

## Phytoestrogens in peri- and postmenopause

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### Summary

Despite increasing interest in alternative therapies for menopausal hot flashes that avoid the use of estrogens, the efficacy and safety of other options are currently not well supported. There is no conclusive evidence that phytoestrogen supplements effectively reduce the frequency or severity of hot flashes and night sweats in postmenopausal women. Many of the studies are of poor quality and results are inconsistent. Women requiring relief for mild vasomotor symptoms may try taking isoflavones. Isoflavones are not as effective as estrogens in relieving hot flashes. There is a, probably weak, indication, but no conclusive evidence, that isoflavones have a beneficial effect on bone health. There also appears to be an association between lifelong soybean intake and a reduction in the risk of breast cancer.

### Introduction

The incidence of climacteric disorders varies individually. One third of perimenopausal women suffer from severe complaints, one third suffer average discomfort, and the other third does not exhibit any symptoms.

Individualized hormone therapy, in the form of estrogen or estrogen-gestagen substitution, is nowadays, the most effective treatment of climacteric complaints caused by a lack of estrogen, such as hot flashes and sweating. Apart from the treatment of climacteric complaints, the benefits of hormone substitution therapy in the prevention of postmenopausal osteoporosis, one of the most relevant age-related diseases, have been established. However, there are risks associated with hormone therapy, particularly in long-term treatment.

Women suffering from climacteric disorders often consult their physician on alternative types of treatment. Many women also treat themselves with herbal preparations without consulting a physician. It is difficult to compile exact statistics on self-medication; according to surveys, ca. 15-17% of the perimenopausal women in Germany use herbal and homeopathic preparations. In particular, women with mild complaints or those who fear the possible side-effects of hormone substitution therapy prefer alternative treatments as a first attempt at therapy.

The results of a survey carried out at the University of Illinois (Chicago) on 500 outpatients between the ages of 40 and 60, showed that 79 % of the women questioned used herbal dietary supplements, 36.5 % even used them on a daily basis. 52 % of the users used one to two supplements per day and 48 % took at least three supplements daily. Soy, camomile, ginkgo and ginseng are common examples. 70 % of the women did not inform their physician about taking the supplements (Mahady et al. 2003).

The range of dietary supplements and other non-prescription, predominantly herbal preparations available for self-medication of climacteric disorders is increasing. It includes, for example, preparations that contain isoflavones, black cohosh (*Cimicifuga racemosa*), evening primrose oil, ginseng, dong quai, yam root, hops, or also vitamin E (Cheema et al. 2007; Geller and Studee 2005; Huntley and Ernst 2003; Kronenberg and Fugh-Berman 2002; NAMS 2004; Nedrow et al. 2006; Ziaei et al. 2007; Tab. 1).

Table 1: Dietary supplements for treatment of climacteric disorders (examples)\*

Supplement	effectiveness vs. placebo
Phytoestrogens: isoflavones from soy and red clover	slight to nonexistent
Black cohosh ( <i>Cimicifuga racemosa</i> ) [+ St. John's Wort ( <i>Hypericum perforatum</i> )]	slight to nonexistent
Dong quai ( <i>Angelica sinensis</i> L.)	no effect
Yam root ( <i>Dioscorea villosa</i> )	no effect
Evening primrose oil ( <i>Oenothera biennis</i> L.)	no effect
Ginseng ( <i>Panax ginseng</i> )	no effect
Ginkgo ( <i>Ginkgo biloba</i> )	no placebo-controlled studies
Liquorice ( <i>Glycyrrhiza glabra</i> )	no placebo-controlled studies
Valerian ( <i>Valeriana officinalis</i> )	no placebo-controlled studies
Hops ( <i>Humulus lupulus</i> )	no placebo-controlled studies
Vitamin E	no effect

\* Cheema et al. 2007; Geller and Studee 2005; Huntley and Ernst 2003; Kronenberg and Fugh-Berman 2002; NAMS 2004; Nedrow et al. 2006; Ziaei et al. 2007

In practice, apart from phytoestrogens, black cohosh (*Cimicifuga racemosa*) is the supplement most frequently used for treating climacteric disorders.

There has been increasing interest in phytoestrogens, particularly in the past few years, and the number of scientific studies and products available continues to grow.

Apart from the treatment of climacteric complaints, there is repeated debate on the role of phytoestrogens as a prophylactic against breast cancer.

Of all phytoestrogens, the isoflavone substance class plays the main role in clinical use.

This article summarizes present scientific data with regard to the advantages and risks of isoflavone supplementation during the climacterium.

### Phytoestrogens – Isoflavones

Phytoestrogens are plant substances that are capable, either themselves or after metabolism, of imitating or modeling the effect of endogenous estrogen. Isoflavones are the main type of phytoestrogens used in the gynecology. Two of the most important sources of isoflavones are soy and red clover.

Isoflavones bind to the estrogen receptor; the affinity to bind to the classical estrogen receptor  $\alpha$  is low, but to estrogen receptor  $\beta$  it is high. Depending on their concentration, the concentration of the endogenous hormones, and the specific end-organ, they can act as estrogens or antiestrogens. However, many effects are transmitted receptor-independent.

Isoflavones may be consumed with food or as a supplement. To guarantee a daily intake of 50 mg isoflavones, 500 ml of soy milk or 200 g of tofu (isoflavone content varies) must be consumed, generally requiring a complete adjustment of dietary habits, which is difficult to maintain over a longer period. Dietary supplements containing red clover and soy are therefore favored.

The studies available are difficult to compare for several reasons: supplements vary in their composition, as with isoflavone supplementation a substance group is consumed, not an individual active ingredient, and in addition, metabolism varies individually. Dietary supplements contain varying combinations of isoflavones, such as genistein, daidzein, glycitein, formononetin and biochanin A. The potent isoflavone equol, for example, is only produced in the intestinal flora (Fig. 1). However, on average, only 30 % of the population in our region are able to produce equol. The percentage is higher among vegetarians.

It is not possible to objectify the individual metabolism of isoflavones before treatment, in clinical practice. (Cassidy et al. 2006; NAMS 2000; Tempfer et al. 2007).

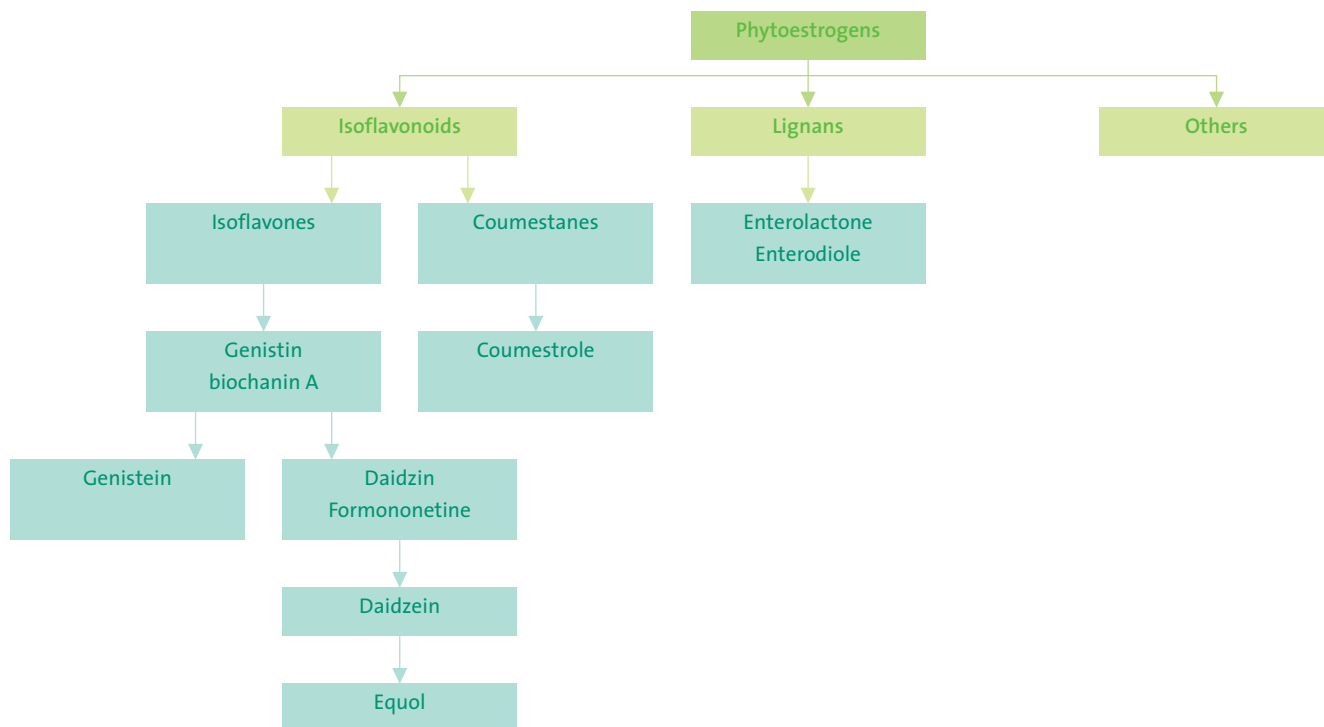


Figure 1: Classification of phytoestrogens

### Problems associated with dietary supplements

Dietary supplements are foodstuffs that contain one or more nutrients in a concentrated form (e. g. vitamins, minerals, and trace elements) but which supply hardly any energy. They are provided in forms that are not typical of food e. g. tablets, capsules or dragées with the purpose of supplementing the diet.

Dietary supplements are not drugs. It is only necessary to register supplements with the Federal Office for Consumer Protection and Food Safety (BVL). Monitoring of dietary supplements and their manufacturers is the responsibility of the food monitoring authorities of the German Federal States. Dietary supplements are regulated by provisions in the “Lebens- und Futtermittelgesetzbuch” (LFGB – German food and animal fodder law). EU and national legislation on the regulation of these products is in preparation. According to the Federal Institute for Risk Assessment (BfR), dietary supplements are superfluous for persons with a normal diet. In particular situations, specific dietary supplementation using individual nutrients may be recommended (BfR; <http://www.bfr.bund.de>).

Dietary supplements are not subject to the same criteria as drugs. There is a lack of studies on their effectiveness that satisfy current criteria. This also applies to possible side effects. Furthermore, supplements are often available as combined preparations, which, if information on the mechanism and efficacy of individual ingredients is lacking, makes evaluation on a scientific basis more difficult or even impossible.

### Isoflavones and climacteric disorders

The idea of treating climacteric disorders with isoflavones is based on epidemiological studies on female Asians, who suffer less from climacteric complaints.

Many studies have been carried out on the treatment of climacteric complaints using phytoestrogens in the form of isoflavones gained from red clover or soy. A review of current studies shows general inconsistencies. The majority of placebo-controlled studies show no significant reduction in vasomotoric symptoms. In some studies, evidence of a slight reduction in climacteric complaints was found. Several meta-analyses of randomized and placebo-controlled studies have been published in recent years, which present a summarized evaluation of the effectiveness of isoflavones.

In 2007, Lethaby et al. published a meta-analysis of 30 randomized and placebo-controlled studies on the subject of “Phytoestrogens and vasomotoric symptoms” (Lethaby et al. 2007). Studies were included in which the participants consumed at least 30 mg of isoflavones per day. Only a few studies show effects of isoflavones which exceed those of the placebo effect; the majority of studies do not show such results. The effectiveness is independent of the isoflavone dose or the severity of the complaints.

The meta-analysis by Coon et al. (2007) on red clover isoflavones also shows no significant reduction in hot flushes.

Nelson et al. (2006) arrives at the same result with regard to red clover preparations. The results of studies on soy preparations are less consistent, even in studies of the highest quality. A daily dose of 50-70 mg of isoflavones reduced the number of hot flushes by an average of one hot flush per day. Increasing the dose does not improve the effectiveness (Tab. 2).

Table 2: Effectiveness of red clover and soy preparations in the treatment of hot flushes (meta-analysis)\*

Preparation	Isoflavone concentration (mg/day)	n (studies) in the meta-analysis	n (patients)	Length of study	Number of hot flushes/day vs. placebo (95 % CI)
Isoflavones (red clover)	40-160	7	497	12-16 weeks	<b>-0.44</b> (-1.47 to 0.58)
Isoflavones (Soy)	40	1	99	1 year	<b>-1.48</b> (-2.49 to -0.48)
Isoflavones (Soy)	50-70	4	353	4-6 weeks	<b>-0.97</b> (-1.82 to -0.12)
Isoflavones (Soy)	50-70	2	152	6 months	<b>-1.22</b> (-2.02 to -0.42)
Isoflavones (Soy)	150	1	177	4-6 weeks	<b>0.71</b> (-1.30 to 2.72)

\* Nelson et al. 2006

CI: confidence interval

The meta-analysis by Howes et al. (2006) showed a slight reduction in hot flushes due to isoflavones, particularly in women with very frequent flushes.

**! Based on the results of these meta-analyses and on practical experience, the effectiveness of isoflavones on vasomotoric complaints must be classed as slight to nonexistent. !**

The therapeutic effect cannot be predicted for individual cases. If complaints are mild and the patient wishes to take a supplement containing isoflavones, the effectiveness must be tested individually. 50 mg of isoflavones are recommended per day. The results should be discussed with the patient after eight to twelve weeks of treatment. If there is no reduction in vasomotoric complaints, supplementation can be discontinued as no further improvements are to be expected. Isoflavones are not recommended for severe vasomotoric complaints as it is unlikely that they will bring about any improvement.

In this context, it is interesting that anamnestic data on the dietary habits of women affected provide evidence to suggest that vegetarians respond better to treatment with isoflavones.

Currently, isoflavones are available in combination with inulin. Inulin is a prebiotic dietary plant fiber that supports the uptake of isoflavones. This effect was examined in a randomized, double blind, cross-over study involving

twelve postmenopausal women. When combined with inulin, higher plasma concentrations of daidzein and genistein were found (Piazza et al. 2007).

Isoflavones are combined with hormone therapy in clinical practice to reduce the dose of hormones or, for example, to slowly taper off hormone treatment. However, so far there are no relevant studies on the effectiveness of this combination therapy.

Urogenital symptoms caused by a lack of estrogen, such as vaginal dryness, cannot be improved by taking isoflavones (Cassidy et al. 2006; Huntley and Ernst 2003; Huntley and Ernst 2004; Krebs et al. 2004; Kronenberg and Fugh-Berman 2002; NAMS 2000; NAMS 2004; Nedrow et al. 2006; Tempfer et al. 2007).

### Isoflavones and bones

Clinical studies show that isoflavones positively influence bone metabolism parameters and bone density, irrespective of how much time has elapsed since the onset of the menopause. However, not all studies support these results. It is particularly problematic that most of the studies on bone density were only carried out over a short period (under one year). In a review of the data available on isoflavones and bones (Messina et al. 2004), isoflavones are not recommended as a replacement for established osteoporosis medication. However, the authors do recommend motivating postmenopausal women to integrate soy products into their diet for the benefit of their bones. According to the clinical data available, an intake of 80 mg isoflavones per day is recommended, whereby epidemiological data from Asia suggest that lower doses are sufficient.

The lack of larger and, in particular, long-term studies and also the lack of fracture data remain a problem (Cassidy et al. 2006; NAMS 2000; Tempfer et al. 2007).

In summary, there are no data available to support a general recommendation on the use of isoflavones for the prevention of osteoporosis. According to current scientific knowledge, negative effects on bone metabolism of postmenopausal women are not to be expected. Isoflavones alone should not be recommended for women with an established risk of developing osteoporosis.

### Isoflavones and the cardiovascular system

It has been experimentally shown that isoflavones have vasodilatory, antithrombotic and anti-atherogenic effects.

In clinical studies it has been shown that isoflavones do not affect the blood pressure. Meta-analyses have repeatedly shown a positive influence on the lipid profile. In 1999, in the USA, the FDA recommended a dose of 25 g of soy protein per day to reduce cardiovascular disease (contains ca. 50 mg of isoflavones).

Since 2006, the American Heart Association has no longer recommended isoflavone supplements for the prevention of cardiovascular disease due to a lack of proof of their effectiveness. Alterations in diet are the decisive factor in the prevention of cardiovascular illness, not dietary supplementation (Cassidy et al. 2006; NAMS 2000; Tempfer et al. 2007).

Isoflavones are not recommended for primary prevention of cardiovascular disease. There are no randomized controlled studies on clinical endpoint cardiovascular diseases such as myocardial infarct or angina pectoris.

### Isoflavones and safety aspects: mamma

Isoflavones can develop estrogenic and anti-estrogenic effects as "phyto-SERMs". Due to this characteristic, in practical use the following clinically relevant questions arise on their effects on mammary gland tissue:

- Is it possible to prevent breast cancer by using isoflavones?
- What effect do isoflavones have on postmenopausal mammary gland tissue?
- Can the use of isoflavones be recommended for patients with breast cancer?

The question of the prevention of breast cancer by a diet rich in soy products has been the subject of many case-control and cohort studies. In a new meta-analysis (Trock et al. 2006) on the prevention of breast cancer by the intake of soy products it was shown that there is more likely to be a preventative effect in premenopausal women (OR = 0.70; 95 % CI = 0.58-0.85) than in postmenopausal women (OR = 0.77; 95 % CI = 0.60-0.98). This observation was not confirmed by all studies. However, it has never been shown that the risk of breast cancer is increased by a diet rich in isoflavones. It is probable that for isoflavones to have a preventative effect, intake must commence during pre-puberty.

There is no proof that dietary supplementation with isoflavones has a preventative effect on postmenopausal breast cancer.

Questions posed by women wishing to supplement their diet as a prophylaxis against breast cancer, with regard to the dose required, when to begin supplementation and how long supplementation should last, cannot be answered.

There are few clinical data on the effects of isoflavones on mammary gland tissue in the postmenopause. The mammographic density of mammary gland tissue does not increase during isoflavone intake (Atkinson et al. 2004; Powles et al. 2008). In a clinical study, no alterations were found in the proliferation marker Ki67 and in estrogen and progesterone receptor expression following a 3-month intake of 36 mg of isoflavones (Cheng et al. 2007). According to current scientific knowledge, based in particular on relevant animal experiments, it is unlikely that isoflavones have a negative effect on mammary gland tissue during the postmenopause. In animal experiments, for instance on macaques, high-dose isoflavone therapy does not have an effect on mammary gland tissue (Foth and Cline 1998). There are no relevant clinical studies on patients with

breast cancer. As the therapeutic effect on severe vasomotor complaints is only mild or even nonexistent, in the case of patients suffering from breast cancer, the lack of data should be taken into account, and the use of isoflavones should be critically evaluated (Antoine et al. 2007; Cassidy et al. 2006; Messina and Wood 2008; NAMS 2000; Rice and Whitehead 2006; Tempfer et al. 2007).

### **Isoflavones and safety aspects: endometrium**

Due to their mode of action, animal and the most clinical studies isoflavones are found to have no estrogenic effect on the postmenopausal endometrium.

In clinical studies lasting a maximum of one year, with isoflavone doses of up to 100 mg per day, no histological alterations of the endometrium were found, and no increase in the thickness of the endometrium was observed in vaginal sonography following isoflavone supplementation during the postmenopause.

In 2004, Unfer and coworkers published the first placebo-controlled study on the long-term effects (five years) of 150 mg of isoflavones per day on the endometrium during the menopause. The study is also the largest of its kind, involving 376 participants. The average age of the postmenopausal women in the study was 50 years when the study commenced. Contradicting previous studies, the authors came to the conclusion that long-term application of phytoestrogens is associated with an increased risk of endometrial hyperplasia. After five years of therapy with isoflavones, five simple (3.2%) hyperplasias and one complex (0.6%) endometrial hyperplasia without abnormalities were diagnosed. After critical examination of the results of the study, the biopsies, 26.8% of which were performed before starting therapy, 25.5% after 30 months and 19.5% after five years, were classified as nonevaluable. Other examinations, such as the determination of endometrial thickness using vaginal sonography to exclude a pre-existing endometrial hyperplasia when the study began, are not mentioned and the participants were included in the evaluation. Despite the critical points of the study, there is, at present, no other study investigating the question of high-dose self-supplementation over a period of several years.

Based on experiments on postmenopausal macaques, it was shown that isoflavone supplementation in addition to estrogen monotherapy has an inhibitive effect on cell proliferation. Future studies could examine whether isoflavone supplementation in combination with low-dose estrogen monotherapy is sufficient to prevent endometrial hyperplasia (Foth et al. 2006). However, in a first clinical study isoflavone supplementation did not lead to adequate protection of the endometrium (120 mg/day) (Murray et al. 2003).

Due to the lack of long-term studies, women taking self-prescribed supplementation should undergo regular prophylactic examinations, which should include vaginal sonography (NAMS2000; Palacios et al. 2007).

### **Possible undesired side effects**

Due to reports of undesired side effects caused by the use of products containing soy and red clover, the BfR issued a statement in April 2007, evaluating the effects of these products on health.

There had been individual reports of predominantly mild, but partially moderately severe symptoms including nausea, constipation, swellings or reddening of the skin. These symptoms were probably a result of allergic reactions, which eased when intake ceased. Such reactions are possibly due to the soy protein contained in the products (BfR; <http://www.bfr.bund.de>).

Taking the frequent use of isoflavones into consideration, side effects are only rarely to be expected.

### **Recommendations**

- The benefits and risks of alternative therapies in the treatment of menopausal complaints cannot be adequately evaluated due to the current lack of scientific data. Such treatments are not an alternative to causative hormone therapy.
- No individual prediction can be made on the effects of isoflavones, and only little, or a complete lack of evidence is found in the studies available.
- If symptoms are mild and the patient wishes to take dietary supplements, based on the data available it is suggested that isoflavones are tested individually.
- The results of the therapy should be discussed with the patient after eight to twelve weeks of treatment.
- If there is no reduction of vasomotor symptoms, intake may be discontinued as no further improvement is to be expected.
- If vasomotor complaints are severe, dietary supplementation, including isoflavones, is not recommended.
- Life style should always be taken into consideration when consulting patients suffering from climacteric complaints. General measures include reducing coffee and nicotine intake, wearing suitable clothing, avoiding heat, getting sufficient exercise, doing relaxation exercises, and following a balanced, healthy diet.

Table 3 summarizes these practical recommendations.

Table 3: Isoflavones – practical recommendations

Indications	Study data available	Dosage
Vasomotor symptoms	effect is moderate to nonexistent, individual treatment if symptoms are mild	ca. 50 mg/d
Urogenital atrophy	no effect	–
Bone protection	positive effects are possible (bone density, metabolic parameters), no fracture data	?
Endometrium	up to 100 mg/day probable lack of estrogenic effects on the endometrium, lack of long-term studies	avoid higher doses, preventative examination
Breast cancer prophylaxis	epidemiological studies: preventative effect in premenopausal women is more likely than in postmenopausal women	dosage? start? duration?

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### Keywords

Isoflavones, hot flushes, endometrium, breast

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#### Conflict of interest

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# CME-Continuing Medical Education

## Phytoestrogens in peri- and postmenopause

### Question 1

How are isoflavones consumed? Which statement is *incorrect*?

- a. As dietary supplements made from soy products
- b. As dietary supplements made from red clover
- c. In a diet rich in soy products, e. g. tofu
- d. In a diet rich in soy products, e. g. soy milk
- e. Vitamin preparations

### Question 2

Which statement is *incorrect* with regard to dietary supplements?

- a. Dietary supplements are foodstuffs that contain one or more nutrients in a concentrated form.
- b. Dietary supplements are available in forms which are not typical of food, e. g. as tablets, capsules, or dragées.
- c. Isoflavones can be taken as dietary supplements.
- d. Dietary supplements are subject to registration with the Federal Office for Consumer Protection and Food Safety (BVL).
- e. Dietary supplements are subject to the same criteria as drugs.

### Question 3

Which of the following substances is *not* an isoflavone?

- a. Genistein
- b. Daidzein
- c. Equol
- d. Biochanin A
- e. Enterolactone

### Question 4

Which statement is *incorrect* regarding the mode of action of isoflavones?

- a. Isoflavones bind to the estrogen receptor.
- b. There is only a slight capacity to bind to the classic estrogen receptor- $\alpha$ .
- c. There is a high capacity to bind to estrogen receptor- $\beta$ .
- d. Many effects are transmitted receptor-independent.
- e. Isoflavones do not bind to the estrogen receptor.

### Question 5

For which patients are phytoestrogens recommended?

- a. For patients suffering from mild climacteric complaints and who do not wish hormone therapy but would like to try treatment with plant hormones.
- b. For patients who do not suffer from climacteric complaints and who would like preventative therapy for osteoporosis as they run a high risk of developing osteoporosis.
- c. For patients suffering from complaints caused by atrophy of the urogenital tract.
- d. For patients suffering from severe hot flushes and sweats.
- e. For patients suffering from severe insomnia.

### Question 6

Isoflavones in the treatment of mild climacteric complaints: which dose would you recommend?

- a. Ca. 5 mg isoflavones per day
- b. Ca. 15 mg isoflavones per day
- c. Ca. 50 mg isoflavones per day
- d. Ca. 150 mg isoflavones per day
- e. Ca. 500 mg isoflavones per day

### Question 7

For which of the following symptoms/indications may treatment with isoflavones as a dietary supplementary be considered?

- a. Urogenital atrophy
- b. Mild hot flushes
- c. Cardiovascular primary prevention
- d. Cardiovascular secondary prevention
- e. Hormonal treatment of endometrial hyperplasia

### Question 8

Isoflavones and breast cancer prophylaxis: which statement is correct, according to current scientific knowledge?

- a. A preventative effect is more likely to be found in premenopausal women than in postmenopausal women.
- b. It has been clearly established that isoflavones prevent breast cancer in premenopausal women.
- c. It has been clearly established that isoflavones prevent breast cancer in postmenopausal women.
- d. It has been clearly established that isoflavones prevent breast cancer in all women.
- e. 150 mg of isoflavones must be taken per day to prevent the development of mammary carcinoma.

### Question 9

Isoflavones and patients with breast cancer: which statement is correct?

- a. Isoflavones constitute the optimal treatment for climacteric complaints.
- b. It has been established that isoflavones do not increase the risk of recurrence.
- c. It has been established that isoflavones increase the risk of recurrence.
- d. Isoflavones should be recommended for all patients with breast cancer.
- e. There are no relevant clinical studies on patients with breast cancer.

### Question 10

Isoflavones and the endometrium in the postmenopause: which statement is *incorrect*?

- a. No histological alterations of the endometrium were found in clinical studies lasting up to one year.
- b. No vaginal-sonographic increase in the width of the endometrium was found during the postmenopause in clinical studies lasting up to one year.
- c. It is established that 50 mg of isoflavones per day prevent endometrial hyperplasia during estrogen monotherapy.
- d. All statements are incorrect.
- e. All statements are correct.