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Dietary intake of phytoestrogens

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Abstract

The dietary intake of phytoestrogens supposedly influences a variety of diseases, both in terms of beneficial and adverse effects. This report describes current knowledge on dietary intakes of phytoestrogens in Western countries, and briefly summarizes the evidence for health effects. The predominant phytoestrogens in the Western diet are the isoflavones and the lignans. The consumer groups with the highest dietary intake of isoflavones are consumers taking dietary phytoestrogen containing supplements (± 40 – 100 mg/d), vegan consumers (± 75 mg/d), soy-based formula fed infants (± 40 mg/d) and consumers of a traditional South East Asian diet (± 25 – 100 mg/d). The dietary isoflavone intake of average Western (including Dutch) consumers and vegetarians is much lower ($\pm <1$ – 2 mg/d and ± 3 – 12 mg/d, respectively). The intake of lignans is less well-studied and is estimated at 1.1 mg/d for the average Dutch consumer. However, this is likely an underestimation. Evaluation of the health implications of phytoestrogens is very complex, mainly because of insufficient data. There is concern about the use of soy-based infant formulae in view of the potential inhibition of the thyroid function. In addition, hypothyroid individuals and women with oestrogen-dependent breast disease are of potential concern. Although adverse health effects of isoflavones in the latter two subgroups have not been reported in the published literature, more research is needed that addresses the toxicological properties of soy or isoflavones for these groups specifically. To date, the effects of lignans on human health are still being investigated.

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Samenvatting

De inname van fyto-oestrogenen via de voeding wordt verondersteld een verscheidenheid aan ziekten te beïnvloeden, zowel in positieve als negatieve zin. Dit rapport beschrijft de huidige kennis van inname van fyto-oestrogenen via de voeding in Westerse (Europese en Noord-Amerikaanse) landen en vat beknopt de bewijzen voor gezondheidseffecten van deze stoffen samen. De hoeveelheid fyto-oestrogenen in de “standaard” Westerse voeding (hoge consumptie van dierlijk vet, geraffineerde granen en suiker, lage consumptie van groenten en fruit) is laag. De belangrijkste fyto-oestrogenen in deze voeding zijn de isoflavonen en de lignanen. Isoflavonen zijn voornamelijk aanwezig in soja en soja-producten, terwijl lignanen voorkomen in zaden, granen, groenten en fruit. Daarnaast zijn er isoflavonenpreparaten voorzien van gezondheidsclaims verkrijgbaar. Dit kan leiden tot hoge innames in sommige groepen van de populatie. De consumentengroepen met de hoogste isoflavoneninname zijn de consumenten die deze fyto-oestrogenen bevattende voedingssupplementen gebruiken (± 40 - 100 mg/d), veganistische consumenten (± 75 mg/d), zuigelingen die gevoed worden met zuigelingenvoeding op sojabasis (± 40 mg/d) en consumenten van een traditioneel Zuidoost-Aziatische voeding (± 25 - 100 mg/d). De inname van isoflavonen via de voeding van gemiddelde Westerse consumenten en vegetariërs is veel lager (respectievelijk <1 - 2 mg/d en ± 3 - 12 mg/d). Van de inname van lignanen is minder bekend. Deze wordt geschat op $1,1$ mg/d voor de gemiddelde Nederlandse consument. Dit is echter waarschijnlijk een onderschatting, omdat recentelijk een aantal nieuwe lignanen zijn geïdentificeerd waarmee geen rekening is gehouden in de innameberekening. De evaluatie van de gezondheidseffecten van fyto-oestrogenen is erg ingewikkeld, voornamelijk vanwege een tekort aan gegevens. Van isoflavonen is bewezen dat zij osteoporosis helpen voorkomen. Tevens is aangetoond dat soja cholesterolniveaus kan verlagen, maar het is niet duidelijk of dit effect toegeschreven kan worden aan de isoflavonen. De effecten op overgangsklachten, kanker, vruchtbaarheid en het immuunsysteem zijn niet eenduidig. Een bewezen negatief effect is de remming van de schildklierfunctie door soja. Isoflavonen spelen hierbij een rol. Een ander mogelijk risico zou het groeibevorderende effect van fyto-oestrogenen op *in vitro* borstkankercellen kunnen zijn. Er is bezorgdheid over het gebruik van op soja gebaseerde zuigelingenvoeding in relatie tot de mogelijke remming van de schildklier. Tevens zijn individuen met een traag werkende schildklier en vrouwen met oestrogeenafhankelijke borstkanker een bron van mogelijke ongerustheid. Ofschoon negatieve gezondheidseffecten van isoflavonen op de twee laatstgenoemde subgroepen niet in de wetenschappelijke literatuur zijn gerapporteerd is meer onderzoek nodig naar de toxicologische eigenschappen van soja en isoflavonen voor specifiek deze groepen. De gezondheidseffecten van lignanen zijn nog onderwerp van studie. De resultaten van de innameschattingen van fyto-oestrogenen geven aan dat er op dit moment geen noodzaak is tot wettelijke normen voor isoflavonen in voeding(ssupplementen). Echter, vanwege de snel veranderende markt, wordt aanbevolen dat binnen enkele jaren dit onderwerp opnieuw wordt bestudeerd.

Summary

The dietary intake of phytoestrogens supposedly influences a variety of diseases, both in terms of beneficial and adverse effects. This report describes current knowledge on dietary intakes of phytoestrogens in Western (European and North-American) countries, and briefly summarizes the evidence for health effects. The phytoestrogen content of the “standard” Western diet (which is high in animal fats, refined grains and sugar, low in fruits and vegetables) is low. The predominant phytoestrogens in this diet are the isoflavones and the lignans. Isoflavones are primarily present in soy and soy-based products, while lignans occur in seeds, grains, fruits and vegetables. In addition, isoflavones are marketed widely, provided with significant health claims, which may result in high intakes in some groups in the population. The consumer groups with the highest dietary intake of isoflavones are consumers taking dietary phytoestrogen containing supplements ($\pm 40\text{--}100$ mg/d), vegan consumers (± 75 mg/d), soy-based formula fed infants (± 40 mg/d) and consumers of a traditional South East Asian diet ($\pm 25\text{--}100$ mg/d). The dietary isoflavone intake of average Western (including Dutch) consumers and vegetarians is much lower ($\pm <1\text{--}2$ mg/d and $\pm 3\text{--}12$ mg/d, respectively). The intake of lignans is less well-studied and is estimated at 1.1 mg/d for the average Dutch consumer. However, this is likely an underestimation, due to a number of recently identified compounds that are not taken into account in the intake calculation. Evaluation of the health implications of phytoestrogens is very complex, mainly because of insufficient data. Isoflavones are proven to prevent osteoporosis. In addition, soy may lower cholesterol levels, but it is not clear whether this effect is due to the isoflavones. The effects on menopausal symptoms, cancer, fertility and the central nervous and immune system are not unequivocal. A proven adverse effect is the inhibition of the thyroid function by soy in which isoflavones play a role. Another possible risk may be the growth-stimulating effect of phytoestrogens on *in vitro* breast cancer cells. There is concern about the use of soy-based infant formulae in view of the potential inhibition of the thyroid function. In addition, hypothyroid individuals and women with oestrogen-dependent breast disease are of potential concern. Although adverse health effects of isoflavones on the latter two subgroups have not been reported in the published literature, more research is needed that addresses the toxicological properties of soy or isoflavones for these groups specifically. To date, the effects of lignans on human health are still being investigated. The results of the intake estimations of phytoestrogens indicate that there is no need for legal standards for isoflavones in food (or food supplements) at this time. However, because of the rapid changing market, it is recommended that within several years this subject be re-evaluated.

1. Introduction

Some naturally occurring compounds present in plants have been found to possess oestrogenic properties. These chemicals have been named “phytoestrogens”. Phytoestrogens display oestrogen-like activity since they are structurally similar to human oestrogens and therefore they can bind to the oestrogen receptor. In this way they are able to mimic or block the action of the human hormone oestrogen, although they are much less potent. These compounds enter the human body via the consumption of plants, especially grains, beans, nuts and seeds.

The four principal groups of phytoestrogens found in food are the isoflavones, coumestans, prenylated flavonoids and lignans. Isoflavones are found primarily in soy-beans and foods made from soy, while coumestans and lignans are found in a variety of fruits, grains and legumes. Prenylated flavonoids are present in hops.

Extensive research worldwide on phytoestrogens has led to many conflicting reports on the risks and benefits of consuming phytoestrogen-rich foods. Studies on populations that traditionally consume diets rich in phytoestrogens (for example Japanese and Chinese) suggest that they may have a beneficial effect on osteoporosis, cardiovascular disease and some cancers. Indeed, the highest levels of these compounds in the diet are found in countries or regions with low incidence of these cancers (Adlercreutz, 1995). In addition, it has been shown in postmenopausal women that habitually high intakes of isoflavones are associated with higher bone mineral density values at both the spine and the hip region (Mei et al., 2001). Finally, phytoestrogens may relieve menopausal symptoms (Kurzer, 2003). These positive findings have led to the manufacturing and retail of phytoestrogen-rich food supplements, claiming to give long-term health or to prevent chronic diseases.

Also, some negative effects of phytoestrogens have been reported, most notably the growth-stimulating effects of soy isoflavones on oestrogen-dependent breast cancer cells (Ju et al., 2002). Although these effects cannot be extrapolated to humans, they may indicate that the supplementation of diets with phytoestrogens may not be completely safe (Kiely et al., 2003; Kurzer, 2003).

In this document the occurrence, the dietary intake and the effects of phytoestrogens are described and discussed. An important document underlying the current study is the report on Phytoestrogens and Health (2003) from the Working Group on Phytoestrogens (FSA) from the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment of the British Food Standard Agency. Here, we summarised the findings of this report and included more recent studies on intake and effects of phytoestrogens.

2. Phytoestrogens: background information¹

2.1 Phytoestrogen classes

Phytoestrogens are defined by the British Working Group on Phytoestrogens of the Committee of Toxicity of Chemicals in Food, Consumer Products and the Environment of the Food Standards Agency (FSA, 2003) as *any plant substance or metabolite that induces biological responses in vertebrates and can mimic or modulate the actions of endogenous oestrogens usually binding to oestrogen receptors*.

The majority of phytoestrogens belong to a large group of substituted phenolic compounds known as flavonoids. Three classes of flavonoid, the isoflavones, coumestans and prenylated flavonoids are phytoestrogens that possess the most potent oestrogenic activity. A class of non-flavonoid phytoestrogens, the lignans has also been identified (Figure 1). The scheme in Figure 1 may not be an exclusive list as other phytoestrogens may be identified as constituents of food in the future.

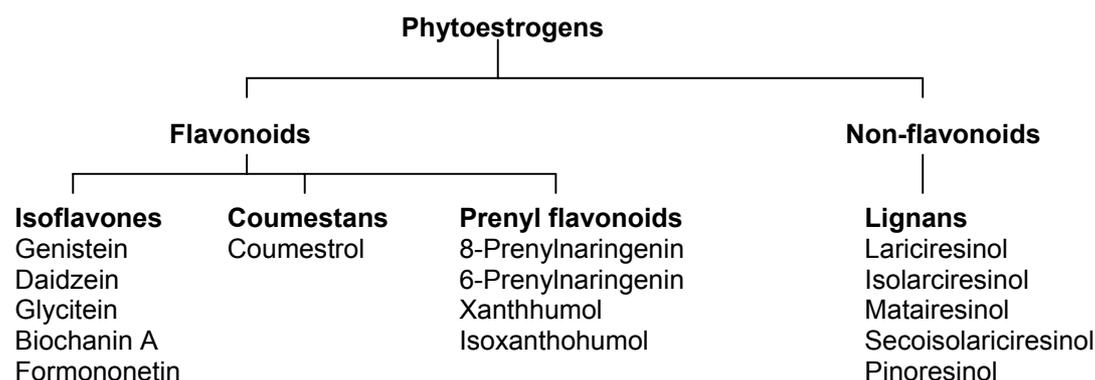


Figure 1. Various groups of phytoestrogens and members of this group (adapted from FSA, 2003).

The phytoestrogen classes mentioned above have a similar structure to oestradiol and are able to bind the estrogen receptor (ER), preferably the ER β , although their binding affinity is lower than that of endogenous estradiol. All the structures of the phytoestrogens possess the phenolic (bottom, left) and hydroxyl (top, right) moieties of the oestradiol structure (Figure 2) and the distances between the two groups in each compound are similar.

As regards estrogenicity of the phytoestrogens, their potency is dependent on the assay used to determine the value and varies considerably. Overall, the phytoestrogen with the highest receptor binding potency is coumestrol, which is \pm 10-500 times less potent than the endogenous ER β . Isoflavones are about 20,000-100,000 times less potent than ER β . Lignans are thought not to be oestrogenic themselves, but are

¹ This chapter is largely based on the report on Phytoestrogens and Health (2003) from the Working Group on Phytoestrogens (FSA) of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment of the British Food Standard Agency.

converted to the oestrogenic compounds enterolactone and enterodiol (the so-called mammalian lignans or enterolignans) by the gut microflora. These compounds have an even lower binding affinity to the estrogen receptor than the isoflavones.

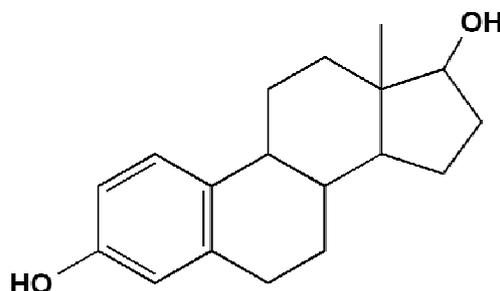


Figure 2. Structure of oestradiol

2.2 Dietary sources of phytoestrogens

The main classes of phytoestrogens and their common dietary sources are shown in Table 1, which suggest only the isoflavones and the lignans are commonly found in a Western diet (high in animal fats, refined grains and sugar, low in fruits and vegetables). It is possible that other phytoestrogen compounds are present in food, which have not been detected. Until recently, most of the available information on concentrations of phytoestrogens in foods is related to isoflavone aglucones (i.e. not bound to glucose). This is due to the limitations in the analytical methods used. Data on the concentrations of isoflavone glucosides or glucones (i.e. bound to glucose), prenylated flavonoids, coumestans and lignans are more limited.

Table 1. Phytoestrogens and common dietary sources (adapted from FSA, 2003)

phytoestrogen class	examples of dietary source
isoflavones	legumes, lentils, chickpeas, soybean
coumestans	young sprouting legumes
lignans	most cereals, linseed, fruit and vegetables
prenylated flavonoids	some beers (hops)

Isoflavones are primarily found in legumes where they often occur as glucosides. Soybeans and soy-based foodstuffs are a particularly rich source of isoflavones, especially genistein and daidzein and to a lesser extent glycitein. Biochanin A and formononetin (which are derivatives of genistein and daidzein) are generally less prevalent in soy and are found mostly in clover and alfalfa sprouts (Bingham et al., 1998). The coumestans of which coumestrol is the most common form, have been found in high concentrations in clover and fresh alfalfa sprouts as well (Humfrey et al., 1998). Lignans are a class of phytoestrogens that exist as minor constituents in many cereals, vegetables and fruit. Linseed (flaxseed) is the richest known source of lignans (Morton et al., 1997; Meagher and Beecher, 2000). Prenylated flavonoids have been found in high concentrations in hops, which are used in some beers. The levels measured in beer are low (Milligan et al., 1999).

There is a considerable variation of phytoestrogen concentrations in different plants. The concentration of these compounds can be influenced by a number of factors including species, strain, crop year and environmental conditions. The concentrations can vary by ~2-3 fold for each factor.

Processing can also alter the phytoestrogen content of foodstuffs. For example fermentation of soy into products such as tempeh, miso and bean paste reduces the isoflavone content with a factor 2-3. Cooking has also been shown to reduce phytoestrogen concentrations. However, baking or frying does not appear to alter the total isoflavone content of foodstuffs.

2.3 Absorption, distribution, metabolism and excretion of phytoestrogens

Isoflavones and lignans are ingested mainly as glucosides and are hydrolyzed by gut bacterial and mammalian enzymes, which releases the deglycosylated compounds daidzein, genistein and glycitein (among others). These may be absorbed or further metabolized by the gut bacteria to many specific (more potent) metabolites, including equol from daidzein and enterodiol and enterolactone from lignans. Research data suggest that once absorbed, isoflavones and lignans are extensively conjugated to glucuronides and sulfates in the liver and excreted in the bile or urine. This inhibits their ability to bind to the oestrogen receptors. As a consequence, the oestrogenically active parent compounds have relatively low concentrations in the blood. Factors influencing absorption and metabolism of phytoestrogens include diet and gut microflora. In human subjects, even those on controlled diets, there is large interindividual variation in the metabolism of isoflavones and lignans, particularly in the production of equol.

There is limited information on how phytoestrogens are handled in the newborn and infants. The pharmacokinetics of absorption in the neonate is unclear but is likely to differ considerably from that of the adult, particularly as the gut microflora in neonates is not fully developed. Data on the levels of isoflavones in the blood of infants fed soy-based formula suggest that they can absorb isoflavones from such formula. (FSA, 2003)

2.4 Concentrations of phytoestrogens in foods

Soy is recognised as the major dietary source of phytoestrogens (e.g. Bingham et al., 1998; USDA-Iowa State University Isoflavone Database, 2002). Soy-based products have been shown to contain significant quantities of total isoflavones with soybeans and soy flour containing the highest quantities (Table 2). Soy derivatives in many forms can serve as ingredients for diet products, act as an alternative for meat products or are included as food ingredients for technological (bread) or cost-effective reasons. In general, commercial processing of soy into food products reduces phytoestrogen concentrations and can alter the chemical form of isoflavones present. Hence, isoflavone concentrations in fermented and soy-based food products are usually lower than in un-processed soy (Table 2). Fruits, vegetables, nuts and cereals are all minor sources of isoflavones (Table 2). Of the other common phytoestrogens the highest concentrations of coumestrol have been found in clover and alfalfa sprouts (Table 2). The highest concentrations of lignans have been found in grains and seeds, in particular linseed and other fibre rich foods (Table 2). Note that Table 2 is a selection of published data and not a complete list of concentrations analysed in foodstuffs. More complete lists can be found in the constructed databases, such as the

United States Department of Agriculture (USDA)-Iowa State University Isoflavones Database (<http://www.nal.usda.gov/fnic/foodcomp/Data/isoflav/isoflav.html>). This database exists since 1998 and is a compilation of internationally published scientific literature on the concentrations of isoflavones in food and is updated when new studies are published. It includes mainly soy-based foods and some figures on isoflavones in pulses and peanuts.

Recently a database called Vegetal Estrogens in Nutrition and the Skeleton (VENUS; <http://www.venus-ca.org>) was developed by a group consisting of Irish, British, Finnish and Dutch researchers (Kiely et al., 2003). The VENUS database was established primarily to facilitate the estimation of exposure levels to phytoestrogens in four European countries, including Italy, the Netherlands, Ireland and the UK (Van Erp-Baart et al., 2003). The researchers collected and evaluated all papers in the literature on phytoestrogens in foods. Only articles in which the sampling procedures as well as the analytical method were described were taken into account. Data on the isoflavone (genistein and daidzein) content of 791 foods, including almost 300 foods commonly consumed in Europe, were collected. Levels of coumestrol, formononetin and biochanin A and two lignans (secoisolarciresinol and matairesinol) in a limited number of foods were also included.

Table 2. Approximate concentrations of total isoflavones, coumestrol and lignans in various foods; adapted from FSA, 2003)

Food	Isoflavones mg/100 g	Coumestrol mg/100 g	Lignans mg/100 g
Beans	0-1.5 ^a	0-3.6 ^a	0.05-0.18 ^b
Bean sprouts, alfalfa	-	4.7 ^a	-
Bread, brown, white	0-0.8 ^c	0	-
cereals i.e. wheat bran, cornflour, maize, oatmeal	<0.1 ^d	-	0.5 ^b
Fruit i.e. apples, banana, oranges, etc.	<0.1 ^d	-	0.1 ^b
Legumes	0-0.58 ^a	-	-
Linseeds (flaxseed)	-	-	60-370 ^b
Nuts, i.e. peanuts, hazel nuts, etc.	<0.1 ^b	0 ^a	0.02-0.33 ^b
Peas, i.e. lentil and split	0.1-2.5 ^a	0 ^a	0-0.20 ^b
Seeds i.e. sunflower, alfalfa, clover	0.01-0.6 ^a	72-561 ^e	-
Soy milk	5-10 ^a	-	-
Soy sauces	0.1-1.6 ^a	-	0.03 ^b
Soy flour	131-198 ^a	0 ^a	0.13 ^a
Soy beans	14-153 ^a	0.05 ^a	0.01-0.27 ^b
Teas i.e. black, green	0.04-0.05 ^a	0 ^a	2.04 ^b
Tempeh	29-53 ^a	-	-
Tofu	13.5-67 ^a	-	-

Adapted from: ^aUSDA-Iowa State University isoflavones database (2002); ^bMazur et al. (1998); ^cLiggins et al. (2002); ^dLiggins et al.(2000); ^eFranke et al. (1995); – signifies not determined

In addition to the analyses of food and food products, the concentrations of isoflavones in infant formulas and breast milk are measured. As can be expected, soy-based infant formula contains high concentrations of isoflavones (Table 3). Cow's milk-based formula contains no detectable isoflavones (Table 3). The concentrations of isoflavones in breast milk of mothers is dependent on the diet. Generally, the highest concentrations of total isoflavones were detected in the breast milk of mothers who followed a vegetarian or vegan diet (Table 3). Still, these are orders of magnitude less than the isoflavone concentrations present in soy-based infant formula.

Table 3. Total isoflavones in milk for infants (adapted from FSA, 2003)

milk	number of samples	total isoflavones
cow's milk-based formula ^a	3	-
soy-based formula ^b	5	18-41 mg/L
breast milk, omnivorous mother ^b	14	0-2 µg/kg
breast milk, vegetarian mother ^b	14	1-10 µg/kg
breast milk, vegan mother ^b	11	2-32 µg/kg

^aMAFF, 1998a; ^b MAFF, 1998b

3. Dietary intake of phytoestrogens by Western populations

As mentioned in the previous chapter, the only classes of phytoestrogens that will be significantly present in Western diets are the isoflavones and the lignans. The intake of coumestans, predominantly present in bean sprouts, of which the consumption in the Netherlands is very low, will be negligible. We considered the intake of prenylated flavonoids negligible as well, as the concentrations in beers are low (Milligan, 1999). As a consequence, in this chapter only the intake of isoflavones and lignans is described.

3.1 Dietary intake of isoflavones

Relatively high isoflavone intakes can be found in typical Asian diets, where soy foods are consumed more commonly than in Western diets. Recent estimates indicate intakes of 20-50 mg/d (Nagata et al., 1997; Chen et al., 1999; Mazur and Adlercreutz 2000) or even higher: 102 mg/d (Ho et al., 2000). Intakes of isoflavones in Western Europe are low. The richest sources of isoflavones in Japan are tofu, miso, natto and fried tofu (Wakai et al., 1999) and these foods are consumed relatively infrequently in Western countries.

Below, an overview is given of the isoflavone intake studies which were performed in Western (European and North-American) countries. The results of these investigations are summarized in Table 4.

The isoflavone intake of Californian women of 50-79 y was estimated at 2.87 mg/d (Horn-Ross et al., 2000a). The research group used their own database on isoflavone concentrations in food (Horn-Ross et al., 2000b) and the food consumption was estimated with food frequency questionnaires. The primary sources of these phytoestrogens were traditional soy-based foods and "hidden" sources of soy (e.g. foods containing added soy protein isolate, soy concentrate, or soy flour, such as doughnuts and white bread).

De Kleijn et al. (2001) calculated an average daily total isoflavone intake of postmenopausal women in the USA of 0.76 mg and the main dietary sources were found to be beans and peas.

A study into the isoflavone intakes in ten European countries reports isoflavone intakes of the same order of magnitude, namely less than 2 mg/d (Keinan-Boker et al. 2002a). These researchers used the USDA-Iowa State University database and only soy foods were included in the calculations.

For the Netherlands, an average intake level for isoflavones (daidzein, genistein, formononetin and biochanin A) of 0.88 mg/d was reported for middle-aged and elderly women (Keinan-Boker et al. 2002b). Daidzein and genistein were the main contributors to the total isoflavone intake. The main sources of isoflavones were peas and beans, nuts, grain products, coffee, tea and soy products. The concentration data were taken from the scientific literature, whereas the consumption of the women was estimated with food frequency questionnaires.

The data of De Kleijn et al. (2001) and Keinan-Boker et al. (2002a and b) are in contrast with the results of Horn-Ross et al. (2001) who reported that intakes were > 3 mg/d and the main dietary sources were, just as in the former study of this

research group (Horn-Ross et al., 2000a) tofu, doughnuts, soy milk and white bread. However, the latest study of this group (Horn-Ross et al., 2002), which was performed with over 100,000 subjects, indicates that the intake of isoflavones is lower than in their previous studies, namely 1.78 mg/d.

The Phytoestrogen Working Group of the FSA combined isoflavone concentration data with British consumption data from the National Diet and Nutrition Survey (1986-1987) The mean exposure to total isoflavones was estimated at 0.6 mg/d for the total population. The authors mention that since the dietary survey was conducted fifteen years ago and the availability and the use of soy and soy-containing foods has increased in recent years, this may be an underestimation (FSA, 2003).

Table 4. Isoflavone intake by adult populations in Western countries

reference and year	n	subjects	country	mean isoflavone intake per day
Horn-Ross, 2000a	447	women, 50-79 y	USA	2.87 mg
De Kleijn et al., 2001	964	postmenopausal women	USA	0.76 mg ¹
Horn-Ross, 2001	2882	women, 35-79 y	USA	3.3 mg
Keinan-Boker, 2002a	35955	whole pop., 35-74	10 European countries	< 2 mg
Keinan-Boker, 2002b	17140	women, 50-69 y	NL	0.88 mg ²
Horn-Ross et al., 2002	111526	women 21-103 y	USA	1.78 mg
FSA, 2003	2197	whole pop.	UK	0.6 mg
Valsta et al., 2003	2862	whole pop.	Finland	0.79 mg (SD 0.67)
Van Erp-Baart et al., 2003	1379	whole pop.	Ireland	0.73 mg 0.17-1.32 ³
Van Erp-Baart et al., 2003	1513	whole pop.	Italy	0.56 mg 0.16-1.36 ³
Van Erp-Baart et al., 2003	335	whole pop.	UK	0.72 mg 0.17-1.49 ³
Van Erp-Baart et al., 2003	4085	whole pop.	NL	0.91 mg 0.20-1.54 ³
Van Erp-Baart et al., 2003	4000	idem, without soy-consumers	NL	0.68 mg

¹median: 0.15 mg; ²geometric mean: 0.39 mg (distribution is skewed); ³5th and 95th percentile of the 2 day-intake

Recently, Valsta et al. (2003) reported isoflavone intakes of the Finnish population of 788 µg/day. This was calculated using the data of the National Dietary Survey FINDIET 1997 and the Finnish National Food Composition Database (Fineli®).

Another recent study is the publication of Van Erp-Baart et al. (2003), who used the VENUS database to estimate the isoflavone mean intake in four European countries. They combined the concentration data with national diet surveys of the different countries. In Ireland, Italy and the UK recent national (or other large) surveys based on 7d diary records were available. For the estimation of the Dutch intake, the Dutch National Food Consumption Survey was used, which describes the consumption pattern of the Dutch population and includes information on the daily consumption over two consecutive days and a record of age, sex and body weight of 6250 individuals (Kistemaker *et al.* 1998).

In the VENUS database (see also Section 2.4) enough analytical data were available to compile a national database for each of the four countries for the estimation of isoflavone (total, daidzein and genistein) intake. All foods and food products consumed in that country were included in the national databases. The concentrations of the foods were either taken directly from the VENUS database, or were calculated using recipes and processing factors (Van Erp-Baart et al., 2003).

The mean isoflavone intake in Ireland, Italy, the Netherlands and the UK, calculated with the compiled national databases is on average less than 1 mg/d (Table 4). The highest intake was found in the Netherlands, namely 913 µg/d.

It appeared that a relevant small group of soy consumers had a significant impact on the outcome of the intake calculation. For the Netherlands the intake level of this small group (n = 85) was about 11 mg/d. Therefore, intakes were also calculated excluding these soy food consumers. The intake of the Dutch population excluding the consumers of soy food was 683 µg/d (Table 4).

Summarizing, the dietary intake of isoflavone in Western countries is only one to several mg/day. The differences between the intake values obtained in the different studies is likely to be (1) the different tables of phytoestrogen levels in foods used by the different researchers and (2) the different diets in the countries. The latter is probably less important, as the difference between the intakes calculated for the three studies performed in the USA is already a factor of 4.

For the Netherlands, results indicate an isoflavone intake of < 1 mg/day for the whole population.

3.2 Isoflavone intake of special subgroups

3.2.1 Isoflavone intake by vegetarians, vegans and soy-consumers

The isoflavone intake by vegetarians, vegans and soy-consumers is expected to be higher than that of the whole population, mainly due to the higher intakes of soy and soy-products. The isoflavone intake of these subgroups has been investigated by several research groups. In this section, an overview of these studies is given and the estimated intakes are presented in Table 5.

The Working Group on Phytoestrogens of the British Committee of Toxicology of the Food Standards Agency (FSA, 2003) combined isoflavone concentration data with British consumption data from the Dietary Survey of Vegetarians of 1994-1995. The mean exposure to total isoflavones was estimated at 2.6 mg/d.

Another recent study into the isoflavone intake by vegetarians is a 7-day duplicate diet study carried out in the UK with 35 vegetarians (Clarke et al., 2003). In this study the participants collected an exact duplicate of all food consumed over a 7-day period gave an estimated intake of 12 mg isoflavones/d.

The Dutch soy-food consumers in the study of Van Erp-Baart et al. (2003; see also the previous section) had a mean isoflavone intake of 11 mg/d, whereas the British and Irish soy-food consumers had lower intakes. Note that the soy-food consumers are not necessarily vegetarians.

Finally, a study into breast feeding vegan mothers (MAFF, 1998b) estimated the mean intake to be 75 mg isoflavones per day.

The 2001 assessment by the FSA is considerably lower than the estimate of the other studies into the isoflavone intake of vegetarians. The reason for this difference is not clear. The intake of the vegetarians and soy-consumers is still low compared to South East Asian intakes (20-100 mg/d). The Western vegan mothers are the only adult subgroup that have an intake of isoflavones comparable to that of Eastern countries.

Table 5. Isoflavone intake by adult soy-consumers, vegetarians and vegans in European countries

Reference	n	subjects	country	isoflavone intake per day
FSA, 2003	415	vegetarians (incl. fish-eaters)	UK	2.6 mg
Clarke et al., 2003	35	vegetarians	UK	12 mg
MAFF, 1998b	11	vegan breast feeding women	UK	75 mg
Van Erp-Baart et al., 2003	85	soy-consumers	NL	11.1(SD 6.7) mg
Van Erp-Baart et al., 2003	15	soy-consumers	UK	3.2 (SD 4.0) mg
Van Erp-Baart et al., 2003	42	soy-consumers	IR	6.0 (SD 8.1) mg

3.2.2 Isoflavone intake by infants

In cow's milk based infant formula and in human breast milk, concentrations of isoflavones are 0-32 µg/kg (the highest concentrations measured in breast milk of vegan mothers). In contrast, in soy-based infant formula, concentrations of 18-41 mg/L made up formula have been measured (see Table 3 in Section 2.3). These concentrations result in an intake of 5 mg/kg/d for 1-2 month old infants and 4.5 mg/kg/d for 4-6 month old infants (MAFF, 1998a). Other studies have indicated higher isoflavone intakes by soy-based formula drinking infants. Setchell et al. (1998) estimated an intake of 4.5-8 mg/kg/d for 4-month old infants (n=7). A Swiss study by Rupp et al. (2000) estimated that infants up to 5 months of age would be exposed to between 3-13 mg/kg/d whilst infants older than 5 months were estimated to be exposed to a maximum of 20 mg/kg/d. In addition, Murphy et al. (1997) reported intakes in the range of 5-12 mg/kg/d.

In the UK, soy-based infant formulae are fed to approximately 1 % of non-breast fed infants aged 4-10 weeks, rising to approximately 2 % of infants aged 10-14 weeks. Similarly, in the Netherlands soy-based infant formula represents ~1 % of the total infant formula available (Kraaij, Numico, personal communication). The infants who drink this formula are allergic or intolerant to cow's milk or their parents chose to feed them a vegan diet. In comparison, it has been estimated that this figure is as much as 25 % for the US.

Table 6. Isoflavone intake by soy-based formula drinking infants

Reference	age	intake mg/kg/d	± intake mg/d*
MAFF, 1998a	1-2 months	5	28
MAFF, 1998a	4-6	4.5	34
Setchell et al., 1998	4 months	4.5-8	32-56
Rupp et al., 2000	up to 5 months	3-13	23-98
Rupp et al., 2000	> 5 months	max. 20	max. 160
Murphy et al. 1997		5-12	

*calculated by multiplying the intake with the average infant weight (Burgmeijer, 1998)

3.2.3 Isoflavone intake by the consumption of food supplements

Extracted phytoestrogens are marketed in numerous forms as dietary supplements. Consumers of these supplements tend to be peri- and postmenopausal women looking for an alternative to hormone therapy. Although there are no approved health claims for phytoestrogens at this time, numerous claims are being made regarding to benefits to heart, bone, breast and general menopausal health. The data supporting those claims are generally not strong. The strongest data show that phytoestrogens reduce the number and intensity of hot flashes, although the reduction is a modest 10-20% (Kurzer, 2003). More information on effects of phytoestrogens can be found in Chapter 4.

Most supplements contain isoflavones derived from soybeans or red clover and some contain botanicals such as black cohosh (*Actaea racemosa* or *Cimicifuga racemosa*, a member of the buttercup family). A web search in January 2001 suggested that there were 50-100 different phytoestrogen supplements available at that time, not including soy protein supplements and energy bars (Kurzer, 2003). Most product labels mention a content of about 40-50 mg per tablet, but amounts of 100 mg and 200 mg are stated as well, all to be taken once a day (Web search October 2003; Nurmi et al. 2002). Similarly, Barnes (2003) mentions that most supplements have a targeted delivery of 50 mg/d.

Analysis of the supplements has shown that the actual phytoestrogen content varied between products and was often less than declared on the label. Nurmi et al. (2002) found that only one product out of eleven was found to contain the same amount of isoflavones as was provided by the producer, while the other ten contained \pm 30-75 % of the content as stated on the product label. Similar findings were reported by Setchell et al. (2001, n=33) and Howes and Howes (2002, n=10). In addition, Tice et al. (2003) reported that contents of 37-43 mg were measured for "40 mg tablets" and 25.6-31.4 mg for "57 mg tablets".

3.3 Dietary intake of lignans

A number of studies investigated the dietary intake of lignans, by calculation of the sum of secoisolariciresinol (SECO) and matairesinol (MAT), the most analysed lignans. The amounts of SECO are usually considerably higher than that of MAT. An overview of the dietary intake studies of lignans is given in Table 7.

In addition to the intake of isoflavones, Horn-Ross et al. (2000b) also estimated a total mean intake of lignans for Californian women (0.18 mg lignans/d). The more recent study of the same research group (Horn-Ross et al., 2002) among over one hundred thousand female teachers reported a somewhat lower intake of 0.11 mg/d for the sum of SECO and MAT. These values are considerably lower than the results of De Kleijn et al. (2001), who estimated the intake of these lignans for postmenopausal women at 0.64 mg/d, mainly coming from fruits. Keinan-Boker et al. (2002b) reported an even higher daily lignan intake for Dutch women, namely 1.1 mg. The main sources of lignans in this study were grain products, fruit and alcoholic beverages (red and white wines). The estimated intake for Dutch women is higher than the estimated intake of lignans by the Finnish, which was recently estimated at 0.3 mg/d (Kilkkinnen et al., 2003) and 0.4 mg/d (Valsta et al., 2003). The main sources of the lignans in the Finnish studies were seeds, cereals, fruit, berries and vegetables.

Table 7. Lignan intake by adult populations in Western countries

reference and year	n	subjects	country	mean lignan intake per day
Horn-Ross et al., 2000a	447	women 50-79 y	USA	0.18 mg
De Kleijn et al., 2001	964	postm ¹ . women	USA	0.64 mg ²
Horn-Ross et al., 2002	111526	women 21-103 y	USA	0.11 mg
Keinan-Boker et al., 2002b	17140	women 50-69 y	NL	1.1 mg ³
Kilkkinnen et al., 2003	2852	whole pop.	Finland	0.32 mg
Valsta et al., 2003	2862	whole pop.	Finland	0.43 mg ⁴

¹postm.: postmenopausal; ²median 0.58 mg; ³geometric mean: 1.0 mg (distribution is skewed) ⁴standard deviation:1.58 mg

Just as for the isoflavones the estimated intake of lignans varies a factor of about 5 between the different studies. Generally the intake of lignans, as the sum of MAT and SECO, is lower than the intake of isoflavones. An exception is the intake by the Dutch women, as reported by Keinan-Boker et al. (2002b), whose intake of lignans is somewhat higher than that of the isoflavones (see Tables 4 and 7).

4 Health risk and health benefits of dietary phytoestrogens to humans²

Breast cancer, prostate cancer, menopausal symptoms, osteoporosis and heart disease share a common epidemiology in that they are rare in South East Asian populations eating traditional diets containing soy products (e.g. Bingham 1998).

In the early 1980s the possible beneficial effects of (soy derived) phytoestrogens in cancer prevention and other hormone-related diseases were first published. Since then literature on possible health benefits of phytoestrogens has expanded exponentially. The present state of knowledge about the risk and benefits of phytoestrogens is reviewed in this chapter.

Menopausal symptoms

The prevalence of symptoms of the menopause, like hot flashes, is lower in South East Asian women as compared to Western women, which may be due among others to differences in the diet. As a consequence, a large number of studies have been performed into the effect of soy-based products or isoflavones on menopausal symptoms. The results of these studies are inconclusive. In general, data support a benefit of soy isoflavones (30-104 mg/d) on hot flash frequency and severity, but the data are ambiguous, as positive results are often not statistically significant and strong placebo responses are observed (FSA, 2003). Kurzer (2003) mentions that only 10-20 % of the effect is due to the isoflavones per se, the rest is due to the placebo effect.

Cardiovascular disease

Many risk factors, such as high blood pressure and diabetes are associated with cardiovascular disease. However, the underlying basis for cardiovascular disease is a combination of atherosclerosis (excessive accumulation of lipids and smooth muscle cells in the artery) and thrombosis (development of fibrinous clots). Hormonal status is known to play a role in the development of cardiovascular disease. The similarity of phytoestrogens to oestrogens (which can decrease cholesterol levels) and the lower cardiovascular disease mortality rates in populations consuming soy suggested that phytoestrogens are protective against cardiovascular disease.

Indeed, there is a considerable body of evidence to indicate that the intake of soy can have beneficial effects on low-density lipoprotein (LDL) and total cholesterol levels, but this requires that the isoflavones be consumed intact in soy protein (Kurzer, 2003; FSA, 2003). There is some evidence that flaxseed-fibre (which is rich in lignans) also has a beneficial effect on cholesterol. The effects of phytoestrogens on other factors important in the risk of cardiovascular disease such as blood pressure, thrombosis or atherosclerosis have not been extensively investigated (FSA, 2003).

Osteoporosis

Osteoporosis is characterised by low bone mass and micro-architectural deterioration of bone tissues with a consequent increase in bone fragility and risk of fracture. Animal studies suggest that dietary isoflavones may exert benefits on bone mineral density and bone turnover. Epidemiological studies suggest that intakes of

² This chapter is largely based on the report on Phytoestrogens and Health (2003) from the Working Group on Phytoestrogens (FSA) of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment of the British Food Standard Agency.

phytoestrogens are associated with higher bone mineral density in populations consuming relatively large amounts of soy. There have been very few intervention studies in humans in this area but results suggest small protective effects in the lumbar spine. Further studies are needed to establish whether these effects are sustained over long periods of time (Kurzer, 2003; FSA, 2003).

Sexual development and fertility

It is established that exposure to potent oestrogens *in utero* can have long-term adverse effects on human development and fertility in males and, more severely, in female offspring. The synthetic oestrogen diethylstilboestrol (DES) is of comparable potency to oestradiol. It was initially developed as a drug to prevent miscarriage and was used widely from the 1940s. The subsequent discovery that *in utero* exposure to DES induced abnormal development of the offspring male and female reproductive system and caused tumors in the cervix after puberty resulted in a ban by the US Food and Drug Administration in 1971. These findings have raised concerns that exposure to phytoestrogens *in utero* may also give rise to similar adverse effects later in life.

A number of *in vivo* studies on the effects of phytoestrogens on the fertility of rodents and primates have been conducted. However, species differences in sexual development and reproductive function between animal models and humans make the interpretation of these studies to humans extremely difficult.

Two studies have specifically examined the effect of soy formula feeding on sexual development and fertility in humans. The data do not provide evidence of obvious adverse clinical effects on sexual development or reproductive health of males and females, apart from small increases in the duration and discomfort of menstruation (Strom et al., 2001). The other study examining the possible association between a number of dietary and environmental factors with premature breast development in girls, reported a weak association with soy formula feeding (Freni-Titulaer et al., 1986). However, both studies were based on recall and did not involve any direct measurements of hormone levels or other parameters in the subjects.

Thyroid gland

It has been known since the 1960s that soy can have an effect on the thyroid gland, as infants fed soy flour-based infant formula were reported to have enlarged thyroid glands. This problem was overcome by using soy protein isolate instead of soy flour and by supplementation of the formula with iodine. This reduced the goitrogenic (= thyroid enlarging) effects of the formula. Since this change in processing and formulation there have been no reports of thyroid enlargement in infants fed soy formula.

While the effect of soy on the thyroid is unambiguous, the role of isoflavones in this effect is still under discussion. Although isoflavones have been shown to significantly inactivate rat and human thyroid enzymes *in vitro*, fortification of the diet with genistein did not change the thyroid function *in vivo* (Doerge and Sheehan, 2002). So, although there is a clear effect of isoflavones on thyroid enzymes, additional factors appear necessary for isoflavones to cause overt thyroid toxicity. These factors include iodine deficiency, but may also include additional soy components, or other dietary factors (Doerge and Sheehan, 2002).

Data from human studies suggest that dietary soy or isoflavones are unlikely to affect the thyroid function in normal individuals with adequate iodine intake. However, for individuals with a lack of dietary iodine and/or very low thyroid activity

(hypothyroidism) it is possible that their thyroid function may be adversely affected by the consumption of soy-based or phytoestrogen-rich foodstuffs and supplements. Also, it is possible that soy-based infant formulae may have the capacity to inhibit thyroid function in infants. However, it is not clear whether the concentrations in these formulae are high enough to realise this inhibition. It is reported that children fed soy formulae have a higher incidence of autoimmune thyroiditis (Fort et al., 1990), but this finding may be biased because children put on soy formula may be more likely to have autoimmune disorders, such as food allergies. Finally, limited epidemiological evidence suggests that phytoestrogen exposure is not associated with thyroid cancer risk (Horn-Ross et al., 2002).

Central nervous system and immune system

Oestrogens are active in the central nervous system (CNS) and are thought to influence behaviour, movement and cognition (among others). They are also involved in the development and maintenance of normal immune function.

Studies suggest the blood brain barrier effectively restricts phytoestrogen transfer to the CNS in adult rodents. However, despite this, relatively high dietary exposures to isoflavones in rodents have been shown to alter protein concentrations and structures in the brain as well as induce behavioral effects. The implications of these findings for humans are unclear. Studies on the effect of soy or isoflavones on cognitive function in humans suggest small effects, but reports are conflicting.

Rodent studies on the effects of isoflavones on immune function have produced inconsistent results. Studies on the effects of soy infant formula on infant immunity are conflicting as well.

Cancer

It has been observed that the rate of breast cancer is lower in women from some populations in Asia compared with Western populations. This has led to the suggestion of a possible reverse association between breast cancer and dietary phytoestrogen intake. Studies in premenopausal women have thus focused on the potential cancer protective effects of phytoestrogens. The idea is that phytoestrogens increase the menstrual cycle length, which is thought to reduce the risk of breast cancer by decreasing the lifetime exposure of women to endogenous oestrogens. Data from studies on premenopausal women suggest that supplementation of the diet with soy or isoflavones produces weak hormonal effects. However, the nature of these effects is inconsistent (FSA, 2003)

The animal data on breast cancer is conflicting. A number of studies have shown that genistein has a protective effect in animal models of chemically induced cancer. However, similar experiments using (*in vitro*) tumour implant models showed that genistein stimulated the growth of established breast cancer cells (FSA, 2003; Kurzer, 2003 and references therein)

In men, increased phytoestrogen consumption has been associated with a reduced risk of prostate cancer. However, reports of hormonal effects in men from dietary soy or isoflavone supplementation are inconsistent, showing no or weak hormonal effects. (FSA, 2003)

It has been suggested that exposure to oestrogens of phytoestrogens during development *in utero*, in infancy or in childhood may play an important role in the programming of hormonal homeostasis and influence the risk of developing cancer later in life. This may, in part, explain why the relatively low risk of certain cancers observed among migrant populations from South East Asia increases in subsequent

generations. Long-term studies should be undertaken to establish the clinical efficacy of phytoestrogens in these conditions in humans (FSA, 2003).

5 Discussion and conclusions

5.1 Intake estimation of isoflavones and lignans

The dietary intake of phytoestrogens is estimated using concentrations in foodstuffs and food consumption. However, the quantity of phytoestrogen concentration data is limited in comparison to the numbers of foods that are consumed. For a number of foods, concentrations can be calculated with conversion factors or recipes, for others data are simply missing. For example, in the study of Van Erp-Baart et al. (2003) the latter was the case for 9 % of the foods.

In addition to missing data on isoflavones for particular food products, there are no or very few data available on particular phytoestrogens. For example the lignans pinoresinol (PINO) and lariciresinol (LARI) were not taken into account in the intake studies, since there is a paucity of data on these compounds in foodstuffs. However, it appears that LARI and PINO are quantitatively more important than secoisolariciresinol (SECO) and matairesinol (MAT), (Milder et al., 2003).

Even if data are available, the isoflavone contents of various products are difficult to estimate, since there is a lack of information on the type of soy ingredients used in the manufacture of meat products and meat-containing mixed dishes and snacks.

Finally, there is variable quality in the analytical data available, particularly in the data obtained from older studies. In addition, there is natural variation in soybean isoflavone values between seasons, crops and varieties, and this has not been taken into account in the intake studies.

For these reasons, the calculated intakes of phytoestrogens are fairly crude estimations. Furthermore, underestimation of the phytoestrogen intake is always possible. For lignans it is even very likely, since the intake of PINO and LARI have not yet been determined in intake studies.

For the estimated intake of isoflavones the ranking of the consumer groups is as follows: consumers taking dietary phytoestrogen containing supplements (± 40 -100 mg/d) \approx vegan consumers (± 75 mg/d) \approx soy-based formula fed infants (± 40 mg/d) \approx average South East Asian consumers (± 25 -100 mg/d) $>$ vegetarian consumers (± 3 –12 mg/d) $>$ average Western consumers ($\pm <1$ -2 mg/d).

The exposure of consumers taking supplements is most likely ± 50 mg/d or lower, since a lot of supplements contain less than stated on the product label. However, products are available which result in a dose of 100 mg/d.

The exposure among all subgroups mentioned above will vary due to the large inter-individual differences in intake, metabolism, bioavailability and gut microflora.

The average isoflavone intake of the whole Dutch population has been estimated as being lower than 1 mg/d.

The intake of lignans was only studied in adults; intake figures for special subgroups (other than men and women) are not available. The intake estimates for adults vary from 0.18 mg/d (USA) to 1.1 mg/d (the Netherlands) and are generally lower than the estimated isoflavone intakes of average Western consumers.

5.2 Effects of phytoestrogens on human health

The evaluation of the public health implications of phytoestrogens is complex. The Working Group on Phytoestrogens of the Committee of Toxicity of the FSA (2003) mentions a number of reasons for this complexity:

Firstly, epidemiological data suggest that a soy-rich diet is associated with a reduction in the risk of a number of diseases. However, many of these studies are of limited value because they do not address specifically the roles of phytoestrogens.

Secondly, it is difficult to interpret experimental results. In experiments, subcutaneous instead of dietary administration is often used and high concentrations of phytoestrogens were given. Furthermore, there are significant interspecies differences in the absorption, distribution, metabolism and excretion (ADME), making extrapolation of the effects seen in animals to humans complex. In addition, many of the studies were short-term intervention studies in adults that did not address the possibility that exposure to phytoestrogens at an earlier age may influence the risk of disease later in life. Furthermore, a significant proportion of the research has been conducted in populations such as the Japanese and the Chinese and thus, extrapolation to Western populations may be confounded by differences in lifestyle, diet, gut microflora, genetic make-up and ADME.

Finally, most research has focused on the isoflavones and thus, relatively little is known about the prenylated flavonoids, coumestans and lignans.

The only beneficial effect of phytoestrogens that has been convincingly demonstrated is the effect of isoflavones on osteoporosis. In addition, soy may lower cholesterol levels, but it is not clear whether this effect is due to the isoflavones. The effects on menopausal symptoms, cancer, fertility and the central nervous and immune system are not unequivocal. In general, presently, the studies that lead to the suggested possible association between a high phytoestrogen intake and an increased health lack a dose-response relationship. Therefore, the evidence is generally not strong and a quantitative health benefit assessment is impossible.

A proven adverse effect of phytoestrogens on human health is the inhibition of the thyroid function by soy, although this effect is likely not caused by the isoflavones alone. Another possible risk may be the growth-stimulating effect on *in vitro* breast cancer cells. While this effect cannot be extrapolated to man, it does suggest that there may be possible risks associated with the addition of phytoestrogens to diets at physiologically relevant concentrations (Kiely et al., 2003; Kurzer, 2003).

5.3 Evaluation of health implications

As mentioned above, the evaluation of the effects of isoflavones on human health is complicated. Furthermore, the calculated intakes are only crude estimations. As a consequence, an evaluation of the risks and benefits of dietary phytoestrogens is difficult.

Several subgroups of the population may be exposed to relatively high amounts of phytoestrogens, especially consumers taking dietary phytoestrogen containing supplements, vegans, soy formula fed infants, and South East Asian consumers.

Barnes (2003) has critically reviewed the available studies on effects of phytoestrogens and concluded that an oral isoflavone dose of 50 mg/d (± 0.7 mg/kg bw/d) should be considered safe in most population groups. The study

suggests that it may also be reasonable to extend this limit of safety to 2 mg/kg bw/d in clinical trials where there is careful monitoring of the participating patients.

When expressed on a body weight basis, infants fed soy formula are likely to have the highest exposure to isoflavones (\pm 4-8 mg/kg bw/d). This is higher than the safe dose mentioned by Barnes (2003). The findings from the effect studies do not provide definitive evidence that soy-based infant formulae can adversely affect the thyroid function of infants. However, they provide evidence of *potential* risks and therefore, there is concern about the use of soy-based infant formulae (FSA, 2003). Therefore, the FSA recommended a revision of the advice of the Department of Health in the UK, who stated in 2002 that, although breastfeeding was preferred, where this was not possible, soy-based infant formulae are suitable for infants who cannot tolerate cow's milk formula or who are fed a vegan diet. The only other country that has issued advice with specific reference to soy-based infant formula is New Zealand. The Ministry of Health in New Zealand recommended that soy-based infant formula should only be fed to infants under medical supervision. It was also advised that clinicians be made aware of the potential interactions of soy-based infant formula with the thyroid function (FSA, 2003).

Until recently soy-based infant formula was the only option for non-breast-fed infants who are allergic to cow's milk or intolerant to lactose. At present, hydrolysed cow's milk is available for those infants with a cow's milk allergy. Hydrolysed cow's milk is considered preferable to soy-based infant formula as soy can also act as an allergen (Kraaij, Numico, personal communication). For infants with a lactose intolerance and for parents who want to give their child a vegan diet, soy-based infant formula is still the only option (other than breast milk).

A number of consumers of phytoestrogen containing food supplements (those with doses > 50 mg/d), vegans and South East Asian people will have an exposure higher than 0.7 mg isoflavones/kg bw/d. On the other hand, their intake will likely be lower than the 2 mg/kg bw/d that was considered safe to use in clinical trials by Barnes (2003). With the present state of knowledge, it cannot be concluded if effects on health (whether beneficial or adverse) will occur on people who have intakes between 0.7 and 2 mg/kg bw/d. Large long-term studies in humans are needed to establish the relationship between dietary phytoestrogens and the development of some diseases, specifically osteoporosis, breast cancer and prostate cancer (FSA, 2003).

For the average Dutch consumer and the vegetarian consumer, the exposure to isoflavones is lower than 0.7 mg/kg bw/d. Nevertheless, the FSA identified individuals with hypothyroidism as a subgroup of potential concern. Although no adverse effects in hypothyroid individuals have been reported, the consumption of phytoestrogen supplements, or a soy-rich diet, may provide sufficient concentrations of phytoestrogens to interfere with thyroid hormone replacement therapy. In addition, the FSA mentions that, although there is no evidence of breast cell proliferative effects in humans by isoflavones, women with oestrogen-dependent breast disease should be cautious with taking phytoestrogen-rich food and supplements.

The intake of lignans was estimated for the Dutch population at 1.1 mg/d, but is likely higher due to the presence of newly discovered lignans in food, which are not taken into account in the present study. Whether the dietary intake of lignans lead to effects on human health is a subject that is still under study.

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