hormonal effects in premenopausal women (approximately 0.73 mg/kg bw/day). Since we do not have data specifically relating to the potential effects of soy phytoestrogens in human infants, particularly in those whose mothers normally consume a *western* diet, we *recommend* that research should be undertaken as a matter of high priority to determine whether ingestion of soy based formulae carries any risk for infants. (See Annex A for list of recommended research proposals). As a result of further research, it may be necessary to consider the potential risk of soy products to other sectors of the population. We *endorse* the advice of the Department of Health that breast milk and cows' milk formulae are the preferred sources of nutrition for infants. However, women who have been advised by their doctor or other health professionals to feed their baby soy-based formulae should continue to do so. The Committee on Medical Aspects of Food Policy has published a more detailed report of the preferred sources of nutrition for infants (Department of Health. Weaning and the Weaning Diet. London: HMSO, 1994. Report of Health and Social Subjects: 45).

July 1996

ANNEX A

Recommended research proposals listed in order of priority

1. Investigation of the bioavailability and excretion of isoflavones in infants.

2. Determination of the phytoestrogen content of breast milk from mothers habitually ingesting soy and follow up infants.

3. Consideration of the differences between the UK population and those habitually ingesting soy (eg Japanese, Chinese), ie. differences in gastric microflora, genetic variability in metabolism and possible adaptation to soy. Consideration of the possible differences in bioavailability and other physiological effects between extensive and non-extensive equol producers.

4. Re-evaluation of the literature on populations exposed to large quantities of soy to look for evidence of harm.

5. Re-evaluation of reports on potency and of oestrogenic/anti-oestrogenic physiological effects of phytoestrogens with a view to establishing an equivalency factor approach.

6. Investigation of the effects of isoflavones on the development of the rat (oral administration).

7. Studies to provide information on absorption, distribution, metabolism and excretion of isoflavones in the rat. Determination of tissue distribution and *in vitro* metabolism of isoflavones by gastro-intestinal contents from rats and from humans (UK and Asian Populations).

References

1. Welshons W V, Rottinghaus G E, Nonneman D J, Dolan-Timpe M and Ross P F (1990). A sensitive bioassay for the detection of dietary oestrogens in animal feeds. J Vet Diag Invest. 2 268-273.

2. Kaldas R S and Hughes C L (1989). Reproductive and general metabolic effects of phytoestrogens in mammals. Repro Tox. 3, 81-89.

3. Stob M. (1983). Naturally occurring food toxicants: estrogens. In: (M Rechnig Jr (Ed)) Handbook of naturally occurring food toxicants. Boca Racon: CRC Press, pp 81-100.

4. Messina M J, Persky V, Setchell K D R and Barnes S (1994). Soy Intake and Cancer Risk: A review of the in vitro and in vivo data. Nutr Cancer 21: 113-131

5. Sheehan D M (1995). The case for expanded phytoestrogen research. Proc Soc Exp Biol Med 208, 3-5.

6. Bennetts H W, Underwood E J, & Shier F L (1946). A specific breeding problem of sheep on subterranean clover pastures in Western Australia. Austral. Vet J. 22, 2-12

7. Croker K P, Lightfoot R J, Johnson T J, Adams N R and Carrick M J (1989). The effects of selection for resistance to clover infertility on the reproductive performances of Merino ewes grazed on oestrogenic pastures. Aust J Agr Res 40, 165-176.

8. Adams N R (1981). A changed responsiveness to oestrogen in ewes with clover disease. J Repro Fertil. 30 (Supplement). 223-230

9. Whitten P L & Naftolin F (1992). Effects of phytoestrogen diet on oestrogen-dependent reproductive processes in immature female rats. Steroids 57, 56-61.

10. Whitten P L, Lewis C, Naftolin F (1993). A phytoestrogen diet induces the premature anovulatory syndrome in lactionally exposed female rats. Tox Repro 49, 1117-1121.

11. Whitten P L, Lewis C, Russel E, Naftolin F (1995). Phytoestrogen influences on the development of behaviour and gonadotropin function. Proc Soc Exp Biol Med 208, 82-86.

12. Levy J R, Faber K A, Ayyash L and Hughes C L (1995). The effect of prenatal exposure to the phytoestrogen genistein on sexual differentiation in rats. Proc Soc Exp Biol Med. 208, 60-66

13. Faber K A and Hughes C L (1991). The effect of neonatal exposure to DES, Genistein and Zearalenone on pituitary responsiveness and sexually dimorphic nucleus volume in the castrated adult rat. Biol of Repro 45, 649-653.

14. Register B, Bethel M A, Thompson D, Walmer D, Blohm P, Ayyash L and Hughes C (1995). The effect of neonatal exposure to DES, Coumestrol and beta-sitosterol on pituitary responsiveness and sexually dimorphic nucleus volume in the castrated adult rat. Proc Soc Exp Biol Med 208, 72-77

15. Adlercreutz H, Honjo H, Higashi A, Fotsis T, Hamalainen E, Hasegawa T, Okada H (1991). Urinary excretion of lignans and isoflavonoid phytoestrogens in Japanese men and women consuming a traditional Japanese diet. Am J Clin Nutr. 54:1093-1100.

16. Barnes S, Grubbs C, Setchell K D R, Carlson J. (1990). Soybeans inhibit mammary tumours in models of breast cancer. In Mutagens and Carcinogens in the Diet. (Ed M Pariza), Wiley-Liss, New York. pp 239-253

17. Coward L, Barnes N C, Setchell K D R, Barnes S (1993). Genistein, Daidzein, and their β-glycoside conjugates: Antitumor isoflavones in soybean foods from american and asian diets. J Agric Food Chem 41: 1961-1967.

18. Lee H P, Gourley L, Duffy S W, Esteve J, Lee J, Day N E (1991). Dietary effects on breast cancer risk in Singapore. Lancet 337: 1197-1200.

19. Jones A E, Price K R, Fenwick G R (1989). Development of a high performance liquid chromatographic method for the analysis of phytoestrogens. J Sci Food Agri 46, 357-364.

20. Price K R and Fenwick G R (1985). Naturally occurring oestrogens in foods - a review. Food Additives and Contaminants. 2, 73-106.

21. Miksicek R J (1995). Estrogenic flavonoids: Structural requirements for biological activity. Proc Soc Exp Biol Med 208, 44-50.

22. Lundh T (1995). Metabolism of oestrogenic isoflavones in domestic animals. Proc Soc Exp Biol Med 201 33-39

23. Moore W E C and Moore L H (1995). Intestinal foras of populations that have a high risk of colon cancer. Appl and Envir Microbiol 61(9), 3202-3207

24. Kelly G E, Joannou G E, Reeder A Y, Nelson C, Waring M A (1995). The variable metabolic response to dietary isoflavones in humans. Proc Soc Exp Biol Med. 210: 40-43.

25. Cruz, M L A, Wong W W, Mimouni F, Hachey D L, Setchell K D R, Klein P D, Tsang R C (1994). Effects of infant nutrition on cholesterol synthesis rates. Pediatric Research 35 (2) 135-140

26. Cassidy A, Bingham S, Setchell K D R (1994). 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.

27. Cassidy A, Bingham S, Setchell K D R (1995). Biological effects of isoflavones

in young women: importance of the chemical composition of soybean products. Brit J Nutr. 74, 587-601.

28. Setchell K D R, Borriello S P, Hulme P, Kirk D N and Axelson M (1984). Nonsteroidal estrogens of dietary origin: possible roles in hormone-dependent disease. Am J Clin Nutr. 40, 569-578

29. Clarkson T B, Anthony M S and Hughes C L (1995). Estrogenic soybean isoflavones and chronic disease. Trends in Endocrinol Metab, 6(1), 11-16.

30. Adlercreutz H, Hanalainen E, Gorbach S, Goldin B (1992). Dietary phytoestrogens and the menopause in Japan. Lancet 339, 1233.

31. Irvine C, Fitzpatrick M, Robertson I and Woodhams D (1995). The potential adverse effects of soybean phytoestrogens in infant feeding. New Zealand Medical Journal , 24 May 1995, 208-209.

32. Private Communication.