British Journal of Nutrition (2003), **89**, Suppl. 1, S3–S4
DOI: 10.1079/BJN2003885

Foreword

The Concerted Action 'Dietary exposure to phyto-oestrogens and related compounds and effects on skeletal tissues (VENUS)' was funded by the European Commission in 1998 (Food and Agroindustrial Research project CT-98-4456), with the aim of creating a European network to stimulate discussion, exchange know-how and co-ordinate research in the field of vegetal oestrogens. The Concerted Action has dealt with exposure in Europe and biological effects on the skeletal tissues.

Phyto-oestrogens were first identified in the diet of South East Asian populations, where they are mainly present in soy, an item that is not widely present on European tables, although it is often used as an ingredient of industrial products. The first challenge for VENUS was the establishment of a quality standard for analytical techniques, so that the increasing literature on these compounds could be evaluated and a database of phyto-oestrogen content in foods could be created. Second, by making use of existing data on population-representative food intake, the VENUS scientists could calculate overall exposure to these compounds and estimate the population distribution. This was achieved in Finland, The Netherlands, Ireland, the UK and Italy. In this Supplement, such issues are dealt with by the papers of Hoikkala *et al.* on analytical techniques, Kiely *et al.* on the methodology used to create the database, van Erp-Baart *et al.* on exposure in Europe and Valsta *et al.* on exposure in Finland.

Before addressing the biological effects, the Concerted Action had to deal with the bioavailability issue, i.e. the absorption, distribution, metabolism and excretion of the different compounds, in relation to the food matrix and the mode of consumption. Here, many intriguing questions have arisen, as well as answers given on the importance of the interaction with host factors such as gut microflora, of environmental factors such as the composition of the diet, and the combination of the two. The paper by Rowland *et al.* provides a good overview of the state-of-the-art and of the pending questions.

The issue of biological effects of phyto-oestrogens is of great complexity. Phyto-oestrogens are a large family of compounds that have in common their capacity to perform like animal oestrogens, somehow interacting with the oestrogen receptors. However, there are at least two types of oestrogen receptor, α and β, as well as oestrogen-related receptors (formerly 'orphan' receptors) that are expressed to a variable extent in different tissues. Furthermore, in addition to 'classical' receptor-mediated actions, oestrogens have been shown to act through other pathways in which binding to the receptors is not required or an oestrogen-responsive element in the genome is not involved. Finally, the combination of endogenous oestrogens and compounds present in food and the environment with the capacity to interact with the oestrogen receptor make such effects extremely variable between individuals. Hence, there is a vast spectrum of possible responses across individuals and across organs and tissues of the same individual.

VENUS investigated the peculiarity of the action on bone tissue, with the aim to evaluate potential use in the prevention of osteoporosis. The Concerted Action decided to move from the cellular level to man. The first step was therefore to investigate whether *in vitro* systems based on bone cells could be used in testing the oestrogenic and anti-oestrogenic effects of plant oestrogens and related compounds. Ideally, the bone tissue could be used as a benchmark for the activity of these compounds, but bone cell systems are rather complex and they may present a variable phenotype, such that the literature often provides contrasting results on the same compound. The Concerted Action examined the characteristics of different cell systems, discussed the most appropriate biomarkers and questioned the applicability of such models to man. This work is reported in the paper by Lieberherr *et al.*

The biological action of phyto-oestrogens on bone has been studied in animal models as well as in human studies. The paper by Coxam reviews the different animal models used to study the effects on bone biology and analyses the scope for their application. Human observational studies have shown associations between isoflavone intake and increased bone mineral density. However, intervention studies are still required to demonstrate an effect specifically. The Concerted Action agreed on the methodological requirements for human studies on osteoporosis prevention and re-evaluated the literature in the light of such criteria (Valtueña *et al.*), indicating the need for longer studies, with a more solid design, in the absence of which the real efficacy cannot established.

The Concerted Action also dealt with food technology and food policy issues, such as the possible scenarios to increase phyto-oestrogen consumption in Europe. The first option would be to increase soy product consumption, with a shift from the Mediterranean to a South East Asian dietary pattern. The second would be the development of functional foods enriched with phyto-oestrogens. The third would be to increase the intake of foods of European origin containing phyto-oestrogens other than isoflavones (e.g. lignans). Each of these options has social, economical, technological, behavioural and legislative factors to be taken into account. Some of them are dealt with in the paper by Fletcher.

There is an expectation about phyto-oestrogens from the public: they are appealing as they are perceived as 'natural' products and are considered free of side-effects. The concern raised by the report of the Women's Health Initiative (Rossouw *et al.* 2002), which showed an increased risk of breast cancer in women using hormone replacement therapy, has induced many women, and even their gynaecologists, to prescribe phyto-oestrogen preparations. As a

result, an increasing number of women consume phyto-oestrogens during menopause, mainly as dietary supplements. However, quality assurance is critical while there is variability in composition and peaks of unknown origin and chemical structure (Setchell *et al.* 2001).

Finally, a crucial question often asked is 'Is phyto-oestrogen intake totally safe?' In this Supplement, the safety issue is dealt with in the paper by Barnes. In the past there has been great concern about the safety of phyto-oestrogens. The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment of the UK Food Standards Agency was given the task to prepare a report on the topic. The group decided to keep a balanced view and included a thorough discussion of beneficial effects, concluding that 'large long-term prospective studies are necessary to establish the relationship between dietary phyto-oestrogens and the development of some diseases specifically osteoporosis, breast and prostate cancer' and that 'an evaluation of the risks and benefits of dietary phyto-oestrogens is critically dependent on the nature, timing, conditions and extent of exposure'.

More work is ongoing on several aspects of phyto-oestrogen research, and we look forward to the outcome in this very stimulating field of nutrition research.

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Editorial note

For practical reasons and to allow comparisons with the previous literature, different measurement units for phyto-oestrogens have been used in this Supplement. Mass units have been used for intake and food composition data, while molar units (as well as mass units) have been used for content in biological fluids. A table with the relative molecular mass of the different compounds is provided below, so that conversions can be performed.

Compound	Relative molecular mass (M_r)
Isoflavones	
Daidzein	254
Daidzin	416
6-*O*-Acetyl daidzin	458
6-*O*-Malonyl daidzin	502
Genistein	270
Genistin	432
6-*O*-Acetyl genistin	474
6-*O*-Malonyl genistin	518
Glycitein	284
Glycitin	446
Acetyl glycitin	488
Malonyl glycitin	532
Formononetin	268
Biochanin A	284
Total isoflavones	250
Lignans	
Matairesinol	358
Enterodiol	302
Enterolactone	298
Equol	242
Secoisolariciresinol	362
Coumestans	
Coumestrol	268